HHS Public Access

Author manuscript

Am J Gastroenterol. Author manuscript; available in PMC 2021 September 01.

Published in final edited form as:

Am J Gastroenterol. 2020 September ; 115(9): 1505–1512. doi:10.14309/ajg.0000000000000670.

Hospital-Acquired Versus Community-Acquired Acute Kidney Injury in Patients with Cirrhosis: A Prospective Study

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Abstract

Objectives: In patients with cirrhosis, differences between acute kidney injury (AKI) at the time of hospital admission (community-acquired) and AKI occurring during hospitalization (hospital-acquired) have not been explored. We aimed to compare patients with hospital-acquired AKI and community-acquired AKI in a large, prospective study.

Methods: Hospitalized patients with cirrhosis were enrolled (N=519) and were followed for 90 days following discharge for mortality. The primary outcome was mortality within 90 days; secondary outcomes were development of *de*-novo chronic kidney disease (CKD)/progression of CKD after 90 days. Cox proportional hazards and logistic regression were used to determine the independent association of either AKI for primary and secondary outcomes, respectively.

Results: Hospital-acquired AKI occurred in 10% and community-acquired AKI occurred in 25%. In multivariable Cox models adjusting for significant confounders, only patients with community-acquired AKI had a higher risk for mortality [adjusting for MELD-Na: hazard ratio (HR) 1.64, 95% confidence interval (CI) 1.04–2.57), p=0.033; adjusting for ACLF: HR 2.44, 95%CI 1.63–3.65, p<0.001). In univariable analysis, community-acquired-AKI (but not hospital-

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Author Contributions:
Study Concept and Design: KRP and ESO
Data Analysis: KRP, HS, CX, and ESO
Manuscript Preparation: KRP, HS, CX, ESO
Manuscript Review: all authors

Conflicts of Interest: Dr. Naga Chalasani has ongoing consulting activities (or had in the preceding 12 months) with NuSirt, AbbVie, Eli Lilly, Afimmune (DS Biopharma), Allergan (Tobira), Madrigal, Shire, Axovant, Coherus, Siemens, Centurion, and Genentech. He has received research support from Lilly, Galectin, Gilead, Exact Sciences, and Cumberland. Dr. Pere Ginès has received research funding from Mallinckrodt, Grifols and Gilead S.A. He has participated on Advisory Boards for Novartis, Promethera, Sequana, Gilead, Martin Pharmaceuticals, Ferring Pharmaceuticals and Grifols. The remaining authors disclose no conflicts.

acquired-AKI) was associated with de novo CKD/progression of CKD (OR 2.13, 95% CI 1.09–4.14, p=0.027), but in multivariable analysis, community-acquired AKI was not independently associated with *de-novo* CKD/progression of CKD. However, when AKI was dichotomized by stage, community-acquired AKI stage 3 was independently associated with *de-novo* CKD/progression of CKD (OR 4.79, 95%CI 1.11–20.57, p=0.035).

Conclusions: Compared to hospital-acquired AKI, community-acquired AKI is associated with increased mortality and *de*-novo CKD/progression of CKD in patients with cirrhosis. Patients with community-acquired AKI may benefit from frequent monitoring after discharge to improve outcomes.

Keywords

acute kidney injury; decompensated cirrhosis; MELD; chronic kidney disease

INTRODUCTION

Hospitalized patients with cirrhosis are highly susceptible to acute kidney injury (AKI) (1–5). In this population, AKI is present in up to 34% at the time of hospital admission (2, 6) and it develops in another 24% during the hospital stay (6). AKI is also associated with progressive loss of kidney function with the development of chronic kidney disease (CKD) which can lead to further episodes of AKI (AKI on CKD) (7). Both AKI and CKD are independently associated with significant morbidity and mortality in patients with cirrhosis (1, 8).

Patients with cirrhosis with AKI at the time of hospital admission [community-acquired AKI (C-AKI)] have well-described clinical courses and outcomes (1, 2, 4, 6). However, there are few data describing outcomes of patients who develop AKI during a hospitalization [hospital-acquired AKI (H-AKI)] (9). In addition, it remains unclear if and how H-AKI differs from C-AKI. Understanding the differences and similarities between C-AKI and H-AKI is critical to improving prognostication and to targeting personalized care before, during, and after hospital discharge. Furthermore, in this population, there is a paucity of studies examining *de-novo* CKD development or CKD progression after AKI. An improved understanding CKD after AKI in cirrhosis is critical given the known impact of CKD on patient outcomes. Thus, we sought to compare risk factors and outcomes between C-AKI and H-AKI in patients with cirrhosis admitted to the hospital. To achieve these goals, we examined mortality, CKD development, and CKD progression in a prospective cohort study of hospitalized patients with cirrhosis.

PATIENTS AND METHODS

STUDY POPULATION:

Unselected patients with cirrhosis who were non-electively admitted to Indiana University Hospital were non-consecutively (based on the availability of research staff) prospectively enrolled from June 2014 to October 2018. The diagnosis of cirrhosis was based on clinical parameters including laboratory tests, endoscopic or radiologic evidence of cirrhosis, evidence of decompensation (hepatic encephalopathy (HE), ascites, variceal bleeding,

jaundice), and liver biopsy where available. Patients were excluded if there was an unclear diagnosis of cirrhosis, if they had prior liver or kidney transplant, if they were on hemodialysis at the time of admission, if they were admitted electively, or if informed consent could not be obtained. This study was reviewed and approved by the institutional review board at our institution.

OUTCOMES:

Patients were followed from the time of hospital admission to assess for outcomes. The primary outcome was mortality up to 90 days from discharge. The secondary outcome was the diagnosis of *de-novo* CKD and/or progression of CKD (see *Definitions: "CKD and CKD Progression* below) based on laboratory results showing diminished eGFR persisting for at least 3 months from the time of AKI event (C-AKI and H-AKI) or from admission (no AKI). Because of limited availability of laboratory data at 3 months, we considered the first available creatinine beyond 3 months and up to 1 year to determine the presence of CKD. The median time to this secondary outcome determination was 114 days.

HOSPITALIZATION DETAILS:

We collected the following data at the time of admission: demographics; cirrhosis etiology (hepatitis C, alcohol, non-alcoholic steatohepatitis, hepatitis C and alcohol use, and other); cirrhosis-related complications; home medications (e.g. non-selective beta blockers, angiotensin converting enzyme inhibitors/angiotensin receptor blockers, non-steroidal anti-inflammatory drugs, diuretics, and rifaximin); co-morbid conditions (e.g. diabetes, hypertension, pre-existing CKD—see *"Definitions: CKD and CKD Progression"*); baseline serum creatinine (see *"Definitions: AKI and AKI Phenotype*"); and baseline estimated glomerular filtration rate (eGFR). We also identified AKI-related hospitalizations in the previous 30 days, reason for hospitalization, vital signs, laboratory data (e.g. complete blood count, metabolic panel, and hepatic panel), and infections (on admission. During the hospitalization, information on daily vital signs and laboratory data, subsequent infections, phenotype of AKI (see "AKI definitions"), precipitants of AKI [e.g. excessive use of diuretics, spontaneous bacterial peritonitis (SBP), non-SBP infections, portal hypertensive related bleeding, intravenous contrast, and other], and details on the management of AKI (e.g. albumin infusions, use of midodrine or octreotide or both, and renal replacement therapy) were recorded. Discharge serum creatinine, eGFR, and medications (e.g. non-selective beta blockers, angiotensin converting enzyme inhibitors/angiotensin receptor blockers, non-steroidal anti-inflammatory drugs, diuretics, rifaximin, and proton pump inhibitor use) were collected. The eGFR, serum creatinine, and number of re-admissions for AKI at the time of secondary outcome determination was also captured.

Cirrhosis severity on admission was calculated using the model for end-stage liver disease (MELD) (10) and Child-Turcotte-Pugh (CTP) (11) scores. Acute on chronic liver failure (ACLF) and its severity (grades 1 to 3) on admission was defined by the CLIF Consortium Organ Failure Score (12).

DEFINTIONS: AKI and AKI PHENOTYPE

AKI—AKI was defined by Kidney Disease Improving Global Outcomes (KDIGO) (13), which have been endorsed by the International Club of Ascites (ICA) (3) as either: (1) a rise in serum creatinine of ≥ 0.3 mg/dL from baseline within 48 hours or (2) increase in creatinine to 1.5 times from baseline, which is known or presumed to have occurred within the prior 7 days. Baseline serum creatinine was defined per the ICA, which was the availability of a serum creatinine within the previous 3 months. If more than one creatinine value was available, the closest to the admission date was used. The median time between baseline creatinine and admission creatinine was 13 days. Patients with AKI at the time of admission were considered to have C-AKI. In those patients who did not have a pre-admission creatinine (N=125), the admission creatinine was used as baseline as recommended (3). For these patients without a prior known baseline creatinine, we categorized those with an absolute change in creatinine of ≥ 0.3mg/dL within 48 hours of admission as having C-AKI, and those with a stable creatinine for 48 hours as not having C-AKI, as previously described (14). Patients without AKI on admission who subsequently developed AKI during the hospitalization (≥48 hours after admission in those without a pre-admission creatinine) were considered to have H-AKI (14). AKI staging and its resolution were defined by KDIGO staging system (13) and by the ICA (3) respectively. Additionally, as previously described (6, 15), stage 1 AKI was further dichotomized into stage 1A (creatinine <1.5 mg/dL) or 1B (≥ 1.5 mg/dL).

AKI Phenotype: Phenotypes of AKI were classified as: hypovolemic (e.g. history of excessive fluid losses or bleeding); hepatorenal syndrome [by the ICA (3)]; acute tubular injury/necrosis [defined by KDIGO (13): history of hypotensive events or presence of shock, urinalysis positive for muddy brown granular, epithelial cell casts, and free renal tubular epithelial cells, or recent use of nephrotoxic drugs]; and other (AKI that cannot be classified in the previous phenotypes).

DEFINITIONS: De-novo CKD and CKD PROGRESSION:

De-novo CKD was defined per KDIGO guidelines, as the persistence of eGFR <60 ml/min per 1.73 m^2 for least 3 months (3, 13) from the time of AKI event or from the time of admission (in those without AKI). Since serum albumin was not uniformly available for each patient, the Modification of Diet in Renal Disease (MDRD)-4 variable equation (16) was used to estimate eGFR over MDRD-6 variable equation. The Chronic Kidney Disease Epidemiology Collaboration equation was not chosen as it does not approximate measured GFR in the setting of cirrhosis with low eGFR (17, 18). CKD was further classified as G3a (eGFR 45–59), G3b (eGFR 30–44), G4 (eGFR 15–29), and G5 (eGFR <15) (13). CKD progression was defined as a decline in CKD category accompanied by a 25% drop in eGFR from baseline (13).

STATISTICAL ANALYSIS:

Patient characteristics were compared by AKI status (C-AKI and H-AKI). Continuous variables were presented as mean ± standard deviation (s.d.) and median with interquartile range (IQR) where appropriate. Categorical variables were presented as percentages.

Differences across groups with respect to categorical variables were analyzed using chi-square and Fishers Exact tests, whereas continuous variables were analyzed using t-test or the Wilcoxon rank sum tests among two groups, or Kruskal-Wallis test or ANOVA among three groups.

Univariate logistic regression analysis was performed to identify risk factors associated with C-AKI and H-AKI. Potential risk factors were chosen *a priori* which included age, gender, cirrhosis etiology, baseline eGFR, co-morbid conditions (diabetes, hypertension, CKD), certain home medications (non-selective beta blockers, non-steroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, diuretics), cirrhosis related complications, and AKI in the previous 30 days. Odd ratios (OR) and their corresponding 95% confidence interval (CI) were reported for risk factors associated for either AKI.

Cause-specific Cox proportional hazard models were used for primary outcome analysis. Logistic regression models were used for our secondary outcome analysis. Liver transplant was considered a competing risk for death in the primary outcome. H-AKI was considered as a time-dependent covariate for the primary outcome analysis. Patients who received a liver transplant or died during the 90-day follow-up were excluded in the secondary outcome analysis. Patients who were lost to follow up were excluded from analysis for both outcomes. Univariate Cox and logistic regression analyses were performed to identify risk factors associated with the primary and secondary outcomes. Variables that were significant on univariate analysis ($p<0.05$) for the primary and secondary outcome were then entered into a multivariable Cox and logistic regression analysis to determine the independent association of either AKI for the primary and secondary outcome, respectively. In addition, survival curves for time to death were estimated by AKI status (no AKI, C-AKI, and H-AKI) using Kaplan Meier method and compared using log rank test. Hazard ratios (HR) and their corresponding 95% CI were reported for the primary outcome and OR and their corresponding 95% CI were reported for the secondary outcome. A two-sided nominal p-value < 0.05 was considered significant. All analyses were performed in SAS version 9.4.

RESULTS

529 patients were enrolled during the study period. Ten patients were on hemodialysis at the time of admission and were excluded, leaving 519 patients for analysis. The mean age was 58 ± 10.7 years and the majority were white (94%) and male (57%). The most common etiologies of cirrhosis were non-alcoholic steatohepatitis (33%), alcohol (29%), and HCV (15%). The mean baseline eGFR and creatinine was 75.1 ± 34.1 ml/min per 1.73 m^2 and 1.1 ± 0.6 mg/dL, respectively. Thirty six percent had CKD (45% stage 3a, 32% stage 3b, 22% stage 4, 1% stage 5); 36% had diabetes; and 41% had hypertension. Most were decompensated (CTP B 32% and CTP C 63%) and had ACLF on admission (62% overall; 28% ACLF grade 2 and 34% grade 3) with a mean MELD-sodium score of 23 ± 7. The prevalence of liver, kidney, brain, coagulation, circulation, and respiratory failure was 11%, 19%, 39%, 12%, 2%, and 2% respectively. The most common reasons for admission were overt hepatic encephalopathy (26%), ascites and volume overload (19%), and variceal bleed (14%). Thirty eight percent had an infection on admission. C-AKI was present in 25%, and

H-AKI occurred in 10% (overall AKI prevalence of 35%). The median days (IQR) to H-AKI was 3 (2, 4). At 90 days, 25% died (N=131) and the median (IQR) days to death was 37 (20, 58); 7% (N=37) underwent liver transplantation. Eight percent (N=43) were lost to follow up during the study period.

COMPARISONS OF PATIENT CHARACTERISTICS BETWEEN C-AKI AND H-AKI:

Demographic and clinical characteristics of patients with C-AKI and H-AKI are compared in Table 1 (comparisons between patients without AKI, C-AKI, and H-AKI can be found in Supplementary Table 1). Patients with C-AKI were significantly older compared to H-AKI patients (p=0.042). There were no significant differences in baseline creatinine (p=0.673) or eGFR (p=0.164). There were no significant differences in etiology of cirrhosis, CKD and its stages, diabetes, hypertension, cirrhosis related complications, etiology for hospital admission, and infections between the two groups (Table 1). The presence of ACLF was significantly higher in patients with C-AKI compared to H-AKI (p=0.011) and was largely related to a higher admission creatinine in C-AKI patients. Accordingly, MELD-Na scores were also significantly higher in patients with C-AKI (29 ± 6 vs. 26 ± 7, p=0.004). However, there were no differences between the two groups for CTP scores (p=0.284). Mean arterial pressure was found to be significantly lower in patients with C-AKI compared to H-AKI patients (76 vs. 83 mmHg, p=0.001). There were no differences between the two groups for white blood cell count (p=0.932).

FACTORS ASSOCIATED WITH C-AKI AND H-AKI:

CKD was associated with C-AKI [OR 2.18 (95% CI 1.43–3.32) and H-AKI [OR 1.83 (95% CI 1.00–3.35) (Supplementary Table 2). However, baseline eGFR was found to be associated with C-AKI [OR 1.02 (95% CI 1.01–1.02), for each ml/min per 1.73 m^2 decrease in eGFR] but not with H-AKI. A history of refractory ascites was associated with both C-AKI [OR 2.43 (95% CI 1.38–4.27)] and H-AKI [OR 4.62 (95% CI 1.76–12.14)]; though controlled ascites was associated with C-AKI only [OR 1.92 (1.02–3.62)]. Similarly, a history of persistent hepatic encephalopathy and previous AKI within 30 days were associated with C-AKI only [OR 1.82 (95% CI 1.08–3.08); and OR 7.45 (95% CI 2.82–19.68), respectively] but not with H-AKI (Supplemental Table 2).

COMPARISONS OF AKI CLINICAL CHARACTERISTICS BETWEEN C-AKI AND H-AKI:

There were significant differences between C-AKI and H-AKI in AKI stage at diagnosis and at peak (Figure 1). The majority of patients in both groups had AKI stage of 1 at the time of diagnosis (C-AKI 59% and H-AKI 90%) and for peak AKI stage (C-AKI 41% and H-AKI 62%). Patients with C-AKI had higher percentage of stage 1B at the time of AKI diagnosis (45% vs. 38% for H-AKI) and for peak stage (30% vs. 24% for H-AKI). Patients with C-AKI were also more likely to have stage 2 and stage 3 AKI at diagnosis and were more likely to have stage 3 AKI at peak.

Non-SBP infection was the most common identifiable precipitant for both groups (C-AKI 13% and H-AKI 36%). However, SBP as a precipitant was more frequent in C-AKI (13%) compared to H-AKI (6%). Similarly, portal hypertensive bleeding was a more common

precipitant in C-AKI (17%) compared to H-AKI (6%). However, excessive diuretic use was more common in H-AKI (14%) compared to C-AKI (7%).

There were significant differences between both groups with regards to AKI phenotype (Supplemental Table 3). The most common AKI phenotype for both groups was hypovolemic (C-AKI 54% and H-AKI 48%). Hepatorenal syndrome was more frequent in C-AKI (14%) compared to H-AKI (4%). Patients with H-AKI had higher progression of AKI compared to C-AKI (58% vs. 28% respectively). However, there were no significant differences between both groups with regards to therapeutic responses to AKI therapy (p=0.083), despite patients with C-AKI having significantly higher use of albumin infusion (81%) compared to H-AKI patients (47%) (p=0.002). There were no significant differences between the two groups in the use of midodrine (28% C-AKI vs. 18% H-AKI, p=0.368) or octreotide (26% C-AKI vs. 6% H-AKI, p=0.064). Moreover, there were no significant differences between the two groups for hospital length of stay [C-AKI median 8 days (4–16) for C-AKI vs. 11 (6–18) for H-AKI; p=0.148]) or hemodialysis use (14% C-AKI vs. 14% H-AKI, p=0.945). Five patients in each group had recurrent AKI during the hospitalization.

COMPARISONS OF OUTCOMES BETWEEN C-AKI AND H-AKI:

On Kaplan Meier analysis, time to death was significantly shorter in patients with C-AKI (log rank p<0.001), with estimated 90-day survival of 54%, 64%, and 83% for C-AKI, H-AKI, and no-AKI, respectively (Figure 2). Comparisons of renal outcomes between C-AKI and H-AKI can be found on Table 2. Patients with C-AKI had numerically lower eGFR and higher creatinine compared to H-AKI patients, 59 ± 31 vs. 72 ± 35 ml/min per 1.73 m^2 and 1.5 ± 1.1 vs. 1.2 ± 0.6 mg/dL, respectively (although these differences were not statistically significant). Patients with C-AKI also had numerically higher *de-novo* CKD/progression of CKD compared to H-AKI (24% C-AKI vs. 15% H-AKI), but this difference was also not statistically significant (p=0.256). There were no significant differences in the number of AKI events between the two groups (p=0.235).

MULTIVARIABLE ANALYSIS FOR OUTCOMES:

Mortality: Both C-AKI and H-AKI were associated with 90-day mortality on univariate Cox regression analysis. Additional factors associated 90-day mortality can be found on Supplementary Table 4. MELD-Na score and ACLF were highly colinear. Thus, two separate Cox multivariable regression models (Model 1 with MELD-Na score and Model 2 with ACLF) were created to examine the association between either AKI and 90-day mortality (Table 3). In both models, C-AKI was independently associated with 90-day mortality [Model 1: HR 1.68 (95% CI 1.07–2.65), p=0.024; and Model 2: 2.47 (95% CI 1.65–3.69), p<0.001] while H-AKI was not. The multivariable Cox regression analysis for each model with peak AKI stages (e.g. 1A, 1B, 2, 3) for both C-AKI and H-AKI can be found in Supplementary Table 5. In both models, peak AKI stage 3 for C-AKI and H-AKI was independently associated with 90-day mortality. Sensitivity analysis showed similar results when patients with recurrent AKI (N=5 C-AKI and N=5 H-AKI) were removed from the analysis.

De-Novo CKD/Progression of CKD: Baseline eGFR, age, and C-AKI were significantly associated with de-novo CKD or progression of CKD on univariate logistic regression analysis (Supplementary Table 6) and were entered into the multivariable analysis. On multivariable logistic regression analysis, C-AKI was not found to be independently associated *de-novo* CKD/progression of CKD. However, when AKI was dichotomized by stage, stage 3 AKI in C-AKI was independently associated with *de-novo* CKD/progression of CKD [OR 4.79, 95%CI 1.11–20.57, p=0.035]. H-AKI alone or when dichotomized by AKI stage was not found to be associated with *de-novo* CKD/progression of CKD on either univariate or multivariable Cox regression analysis.

DISCUSSION

In this prospective study of hospitalized patients with cirrhosis, we found significant similarities and differences in risk factors for patients with C-AKI and H-AKI. Both C-AKI and H-AKI were more common in patients with pre-existing CKD and refractory ascites; only C-AKI was more common in patients with persistent hepatic encephalopathy and previous AKI. Importantly, we found significant differences between the two groups for mortality, where patients with C-AKI are at a significantly higher risk for mortality at 90 days compared to patients with H-AKI. This difference is likely related to prompt in-hospital recognition and treatment of H-AKI compared to C-AKI, which may develop and progress at home before the patient comes to clinical attention. This explanation supports our finding that patients with H-AKI had significantly lower AKI stage both at AKI diagnosis and at peak. In addition, similar to others (1, 6, 19), we found that increased severity of either AKI is independently associated with mortality. Differences in mortality could also be due to differences in underlying liver disease severity, with significantly higher ACLF grades and admission MELD-Na scores in patients with C-AKI. However, C-AKI, and not H-AKI, remained significantly associated with mortality after adjusting for these markers, suggesting that the effect is independent of underlying liver disease severity. Moreover, serum sodium, bilirubin, and INR were all similar between the groups; the differences in the admission MELD-Na scores may simply be a function of the higher admission creatinine in C-AKI. Nevertheless, our findings suggest (1) prompt identification and treatment of AKI impacts outcomes and (2) patients with C-AKI should be followed closely after discharge, and if eligible, evaluated for liver transplantation.

The development of CKD after AKI and its risk factors have been well described in patients without cirrhosis (19). CKD is independently associated with poor outcomes in patients with cirrhosis (1, 20) and therefore identifying risk factors for CKD is important as it may help identify high-risk patients who require closer monitoring. In our study, we found an incidence of *de-novo* CKD of 15% after AKI. We also found that 6% of patients with underlying CKD had progression to higher stages post AKI. The former findings differ from a recent cohort study where the incidence of *de-novo* CKD was found to be 26% after an AKI episode in patients with cirrhosis (7). Our observational study design focusing on inpatients and higher mortality rate may account for this difference.

Another relevant finding to our study was that peak AKI stage 3 in C-AKI was independently associated with *de-novo* CKD/progression of CKD. Severity of AKI is a well-

known factor associated with *de-novo* CKD/progression of CKD in the general population (21–23). In our cohort, the lack of a significant association between AKI stage and *de-novo* CKD development/progression of CKD in those with H-AKI may be due to the relatively small number of patients with stage 3 H-AKI. Patients with C-AKI were also older and had lower baseline eGFR compared to the other patients. Both of these factors have been shown to be consistently associated with CKD development in the general population (21, 24, 25). Additionally, C-AKI on its own is a known risk factor for *de-novo* CKD development/ progression of CKD (26). The underlying mechanisms for this higher risk are unknown but could be attributed to aforementioned factors. Interestingly, diabetes was not associated with *de-novo* CKD/progression of CKD on univariate analysis (19). The reasons for the lack of an association remain unclear, though it may be related the high mortality rate in our cohort and therefore shorter duration of disease.

This study has several limitations. First, we were unable to adjudicate phenotypes of CKD. Knowledge on the phenotype of CKD, in particular hepatorenal-CKD (3), formerly known as hepatorenal type 2, would have both prognostic and therapeutic implications. Similarly, since urine protein or urine micro-albumin were not collected routinely, we were unable to classify earlier stages of CKD (e.g. stage 1–2) or to further classify CKD based on albuminuria (e.g A1-A3). Further prospective study with urine collection and incorporation of biomarkers would be needed to understand the transition from AKI to CKD and its phenotypes. Finally, because of non-consecutive enrollment in our study, it is possible that not all AKI events were captured which could affect the prevalence of AKI and therefore its impact on CKD outcomes.

Despite the limitations in our study, there also several strengths. Our sample size was large which allowed for meaningful comparisons between C-AKI and H-AKI. Knowledge of these comparisons provide a better understanding on the risk factors, disease course, and outcomes of either AKI, which have not been described in detail in a cirrhosis population previously. Furthermore, knowledge of risk factors and disease course for either AKI is important as it may help identify high-risk patients in whom strategies for prevention and post-discharge care can be appropriately implemented. In addition, with our long follow up period after discharge, we were able to capture both *de-novo* CKD and progression of CKD as well as to evaluate for risk factors associated with these outcomes.

In conclusion, pre-existing CKD and refractory ascites are risk factors for C-AKI and H-AKI. C-AKI is independently associated with short-term mortality and patients with C-AKI stage 3 are at a higher risk for *de*-novo CKD or progression of CKD. Therefore, patients with C-AKI should be monitored closely after discharge, and preventive strategies are urgently needed to improve outcomes. Ultimately, further studies are needed to validate our findings and to determine the importance of C-AKI and H-AKI in this population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Grant Support:

This publication was made possible, in part, with support from the Indiana Clinical and Translational Sciences Institute funded, in part by Award Number KL2TR001106 from the National Institutes of Health, National Center for Advancing Translational Sciences, Clinical and Translational Sciences Award. Research reported in this publication was supported, in part, by the National Institute of Diabetes and Digestive and Kidney Diseases of the National Institutes of Health under award number K23DK109202 (ESO). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Listing of Abbreviations:

AKI	acute kidney injury
CKD	chronic kidney disease
C-AKI	community acquired AKI
H-AKI	hospital acquired AKI
HE	hepatic encephalopathy
SBP	spontaneous bacterial peritonitis
eGFR	estimated glomerular filtration rate
MELD	Model for end-stage liver disease
CTP	Child-Turcotte-Pugh
ACLF	acute on chronic liver failure
CLIF-C OF	CLIF Consortium Organ Failure score
KDIGO	Kidney Disease Improving Global Outcomes
ICA	International Club of Ascites
IQR	interquartile range
MDRD	Modification of Diet in Renal Disease
OR	odds ratio
HR	hazard ratio
CI	confidence interval

REFERENCES:

1. 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]
2. Garcia-Tsao G, Parikh CR, Viola A. Acute kidney injury in cirrhosis. Hepatology 2008;48:2064–77. [PubMed: 19003880]
3. Angeli P, Gines P, Wong F, et al. Diagnosis and management of acute kidney injury in patients with cirrhosis: revised consensus recommendations of the International Club of Ascites. Gut 2015;64:531–7. [PubMed: 25631669]

4. Wong F, O'Leary JG, Reddy KR, et al. New consensus definition of acute kidney injury accurately predicts 30-day mortality in patients with cirrhosis and infection. Gastroenterology 2013;145:1280–8 e1. [PubMed: 23999172]
5. O'Leary JG, Levitsky J, Wong F, et al. Protecting the Kidney in Liver Transplant Candidates: Practice-Based Recommendations From the American Society of Transplantation Liver and Intestine Community of Practice. Am J Transplant 2016;16:2516–31. [PubMed: 26990924]
6. Huelin P, Piano S, Sola E, et al. Validation of a Staging System for Acute Kidney Injury in Patients With Cirrhosis and Association With Acute-on-Chronic Liver Failure. Clin Gastroenterol Hepatol 2017;15:438–445 e5. [PubMed: 27720915]
7. Maiwall R, Rao Pasupuleti SS, Bihari C, et al. Incidence, Risk Factors, and Outcomes of Transition of Acute Kidney Injury to Chronic Kidney Disease in Cirrhosis: A Prospective Cohort Study. Hepatology 2019.
8. Wong F, Reddy RK, O'Leary JG, et al. Impact of Chronic Kidney Disease on Outcomes in Cirrhosis. Liver Transpl 2019.
9. Patidar KR, Xu CJ, Shamseddeen H, et al. Development and Validation of a Model to Predict Acute Kidney Injury in Hospitalized Patients With Cirrhosis. Clinical and Translational Gastroenterology 2019;10.
10. Kamath PS, Wiesner RH, Malinchoc M, et al. A model to predict survival in patients with end-stage liver disease. Hepatology 2001;33:464–70. [PubMed: 11172350]
11. Pugh RN, Murray-Lyon IM, Dawson JL, et al. Transection of the oesophagus for bleeding oesophageal varices. Br J Surg 1973;60:646–9. [PubMed: 4541913]
12. Jalan R, Saliba F, Pavesi M, et al. Development and validation of a prognostic score to predict mortality in patients with acute-on-chronic liver failure. J Hepatol 2014;61:1038–47. [PubMed: 24950482]
13. Group KAW. KDIGO clinical practice guideline for acute kidney injury. Kidney Int 2012;Suppl:1–138.
14. Broce JC, Price LL, Liangos O, et al. Hospital-acquired acute kidney injury: an analysis of nadir-to-peak serum creatinine increments stratified by baseline estimated GFR. Clin J Am Soc Nephrol 2011;6:1556–65. [PubMed: 21700828]
15. European Association for the Study of the Liver. Electronic address eee, European Association for the Study of the L. EASL Clinical Practice Guidelines for the management of patients with decompensated cirrhosis. J Hepatol 2018;69:406–460. [PubMed: 29653741]
16. 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]
17. Macias LB, Poblet MS, Perez NN, et al. Assessment of the Renal Function in Potential Donors of Living Kidney Transplants: Expanded Study. Transplant Proc 2015;47:2603–7. [PubMed: 26680048]
18. Asrani SK, Jennings LW, Trotter JF, et al. A Model for Glomerular Filtration Rate Assessment in Liver Disease (GRAIL) in the Presence of Renal Dysfunction. Hepatology 2019;69:1219–1230. [PubMed: 30338870]
19. Inker LA, Astor BC, Fox CH, et al. KDOQI US commentary on the 2012 KDIGO clinical practice guideline for the evaluation and management of CKD. Am J Kidney Dis 2014;63:713–35. [PubMed: 24647050]
20. Wong F, Reddy KR, O'Leary JG, et al. Impact of Chronic Kidney Disease on Outcomes in Cirrhosis. Liver Transpl 2019;25:870–880. [PubMed: 30908855]
21. Lo LJ, Go AS, Chertow GM, et al. Dialysis-requiring acute renal failure increases the risk of progressive chronic kidney disease. Kidney Int 2009;76:893–9. [PubMed: 19641480]
22. Chawla LS, Amdur RL, Amodeo S, et al. The severity of acute kidney injury predicts progression to chronic kidney disease. Kidney Int 2011;79:1361–9. [PubMed: 21430640]
23. He L, Wei Q, Liu J, et al. AKI on CKD: heightened injury, suppressed repair, and the underlying mechanisms. Kidney Int 2017;92:1071–1083. [PubMed: 28890325]
24. Garg AX, Papaioannou A, Ferko N, et al. Estimating the prevalence of renal insufficiency in seniors requiring long-term care. Kidney Int 2004;65:649–53. [PubMed: 14717937]

25. Hallan SI, Dahl K, Oien CM, et al. Screening strategies for chronic kidney disease in the general population: follow-up of cross sectional health survey. BMJ 2006;333:1047. [PubMed: 17062598]

26. Soto K, Campos P, Pinto I, et al. The risk of chronic kidney disease and mortality are increased after community-acquired acute kidney injury. Kidney Int 2016;90:1090–1099. [PubMed: 27658322]

WHAT IS THE CURRENT KNOWLEDGE?

- Patients with cirrhosis with AKI at the time of hospital admission [community-acquired AKI (C-AKI)] have well-described clinical courses and outcomes.
- There are few data describing outcomes of patients who develop AKI during a hospitalization [hospital-acquired AKI (H-AKI)] and how H-AKI differs from C-AKI.
- Understanding the differences and similarities between C-AKI and H-AKI is critical to improving prognostication and to targeting personalized care before, during, and after hospital discharge.

WHAT IS NEW HERE

- Chronic kidney disease (CKD) and refractory ascites are risk factors for both H-AKI and C-AKI.
- C-AKI and is independently associated with mortality and C-AKI patients with stage 3 AKI are at higher risk for *de*-novo CKD or progression of CKD. Therefore, patients with C-AKI may warrant closer monitoring post discharge.

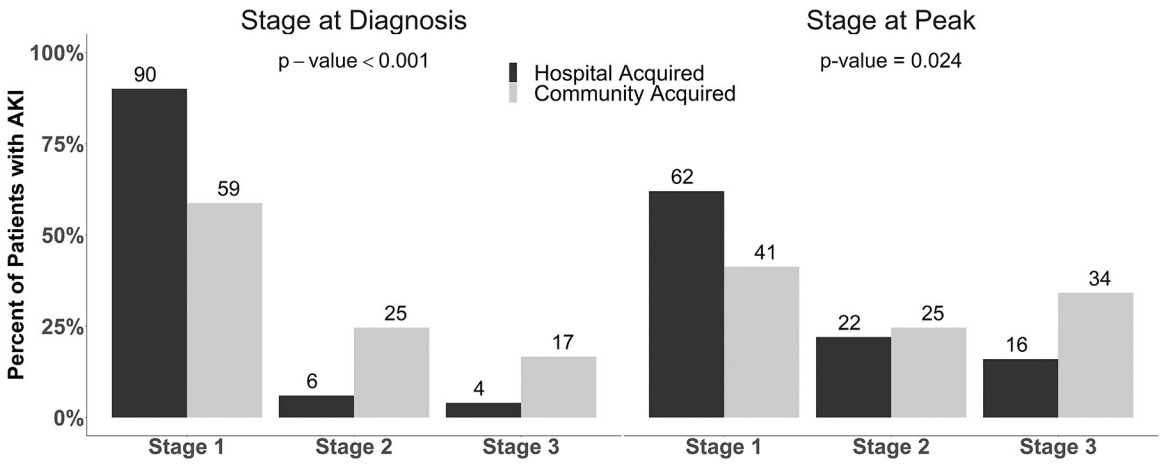

Figure 1: Comparisons Between Community-Acquired AKI and Hospital-acquired AKI for AKI stage at Diagnosis and Peak.

AKI: acute kidney injury

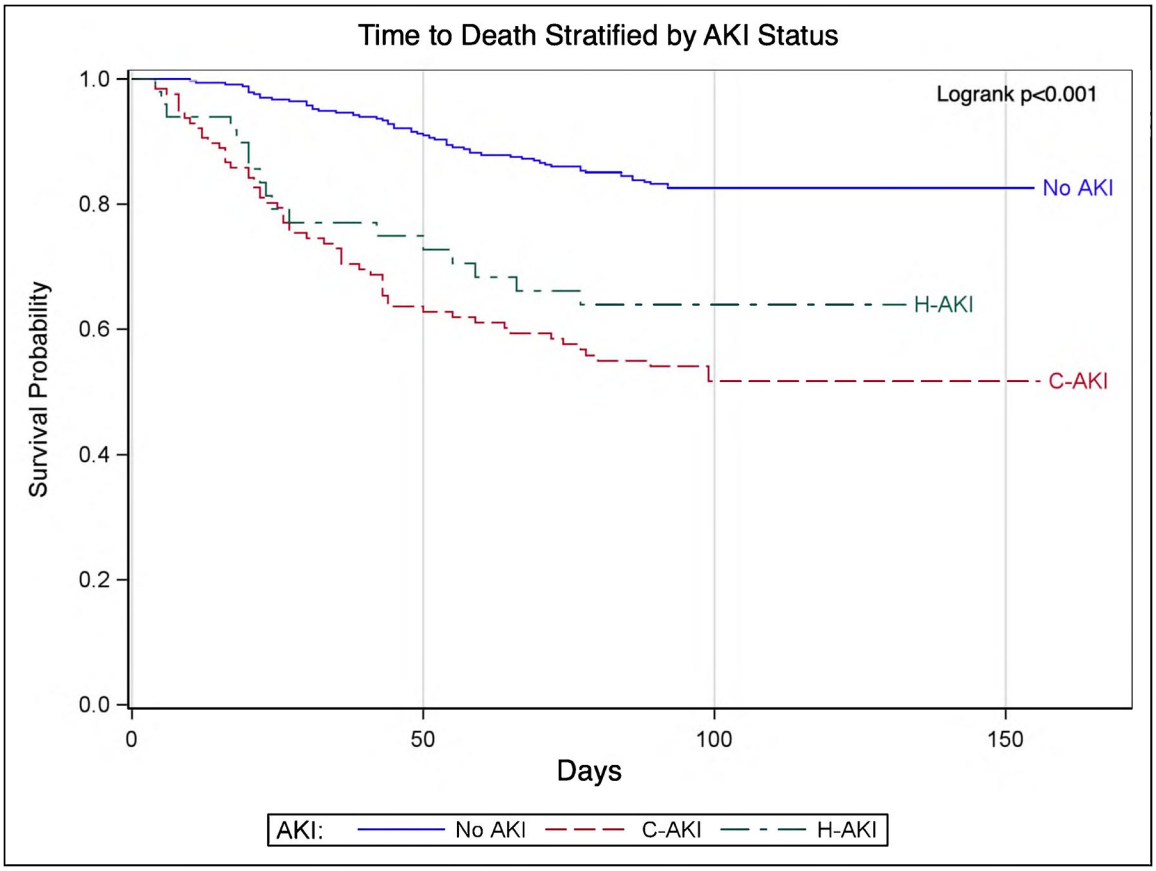

Figure 2: Kaplan Meier Curve for Time to Death Stratified by AKI status.

AKI: acute kidney injury; C-AKI: community-acquired AKI; H-AKI: hospital-acquired AKI.

Table 1:

Comparisons of Patient Characteristics Between Community Acquired AKI and Hospital Acquired AKI

Characteristic	H-AKI N=50	C-AKI N=128	P-value
Age (s.d.)	55 (11)	59 (11)	0.042
Gender, %male	60	57	0.718
Race, %white	98	94	0.448
Baseline Creatinine mg/dL (s.d.)	1.3 (0.7)	1.3 (0.7)	0.673
Baseline eGFR ml/min per 1.73 m^2 (s.d.)	73 (40)	65 (32)	0.164
History of CKD, %			
Stage 3a/3b/4/5	12/16/16/0	17/6/16/1	0.820
History of Diabetes, %	36	38	0.852
History of Hypertension, %	40	48	0.357
Etiology of Cirrhosis, %			
Alcohol	36	26	
Hepatitis C	10	18	0.512
Alcohol and Hepatitis C	8	7	
Non-alcoholic Steatohepatitis	34	33	
Other	12	16	
History of Hepatic Encephalopathy, %			
None/Controlled/Persistent	30/32/38	21/34/45	0.443
History of Esophageal Varices, %			
None/Non-Bleeding/Bleeding	46/32/22	48/24/29	0.563
History of Ascites, %			
None/Controlled/Refractory	10/14/76	15/26/59	0.111
History of Hepatocellular Carcinoma, %	4	21	0.091
History of previous AKI *, %	4	21	0.107
Admission Laboratory (s.d.)			
Sodium, mmol/L	131 (8)	130 (6)	0.709
Creatinine, mg/dL	1.3 (0.6)	2.4 (1.1)	<0.001
INR	2.0 (0.8)	1.9 (0.7)	0.642
Total Bilirubin, mg/dL	6.9 (6.4)	7.4 (9.2)	0.739
Albumin, g/dL	2.6 (0.6)	2.6 (0.6)	0.047
WBC, 10^9	9.7 (7.3)	9.1 (5.1)	0.582
Admission MAP, mmHg (s.d.)	83 (15)	76 (11)	0.001
Admission MELD-Na (s.d.)	26 (7)	29 (6)	0.001
Admission CTP score (s.d.)	11 (2)	11 (2)	0.284
Admission CTP class, %			
A/B/C	2/20/78	0/26/74	0.203
Admission ACLF, %			

Characteristic	H-AKI N=50	C-AKI N=128	P-value
No ACLF/Grade 1/Grade 2/Grade 3	32/0/12/56	13/1/28/58	0.011
Reason for Admission, n (%)			
Overt Hepatic Encephalopathy	11 (22)	40 (31)	
Portal Hypertensive Related Bleeding	2 (4)	10 (8)	0.124
Ascites/Anasarca	14 (28)	32 (25)	
Other	11 (22)	18 (14)	
Liver-Unrelated	12 (24)	28 (21)	
Concurrent Infection on Admission, n (%)	29 (58)	66 (52)	0.439

*30 days prior admission; GFR: estimated glomerular filtration rate; CKD: chronic kidney disease; WBC: white blood cell count; MAP: mean arterial pressure; MELD-Na: Model for Endstage Liver Disease Sodium; CTP: Child-Turcotte-Pugh; ACLF: acute on chronic liver failure

Table 2:

Comparison of Renal Outcomes Between Community Acquired AKI and Hospital Acquired AKI

	H-AKI N=33	C-AKI N=71	P-value
Discharge Creatinine m/dL (s.d.)	1.3 (0.9)	1.5 (1.0)	0.449
Discharge eGFR ml/min per 1.73 m^2 (s.d.)	66 (31)	57 (27)	0.133
Creatinine mg/dL at ≥ 90 days (s.d.) *	1.2 (0.6)	1.5 (1.1)	0.148
eGFR ml/min per 1.73 m^2 at ≥ 90 days (s.d.) *	72 (35)	59 (31)	0.121
Hemodialysis at ≥ 90 days, % *	2 (9)	6 (14)	0.706
CKD Outcomes, %			
De-Novo CKD	5 (15)	11 (16)	0.256
Progression of CKD	0 (0)	6 (9)	
Number of AKI Events Post Discharge, median (IQR) *	1(0–1)	1 (1–2)	0.235

* Recorded at the time of secondary outcome determination.

eGFR: estimated glomerular filtration rate; CKD: chronic kidney disease; IQR: interquartile range

Table 3:

Multivariable Cox Regression Analysis for 90-day Mortality

	HR (95% CI)	P-value
Model 1		
C-AKI (vs. no AKI)	1.68 (1.07–2.65)	0.024
H-AKI (vs. no AKI) *	1.29 (0.72–2.32)	0.399
Baseline eGFR	1.00 (0.99–1.00)	0.142
MELD-Sodium	1.08 (1.05–1.12)	<0.001
Admission Albumin	0.69 (0.50–0.96)	0.028
Admission WBC	1.03 (1.00–1.07)	0.056
Infection	1.17 (0.80–1.71)	0.414
Refractory Ascites	1.14 (0.79–1.65)	0.491
Model 2		
C-AKI (vs. no AKI)	2.47 (1.65–3.69)	<0.001
H-AKI (vs. no AKI) *	1.53 (0.86–2.71)	0.145
ACLF Grade 3	1.73 (1.09–2.76)	0.020
Baseline eGFR	0.99 (0.99–1.00)	0.024
Admission Albumin	0.61 (0.45–0.84)	0.002
Admission WBC	1.06(1.02–1.09)	0.001
Infection	1.30 (0.90–1.88)	0.164
Refractory Ascites	1.09 (0.76–1.58)	0.629

* H-AKI is a time dependent co-variate

Variables included in the analysis: H-AKI, C-AKI, age, MELD-sodium (Model 1), ACLF grades 1–3 (Model 2), admission albumin, admission WBC, infection, and refractory ascites.

MELD-Na: Model for Endstage Liver Disease Sodium; ACLF: acute on chronic liver failure; C-AKI: community acquired acute kidney injury; H-AKI: hospital acquired acute kidney injury; WBC: white blood cell count; eGFR: estimated glomerular filtration rate