Research Article
Cirrhosis and Liver Failure

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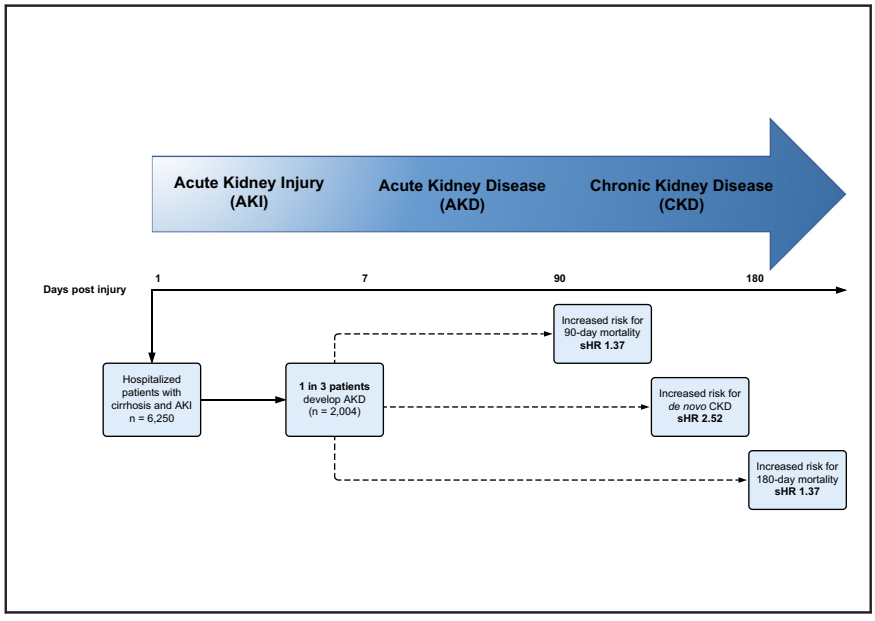
Acute kidney disease is common and associated with poor outcomes in patients with cirrhosis and acute kidney injury

Graphical abstract



Highlights

- AKD develops in 1 in 3 patients with cirrhosis and AKI.
- AKD is independently associated with worse 90- and 180-day survival.
- AKD is independently associated with *de novo* chronic kidney disease.

Authors

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Lay summary

In a nationwide US cohort of hospitalized patients with cirrhosis and acute kidney injury, acute kidney disease developed in 1 in 3 patients and was associated with worse survival and chronic kidney disease. Interventions that target acute kidney disease may improve outcomes of patients with cirrhosis and acute kidney injury.

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Acute kidney disease is common and associated with poor outcomes in patients with cirrhosis and acute kidney injury

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Background & Aims: Acute kidney disease (AKD) is the persistence of acute kidney injury (AKI) for up to 3 months, which is proposed to be the time-window where critical interventions can be initiated to alter downstream outcomes of AKI. In cirrhosis, AKD and its impact on outcomes have been scantly investigated. We aimed to define the incidence and outcomes associated with AKD in a nationwide US cohort of hospitalized patients with cirrhosis and AKI.

Methods: Hospitalized patients with cirrhosis and AKI in the Cerner-Health-Facts database from 1/2009-09/2017 (n = 6,250) were assessed for AKD and were followed-up for 180 days. AKI and AKD were defined based on KDIGO and ADQI AKD and renal recovery consensus criteria, respectively. The primary outcome measure was mortality, and the secondary outcome measure was *de novo* chronic kidney disease (CKD). Competing-risk multivariable models were used to determine the independent association of AKD with primary and secondary outcomes.

Results: AKD developed in 32% of our cohort. On multivariable competing-risk analysis adjusting for significant confounders, patients with AKD had higher risk of mortality at 90 (sub-distribution hazard ratio [sHR] 1.37; 95% CI 1.14-1.66; p = 0.001) and 180 (sHR 1.37; 95% CI 1.14-1.64; p = 0.001) days. The incidence of *de novo* CKD was 37.5%: patients with AKD had higher rates of *de novo* CKD (64.0%) compared to patients without AKD (30.7%; p <0.001). After adjusting for confounders, AKD was independently associated with *de novo* CKD (sHR 2.52; 95% CI 2.01-3.15; p <0.001) on multivariable competing-risk analysis.

Conclusions: AKD develops in 1 in 3 hospitalized patients with cirrhosis and AKI and it is associated with worse survival and *de novo* CKD. Interventions that target AKD may improve outcomes of patients with cirrhosis and AKI.

Lay summary: In a nationwide US cohort of hospitalized patients with cirrhosis and acute kidney injury, acute kidney disease developed in 1 in 3 patients and was associated with worse survival and chronic kidney disease. Interventions that target acute kidney disease may improve outcomes of patients with cirrhosis and acute kidney injury.

Keywords: kidney failure; ascites; acute kidney injury; acute kidney injury recovery; portal hypertension.
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Introduction

Acute kidney injury (AKI) is a frequent complication occurring in hospitalized patients with cirrhosis, where up to 53% have an AKI at the time of admission or develop it during hospitalization.[1–5] In this setting, AKI is associated with high in-hospital mortality[1–7] which is directly linked to the severity of injury.[1,6–8] In patients without cirrhosis, AKI predisposes to the development of chronic kidney disease (CKD),[9–12] supporting the concept that AKI and CKD may not always be mutually exclusive events and likely represent a continuum,[10,13] where sustained AKI may develop into *de novo* CKD. Recently, this association has been described in patients with cirrhosis but limited to few single center studies.[4,14,15]

Acute kidney disease (AKD) is the persistence of AKI for up to 3 months (at which point it is considered CKD) and has been proposed to be the window where interventions can be initiated to prevent poor downstream outcomes of AKI such as death and *de novo* CKD.[13] In patients with cirrhosis, AKD, its risk factors and impact on outcomes have been scantly investigated.[16] Furthermore, in this population, there is a paucity of studies examining the risk for *de novo* CKD in patients who develop AKD.[16] An improved understanding of incidence and risk factors associated with *de novo* CKD in cirrhosis is important given the known impact of CKD on patient outcomes.[14,17,18] Hence, better characterization of AKD and its associated outcomes are critical to improving prognostication and to targeting personalized care during and after hospital discharge. Thus, the aim of this study is to define the incidence, risk factors and outcomes associated with AKD in a nationwide US cohort of hospitalized patients with cirrhosis and AKI.

Patients and methods

Data source

Consecutive patients with cirrhosis who were hospitalized between January 1, 2009, and September 1, 2017, were identified in the Cerner Health Facts Database (Cerner Corporation, Kansas

City, Missouri). Cerner Health Facts is a deidentified, Health Insurance Portability and Accountability Act compliant database that includes over 700 US hospitals and health care systems. Information contributed to the database includes hospital characteristics, vital sign data, laboratory data, pharmaceutical data, and procedural codes (through ICD 9th or 10th revision diagnosis codes and current procedural terminology codes) and the degree of data contributed varies by center/health system. Cirrhosis and its etiology, liver-related complications, comorbidities, infections, history of liver or kidney transplantation, and hemodialysis (HD) status were extracted through ICD-9 and 10 codes (primary or secondary diagnosis). We used previously validated ICD-9 and 10 codes where available,[5,19,20] summarized in Table S1. This study was approved by the Indiana University Institutional Review Board.

Study population

Patients with cirrhosis over the age of 18 with AKI (*see Definitions: AKI, AKD, and CKD)* were included. We excluded patients admitted for surgical reasons, those with inadequate data to discern AKD (*see Definitions: AKI, AKD, and CKD)*, those who died or were discharged to a hospice prior to determining AKD, and those who had undergone a prior liver or kidney transplant. For patients with multiple qualifying AKI-related hospitalizations during the study period, we only considered the initial hospitalization.

Outcomes

Patients were followed-up from the time of AKI to assess outcomes. The primary outcome was mortality at 90 and 180 days from the time of AKD. The former time range was chosen to evaluate the impact of AKD on mortality within the AKD time-window (*i.e.*, ≥7-90 days) and the latter was chosen to evaluate the longer term impact of AKD on mortality. The secondary outcome was the diagnosis of *de novo* CKD based on laboratory results showing diminished estimated glomerular filtration rate (eGFR) persisting for ≥3 months from the time of AKI.[9] Because not all patients had laboratory data at 3 months, we considered the first available eGFR beyond 3 months and up to 6 months to determine the presence of CKD. The median time to this secondary outcome determination was 125 days.

Definitions: AKI, AKD, AND CKD

AKI

AKI was defined by Kidney Disease Improving Global Outcomes (KDIGO),[21] which have been endorsed by the International Club of Ascites (ICA)[22] as either: (1) a rise in serum creatinine (sCr) of ≥0.3 mg/dl from baseline within 48 hours or (2) increase in sCr to 1.5x baseline, which is known or presumed to have occurred within the prior 7 days. AKI stage was defined by the AKI-KDIGO staging system[21] which has also been endorsed by the ICA .[22] Patients with AKI at the time of admission were considered to have community-acquired AKI .[4] Patients without AKI on admission who subsequently developed AKI during the hospitalization were considered to have hospital-acquired AKI .[4,23] AKI recovery was defined by the return of sCr to a value within 0.3 mg/dl of the baseline sCr value within 7 days of AKI onset.[13] Recurrent AKI was determined if a patient met KDIGO AKI criteria after 48 hours of AKI recovery .[13]

Baseline sCr was also defined per the ICA,[22] which was based on the availability of sCr within the previous 3 months. If more than 1 sCr value was available, the closest to admission time was used. In patients who did not have a baseline sCr within the previous 3 months, the last sCr value between month 4 and 1 year before admission was used as the baseline. If a sCr was not available within 1 year of hospitalization, the first sCr value at hospitalization was considered as baseline as recommended by the ICA.[22] The median time between baseline sCr and admission sCr was 33 days.

AKD

AKD was defined by the Acute Disease Quality Initiative (ADQI) AKD and renal recovery consensus statement as AKI stage 1 or greater (as defined by KDIGO) that is present ≥7-90 days after an AKI episode.[13] AKD recovery was defined as return of sCr within 0.3 mg/dl of baseline sCr within 8-90 days of AKI onset.[13] Recurrent AKI was defined by the KDIGO AKI criteria utilizing the baseline sCr that was used for the index AKI hospitalization.

CKD

De novo CKD was defined per KDIGO guidelines, as the persistence of eGFR <60 ml/min per 1.73 m^2 for ≥3 months from the time of the AKI event in patients who did not have baseline CKD.[9] The Chronic Kidney Disease Epidemiology Collaboration equation was chosen to calculate eGFR.[24] Since multiple eGFR values prior to hospitalization were not available for all patients, history of baseline CKD was determined by inpatient ICD-9/10 codes (Table S1). AKD that persisted beyond 90 days was also considered as *de novo* CKD as recommended by the ADQI AKD and renal recovery consensus statement.[13] *De novo* CKD was further classified as G3a (eGFR 45-59), G3b (eGFR 30-44), G4 (eGFR 15-29), and G5 (eGFR <15).[9] Patients with AKD that persisted beyond 90 days but had an eGFR >60 ml/min per 1.73 m^2 were classified as either stage 1 (eGFR >90) or stage 2 (eGFR 60-90).[9]

Hospitalization details

Demographic details (age, sex, race, body mass index), comorbid conditions (via Charlson comorbidity index[25,26] excluding liver disease component), hospital type (rural, urban teaching, urban non-teaching), mean arterial blood pressure (MAP) and laboratory data (white blood cell count, sodium, albumin, sCr, total bilirubin, international normalized ratio) at the time of AKI, as well as baseline sCr and sCr at time of AKD determination, were extracted. Pharmacological data on relevant cirrhosis-related medications (diuretics, non-selective beta blockers, and midodrine) that were administered after AKI were extracted. Cirrhosis etiology (alcohol, hepatitis C, non-alcoholic steatohepatitis [NASH], and other) and data on cirrhosis-related complications (esophageal variceal hemorrhage, ascites, hepatic encephalopathy, spontaneous bacterial peritonitis [SBP]) and non-SBP infections were obtained via inpatient ICD-9 and 10 codes (see Table S1). In addition, intensive care unit (ICU) transfer, vasopressor and mechanical ventilation use, and the initiation of HD was extracted. We considered cirrhosis severity using the model for end-stage liver disease-sodium score (MELD-Na)[27] at the time of AKI.

Statistical analysis

Patient clinical and laboratory characteristics were compared by AKD status (no-AKD and AKD). Continuous variables were presented as median IQR and categorical variables were presented

as percentages. Differences across groups with respect to continuous variables were analyzed using the Wilcoxon rank sum tests and categorical variables were analyzed using chi-square tests.

AKD risk factor analysis
Univariate logistic regression analysis was performed to identify variables associated with AKD. Significant variables (p <0.1) were then entered into a multivariable model to determine the independent association of each risk factor with AKD development. The final list of covariates was also determined by removing variables that caused high collinearity, as accessed by variance inflation factors. Odd ratios (ORs) and their corresponding 95% CIs were reported.

Primary outcome analysis
Mortality with AKD and no-AKD was compared using Fine and Gray competing risks regression, with creation of a cumulative incidence function. Liver transplantation during the follow-up period was considered as a competing risk, and patients lost to follow-up were censored. Differences between cumulative incidence functions were determined using Gray's test. Univariate competing-risk regression analyses were performed to identify factors associated with the primary outcome. Variables that were significant on univariate analysis (p <0.1) for the primary outcome were then entered into a multivariable competing-risk analysis to determine the independent association between AKD and the primary outcome. Variance inflation factors were used to remove variables with high collinearity. Subdistribution hazard ratios (sHRs) and their corresponding 95% CIs were reported.

Secondary outcome analysis
The association between *de novo* CKD and AKD was assessed using Fine and Gray competing risks regression. Death or liver transplantation during the follow-up period were considered as competing risks. Patients who did not have a documented sCr within 90-180 days or had baseline CKD were excluded. Multivariable competing-risk analyses were performed to assess the association between AKD and *de novo* CKD. Final covariates chosen for multivariable modeling where those that were significant on univariate analysis (p <0.1). SHRs and their 95% CIs were reported.

Sensitivity analysis
A sensitivity analysis was performed for the primary outcome excluding patients with hepatorenal syndrome (HRS) and on HD. For the secondary outcome, a sensitivity analysis was performed excluding patients with persistent AKD beyond 90 days but with eGFR >60 ml/min per 1.73 m^2.

A 2-sided nominal p value <0.05 was considered statistically significant. All analytic assumptions were verified, and all analyses were performed using SAS v9.4 (SAS Institute, Cary, NC).

Results

Six thousand two-hundred and fifty patients met inclusion criteria and were analyzed. Characteristics between patients who were excluded and included were similar (Table S2). The median age (IQR) was 61 (53, 70) years and the majority were white (69.5%) and male (61.0%). The most common etiologies of cirrhosis were NASH (39.9%) followed by alcohol (25.2%) and hepatitis C (17.8%). The median baseline sCr was 1.0 (0.70, 1.63) mg/dl and 36.4% had CKD. The median MELD-Na score at the time of AKI was 23 (17, 28) and the incidence of AKD was 31.6% (n = 2,004). At the time of AKD determination, 313 patients were on hemodialysis.

Comparisons of patient and clinical characteristics between AKD and no-AKD

Demographic and clinical characteristics of patients with AKD and no-AKD are compared in Table 1. Patients with AKD were more likely to have CKD at baseline compared to patients without AKD, 55.8% *vs.* 27.2% (p <0.001) and had significantly higher median baseline sCr, 1.19 (0.79, 2.50) *vs.* 0.98 (0.70, 1.43) mg/dl (p <0.001), respectively. Patients with AKD were more likely to have a higher body mass index, NASH, hypertension, ascites, and community-acquired AKI (Table 1). In addition, patients with AKD had significantly higher median sCr at the time of AKI compared to patients without AKD, 2.51 (1.63, 4.50) *vs.* 1.51 (1.13, 2.13) mg/dl (p <0.001), respectively. Accordingly, MELD-Na scores were also significantly higher in patients with AKD (25[21,30] *vs.* 22[16,27] in no-AKD, p <0.001), a higher percentage of whom had stage 3 AKI at the time of diagnosis (22.3% *vs.* 13.2% in the no-AKD group). Patients with AKD also had higher rates of peak AKI stage 3 within 7 days of AKI onset, 60.8% *vs.* 16.5% in the no-AKD group, respectively. Correspondingly, patients with AKD had higher rates of albumin (p <0.001) and midodrine (p <0.001) use within 7 days of AKI onset (Table 1).

There were no significant differences between the 2 groups regarding ICU admission and mechanical ventilation use within 7 days of AKI onset or at any time during the hospitalization. However, patients with AKD had higher rates of vasopressor use within 7 days of AKI onset, 7.3% AKD *vs.* 5.3% no-AKD (p = 0.002) and for any use during the hospitalization, 20.0% AKD *vs.* 15.2% no-AKD (p <0.001). Patients with AKD had a significantly longer hospital length of stay compared to patients without AKD, 11 (6, 17) days *vs.* 9 (5, 14) days (p <0.001), and higher in-hospital mortality at 18.5% *vs.* 11.4% in patients without AKD (p <0.001).

Factors associated with AKD

Univariate analysis for factors associated with AKD are shown in Table S3. On multivariable analysis, independent risk factors for AKD were peak AKI stage 2/3 (OR 9.37; 95% CI 7.02, 12.50; p <0.001), CKD (OR 3.14; 95% CI 2.49, 3.96; p <0.001), ascites (OR 1.60; 95% CI 1.27, 2.00; p <0.001), obesity (OR 1.48; 95% CI 1.20, 1.86; p = 0.001), community-acquired AKI (OR 1.63; 95% CI 1.25, 2.14; p <0.001), serum albumin at time of AKI (OR 1.37; 95% CI 1.07, 1.75; p = 0.013), and MAP at time of AKI (per 1 mmHg decrease, OR 1.01; 95% CI 1.00, 1.03; p <0.001) (Table 2). Etiology of cirrhosis, presence of diabetes or hypertension, and requiring vasopressors within 7 days of AKI onset were not associated with AKD (Table 2).

Comparison of outcomes between AKD and no-AKD

The distribution of patients analyzed for outcomes can be found in Fig. S1.

Primary outcome

Comparisons of the cumulative incidence of mortality between AKD and no-AKD groups can be found in Fig. 1. The cumulative incidence of mortality was significantly higher in patients with AKD compared to those without AKD: 90-day 31.7% (95% CI 0.30, 0.34) *vs.* 20.1% (95% CI 0.19, 0.21); 180-day 36.0% (95% CI 0.34,

Table 1. Comparison of patient and clinical characteristics between patients with and without AKD.

	No-AKD n = 4,246	AKD n = 2,004	*p* value
Age	60 (52, 69)	61 (53, 70)	0.017
Race, n (%)			
White	3,033 (71.4)	1,311 (65.4)	<0.001
Black	557 (13.1)	401 (20.0)	
Other	656 (15.5)	292 (14.6)	
Sex, n (%) male	2,560 (60.3)	1,254 (62.6)	0.181
Type of hospital, n (%)			
Rural	863 (20.3)	481 (24.0)	
Urban, non-teaching	667 (15.7)	328 (16.4)	0.001
Urban, teaching	2,716 (64.0)	1,195 (59.6)	
Etiology of cirrhosis, n (%)			
Hepatitis C	731 (17.2)	382 (16.6)	0.081
Alcohol	1,164 (27.4)	409 (20.4)	<0.001
Non-alcoholic steatohepatitis	1,605 (37.8)	888 (44.3)	<0.001
Other	227 (17.6)	108 (18.7)	0.992
Ascites, n (%)	2,524 (59.4)	1,411 (70.4)	<0.001
Hepatic encephalopathy, n (%)	1,099 (25.9)	544 (27.1)	0.304
Esophageal variceal hemorrhage, n (%)	208 (4.9)	52 (2.9)	<0.001
Charlson comorbidity index (excl. liver)**	2 (1, 4)	3 (2, 6)	<0.001
BMI, kg/m^2	27 (23, 33)	28 (24, 34)	<0.001
Diabetes, n (%)	2,197 (51.7)	1,073 (53.5)	0.192
Hypertension, n (%)	2,471 (58.2)	1,340 (66.9)	<0.001
Chronic kidney disease, n (%)	1,154 (27.2)	1,118 (55.8)	<0.001
Baseline serum creatinine, mg/dl	0.98 (0.70, 1.43)	1.19 (0.79, 2.50)	<0.001
MAP at time of AKI, mmHg	80 (71, 92)	81 (72, 94)	0.008
Laboratory at time of AKI			
WBC, 10^9	9.2 (6.1, 13.4)	8.8 (6.1, 13.3)	0.302
Sodium, mmol/L	134 (127, 139)	134 (128, 138)	0.489
Creatinine, mg/dl	1.51 (1.13, 2.13)	2.51 (1.63, 4.50)	<0.001
Albumin, g/dl	2.8 (2.3, 3.4)	2.6 (2.1, 3.2)	<0.001
Total bilirubin, mg/dl	1.7 (0.8, 4.0)	1.5 (0.7, 3.7)	0.008
INR	1.4 (1.2, 1.7)	1.4 (1.2, 1.8)	0.290
MELD-Na score at time of AKI	22 (16, 27)	25 (21, 30)	<0.001
Stage of AKI at time of diagnosis, n (%)			
1	3,435 (80.9)	1,219 (60.8)	
2	564 (5.8)	339 (16.9)	<0.001
3	247 (13.3)	446 (22.3)	
Community-acquired AKI, n (%)	1,888 (44.5)	1,042 (52.0)	<0.001
SBP, n (%)	162 (3.8)	83 (4.1)	0.581
Non-SBP infection, n (%)	1,227 (28.9)	672 (33.5)	<0.001
Peak AKI stage within 7 days post AKI, n (%)			
1	2,787 (65.6)	373 (18.6)	
2	759 (17.9)	413 (20.6)	<0.001
3	700 (16.5)	1,218 (60.8)	
Midodrine use within 7 days post AKI	263 (6.2)	314 (15.7)	<0.001
NSBB use within 7 days post AKI	628 (14.8)	344 (17.2)	0.017
Diuretic use within 7 days post AKI	1,076 (25.3)	574 (28.6)	0.006
Albumin use within 7 days post AKI	595 (14.0)	488 (24.4)	<0.001
ICU admission within 7 days post AKI, n (%)	915 (21.5)	467 (23.3)	0.127
ICU interventions within 7 days post AKI, n (%)			
Mechanical ventilation	417 (9.8)	205 (10.2)	0.647
Vasopressor use	226 (5.3)	147 (7.3)	0.002
Serum creatinine at time of AKD determination, mg/dl	1.05 (0.80, 1.46)	2.56 (1.60, 4.29)	<0.001

Continuous variables presented as median (interquartile range) and categorical variables were presented as percentages. Differences across groups with respect to continuous variables were analyzed using the Wilcoxon rank sum tests and categorical variables were analyzed using chi-square tests.
AKD, acute kidney disease; AKI, acute kidney injury; ICU, intensive care unit; INR, international normalized ratio; MAP, mean arterial pressure; MELD-Na, model for end-stage liver disease-sodium; NSBB, non-selective beta blocker; SBP, spontaneous bacterial peritonitis; WBC, white blood cell count.
**Score is without liver disease component.

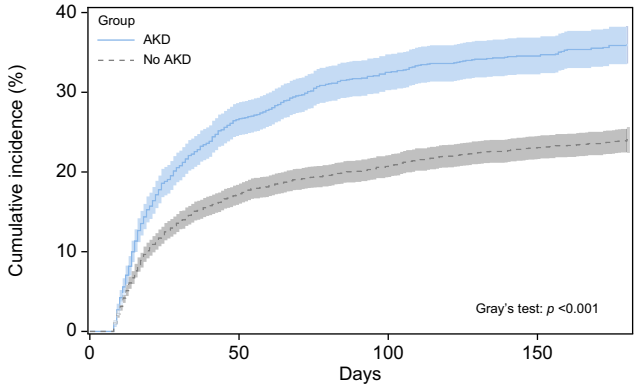
0.38) *vs.* 24.0% (95% CI 0.23, 0.26) (p <0.001). On univariate competing-risk analysis, AKD was associated with an increased risk of death at 90 (sHR 1.66; 95% CI 1.49, 1.86; p <0.001) and 180 (sHR 1.61; 95% CI 1.45, 1.49; p <0.001) days. Additional factors associated with mortality are shown in Table S4. On multivariable competing-risk analysis (Table 3), AKD was independently associated with an increased risk of mortality at 90 (sHR 1.37; 95% CI 1.14, 1.65; p = 0.001) and 180 (sHR 1.37; 95% CI 1.14, 1.64; p = 0.001) days. Sensitivity analysis showed similar results when patients with HRS (n = 340) or on HD (n = 313) were removed from the analysis. Furthermore, to analyze if patients who did not recover from AKD had a worse prognosis than patients who recovered from AKD, a subgroup analysis was performed. After adjusting for significant factors associated with mortality

Table 2. Multivariable analysis for acute kidney disease risk factors.

Risk factor	OR (95% CI)	*p* value
Age	1.00 (0.99, 1.01)	0.632
Race (white *vs.* non-white)	0.71 (0.56, 0.88)	0.002
Sex (male *vs.* female)	1.03 (0.83, 1.27)	0.820
Obesity (BMI >30 kg/m^2)	1.48 (1.20, 1.86)	0.001
Type of hospital (urban *vs.* rural)	1.02 (0.81, 1.29)	0.977
Ascites	1.60 (1.27, 2.00)	<0.001
Variceal hemorrhage	0.76 (0.46, 1.23)	0.261
Hepatitis C	1.02 (0.73, 1.44)	0.896
Alcohol-associated liver disease	0.87 (0.63, 1.20)	0.405
Non-alcoholic steatohepatitis	1.33 (0.99, 1.80)	0.062
Hypertension	1.01 (0.80, 1.28)	0.923
Chronic kidney disease	3.14 (2.49, 3.96)	<0.001
MAP at time of AKI (per 1 mmHg decrease)^	1.01 (1.01, 1.02)	<0.001
MELD-Na at time of AKI (per 1 unit increase)	1.01 (1.00, 1.03)	0.089
Serum albumin at time of AKI (per 1 g/dl decrease)	1.35 (1.18, 1.56)	<0.001
Vasopressor use within 7 days post AKI^	0.91 (0.64, 1.30)	0.602
NSBB use within 7 days post AKI	0.89 (0.68, 1.16)	0.391
Diuretic use within 7 days post AKI	1.03 (0.82, 1.30)	0.775
Midodrine use within 7 days post AKI	1.40 (1.03, 1.90)	0.031
Albumin use within 7 days post AKI	1.37 (1.07, 1.75)	0.013
Any infection	0.89 (0.71, 1.10)	0.602
Community-acquired *vs.* hospital-acquired AKI	1.63 (1.25, 2.14)	<0.001
Stage of AKI at diagnosis (stage 2/3 *vs.* 1)*	0.92 (0.68, 1.23)	0.553
Peak AKI stage within 7 days post AKI (stage 2/3 *vs.* 1)*	9.37 (7.02, 12.50)	<0.001

Significant variables (p <0.1) found on univariate analysis (Table S3) were entered into a multivariable logistic regression model to determine the independent association of each risk factor for AKD development.
AKI, acute kidney injury; MAP, mean arterial pressure; MELD-Na, model for end-stage liver disease-sodium; NSBB, non-selective beta blocker; OR, odds ratio.
^no collinearity was found between the 2 variables.
*no collinearity was found between the 2 variables.

(Table S5), patients with AKD non-recovery had a significantly higher risk of death at 90 (sHR 1.68; 95% CI 1.19, 2.39; p = 0.003) and 180 (sHR 1.64; 95% CI 1.18, 2.28; p = 0.004) days, compared to patients who recovered from AKD.



N° at risk				
AKD	2,004	1,145	925	809
No AKD	4,246	2,554	2,331	2,035

Fig. 1. Comparisons of cumulative incidence of mortality between AKD and no-AKD. Differences between cumulative incidence functions were determined using Gray's test. AKD, acute kidney disease.

Secondary outcome

One thousand one hundred and forty-six patients were alive with available sCr within 90-180 days (n = 911 no-AKD and n = 235 AKD). The incidence of *de novo* CKD was 37.5% (n = 430), with the following distribution of CKD stages: G2 6.0% (n = 26), G3a 37.7% (n = 162), G3b 29.8% (n = 128), G4 18.1% (n = 78), and G5 8.4% (n = 36). Patients with AKD had significantly higher rates of *de novo* CKD at 64.0% (n = 150) compared to patients without AKD at 30.7% (n = 280) (p <0.001). Accordingly, patients with AKD had significantly higher sCr at the time of CKD determination compared to patients without AKD, 1.20 (0.84, 1.7) *vs.* 1.00 (0.74, 1.39) (p <0.001), respectively (Fig. 2). AKD, non-white race, female sex, peak AKI stage 2/3, ascites, and recurrent AKI were associated with *de novo* CKD on univariate competing-risk analysis (Table S6). On multivariable competing-risk analysis, AKD was found to be independently associated with *de novo* CKD (sHR 2.52; 95% CI 2.01, 3.15; p <0.001) (Table 4). A sensitivity analysis excluding patients with persistent AKD and eGFR >60 showed a continued independent association with *de novo* CKD, albeit the sHR was mildly reduced to 2.10 (95% CI 1.65, 2.68; p <0.001).

Discussion

In this large nationwide US cohort of hospitalized patients with cirrhosis and AKI we sought to define the incidence of AKD, its risk factors and impact on mortality and *de novo* CKD. We found AKD to be common, affecting 1 in 3 patients with AKI, and occurring more frequently in patients with CKD, obesity, ascites, higher stages of AKI, community-acquired AKI, and lower serum albumin. Interestingly, we did not find the etiology of cirrhosis (*e.g.* NASH), nor diabetes or hypertension to be independently associated with AKD; these factors were associated with AKD on univariate analysis but not on multivariable analysis. Possibly these results could have been confounded by obesity and CKD in the model. Importantly, patients with AKD (and AKD non-recovery) are at a significantly higher risk of short- and longer term mortality compared to patients without AKD. In addition, AKD remained significantly associated with mortality after adjusting for MELD-Na and AKI stage, suggesting that the effect is independent of underlying liver disease severity and AKI severity. Therefore, our findings suggest that prompt management of AKI, especially in those at risk of AKD, impacts outcomes and patients with AKD should be followed closely after discharge. Examples of the former and latter could be considering early nephrology consultation with follow-up[13,28–30] and frequent lab monitoring/medication adjustments based on kidney function during and after hospitalization,[31,32] as well as evaluation for liver transplantation in eligible patients.

In critically ill ICU patients with cirrhosis and AKI, maintaining higher MAP early after onset of injury has been found to be associated with AKI recovery.[33] Increasing MAP during vasoconstrictive therapy in patients with HRS has also been associated with improvement in kidney function.[34] In line with these studies, we found lower MAP to be significantly associated with AKD/AKI non-recovery. Hence, increasing MAP with sufficient volume replacement or aggressively treating hypotension via early use of vasoconstrictors could prevent AKD. Similarly, we found the rates of non-selective beta blocker and diuretic use within 7 days of AKI onset to be significantly higher in patients with AKD, both of which could reduce MAP. Thus, discontinuing hypotensive medications such as non-selective beta blockers and

Table 3. Multivariable analysis for factors associated with 90- and 180-day mortality.

	90-day		180-day	
	sHR (95% CI)	*p* value	sHR (95% CI)	*p* value
AKD^	1.37 (1.14, 1.66)	0.001	1.37 (1.14, 1.64)	0.001
Age	1.02 (1.02, 1.03)	<0.001	1.02 (1.02, 1.03)	<0.001
Sex (male *vs.* female)	—*	—*	1.08 (0.91, 1.26)	0.382
Ascites	1.43 (1.19, 1.73)	<0.001	1.40 (1.17, 1.67)	<0.001
Variceal hemorrhage	1.14 (0.82, 1.57)	0.415	1.18 (0.87, 1.60)	0.292
Hepatic encephalopathy	1.83 (1.54, 2.17)	<0.001	1.75 (1.49, 2.05)	<0.001
Diabetes	1.23 (1.03, 1.47)	0.020	1.25 (1.06, 1.48)	0.009
Hypertension	0.80 (0.67, 0.96)	0.014	0.83 (0.70, 0.99)	0.039
Chronic kidney disease	0.96 (0.79, 1.17)	0.681	0.94 (0.78, 1.13)	0.497
MAP at time of AKI (per 1 mmHg decrease)	1.00 (0.99, 1.00)	0.122	0.99 (0.99, 1.00)	0.040
MELD-Na at time of AKI (per 1 unit increase)	1.05 (1.04, 1.06)	<0.001	1.05 (1.02, 1.06)	<0.001
Any infection	1.22 (1.03, 1.45)	0.024	1.19 (1.01, 1.41)	0.034
Peak AKI stage (stage 2/3 *vs.* 1)^	1.17 (0.96, 1.43)	0.115	1.17 (0.93 - 1.34)	0.240
ICU transfer during hospitalization	1.09 (0.91, 1.32)	0.350	1.09 (0.91, 1.30)	0.340
Mechanical ventilation during hospitalization	2.07 (1.68, 2.54)	<0.001	1.94 (1.59, 2.35)	<0.001
Vasopressor use during hospitalization	1.24 (1.03, 1.50)	0.024	1.33 (1.11, 1.56)	0.002
Any recurrent AKI during follow-up	1.33 (1.13, 1.57)	0.001	1.43 (1.22, 1.67)	<0.001

Univariate competing-risk regression analyses were performed to identify factors associated with the primary outcome (Table S4). Variables that were significant on univariate analysis (p <0.1) for the primary outcome were then entered into a multivariable competing-risk analysis to determine the independent association between AKD and the primary outcome. Liver transplant was considered the competing risk and patients lost to follow-up were censored from the analysis.
AKI, acute kidney injury; ICU, intensive care unit; MAP, mean arterial pressure; MELD-Na, model for end-stage liver disease-sodium; NSBB, non-selective beta blocker; OR, odds ratio; sHR, subdistribution hazard ratio.
^no collinearity was found between the 2 variables.
*not significant on univariate analysis.

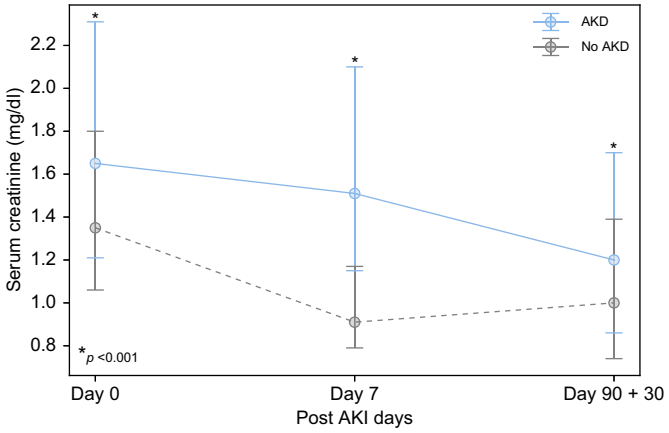


Fig. 2. Time-course of serum creatinine from time of AKI (Day 0), AKD (Day 7), and CKD (Day 90+30) in 1,146 patients who survived at least 3 months with available serum creatinine data. Values are median and interquartile range. Comparisons at each time point were made by Wilcoxon rank sum test. *p <0.001. AKD, acute kidney disease; AKI, acute kidney injury; CKD, chronic kidney disease.

Table 4. Multivariable competing-risk analysis for factors associated with *de novo* chronic kidney disease.

	sHR (95% CI)	*p* value
AKD	2.52 (2.01, 3.15)	<0.001
Sex (male *vs.* female)	0.72 (0.59, 0.87)	0.001
Race (white *vs.* non-white)	0.76 (0.62, 0.93)	0.007
Ascites	1.17 (0.95, 1.45)	0.147
Hepatic encephalopathy	0.62 (0.48, 0.81)	<0.001
Alcohol associated liver disease	0.88 (0.71, 1.10)	0.276
Diabetes	0.87 (0.72, 1.10)	0.157
Any infection	0.78 (0.62, 0.98)	0.031
Peak AKI stage (stage 2/3 *vs.* 1)	0.91 (0.73, 1.12)	0.343
Mechanical ventilation use during hospitalization	0.52 (0.35, 0.77)	0.001
Any recurrent AKI during follow-up	2.28 (1.86, 2.79)	0.001

Univariate competing-risk regression analyses were performed to identify factors associated with the primary outcome (Table S6). Variables that were significant on univariate analysis (p <0.1) for the secondary outcome were then entered into a multivariable competing-risk analysis to determine the independent association between AKD and secondary outcome. Liver transplant/death was considered the competing risk.
AKD, acute kidney disease; AKI, acute kidney injury; sHR, subdistribution hazard ratio.

diuretics after the onset of injury could also reduce the occurrence of AKD. It is important to note, per current guidelines, the withdrawal of vasodilators (*e.g.*, non-selective beta blockers) and diuretics are recommended once AKI is recognized.[22] Hence, our results also provide insights into potential targets for focused quality improvement interventions for AKI management in cirrhosis. Further studies are needed to assess whether these strategies decrease AKD occurrence.

De novo CKD after AKI and its risk factors have been well described in patients without cirrhosis.[9–12] CKD is independently associated with poor outcomes in patients with cirrhosis[14,17,18] and therefore identifying risk factors for *de novo* CKD, particularly after an AKI event, is crucial. AKD is the transitional disease state between AKI and CKD and could be an important modifiable risk factor for *de novo* CKD; it may help identify high-risk patients who require closer monitoring and potential therapeutic interventions.[13] In our study, we found an incidence of *de novo* CKD of 37.5% after AKI, while patients with AKD had significantly higher rates of *de novo* CKD (64%) compared to patients without AKD (30.7%). The former findings differ from prior single center studies where the incidence of *de novo* CKD ranged from 15%-26% after AKI.[4,14,15] The higher rates of *de novo* CKD in our study could be related to the lower observed rates of mortality compared to the aforementioned studies.

Another relevant finding to our study was that AKD was independently associated with *de novo* CKD, where patients with AKD have a 2-fold increased risk. Females also had a higher risk of

CKD. The underlying mechanisms for the latter are unknown but could be attributed to higher rates of mortality observed in men compared to women[35,36] and potentially due to sex-based differences in eGFR calculation .[36,37] Interestingly, the severity of AKI was not associated with *de novo* CKD. Severity of AKI is a well-known factor associated with *de novo* CKD in the general population.[12,38–40] The reasons for the lack of an association are unclear, though it could be related to our use of strict definitions of baseline sCr, exclusion of patients with CKD at baseline, younger patient population, and accounting death as a competing risk.[41–44] It is important to note that our findings are in line with a prior study in cirrhosis that also showed no independent association between severity of AKI and *de novo* CKD.[15]

This study has several limitations. First, due to the nature of the dataset, we lacked additional granular details on several of the variables, such as details required to discern AKI and CKD phenotypes. Although it could be inferred that patients without AKD are likely to have hypovolemic or pre-renal AKI, a study that incorporated point of care echocardiography found 25% of patients with cirrhosis and AKI continued to be volume deplete after resuscitation.[45] Nevertheless, accurate phenotyping of AKI and CKD, particularly HRS and HRS-CKD (formally known as type 2 HRS), would have both prognostic and therapeutic implications (*e.g.*, HRS may not be regarded as AKD since therapy can last up to 14 days[46]). Though, it is important to note that AKD continued to be independently associated with poor outcomes on sensitivity analysis when patients with HRS (via diagnosis code and those on treatment for HRS) were removed. This suggests that regardless of AKI phenotype, patients with cirrhosis and AKD have worse prognosis. Similarly, although we used validated ICD-9/10 codes to capture hospitalized patients with cirrhosis (positive predictive value >90%), the possibility of cirrhosis misclassification may exist. Moreover, since urine protein or urine micro-albumin and kidney imaging were not available, we were unable to classify stages of AKD[13] or to further phenotype CKD.[9] Further multicenter prospective studies with urine collection and incorporation of biomarkers would be needed to understand the transition from AKI to AKD and CKD and its phenotypes.

Despite the limitations in our study, there were also several strengths. Our large sample size derived from a broad sample of urban and rural hospitals across the US provides a representative real-world estimate for AKD based on guideline-based definitions, which have not been described in detail in a US-based hospitalized cirrhotic population previously. Knowledge of these estimates can help guide the design of interventional studies focused on improving AKI/AKD recovery and survival in this population. Furthermore, knowledge of risk factors and disease course for AKD is important as it may help identify high-risk patients in whom strategies for post-discharge care (*e.g.*, early nephrology consultation, medication management via pharmacist involvement, and liver transplantation referral in patients who qualify) can be appropriately implemented. In addition, with the long follow-up period after discharge, we were able to capture both *de novo* CKD as well as to evaluate risk factors associated with this outcome.

In conclusion, pre-existing CKD, severe AKI, ascites, obesity, serum albumin at time of AKI, and MAP at time of AKI are independent risk factors for AKD. AKD and non-recovery from AKD are independently associated with worse short- and longer term mortality and patients with AKD are at a higher risk of *de novo* CKD. Therefore, patients with AKD should be monitored closely after discharge, and preventive/therapeutic strategies are urgently needed to improve outcomes. Ultimately, further prospective studies evaluating the natural history of AKI/AKD to CKD are needed to validate our findings and to determine the importance of AKD in this population.

Abbreviations

ADQI, Acute Disease Quality Initiative; AKI, acute kidney injury; AKD, acute kidney disease; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HD, hemodialysis; HR, hazard ratio; HRS, hepatorenal syndrome; ICA, International Club of Ascites; ICU, intensive care unit; KDIGO, Kidney Disease Improving Global Outcomes; MAP, mean arterial pressure; MELD-Na, model for end-stage liver disease-sodium; NASH, non-alcoholic steatohepatitis; OR, odds ratio; SBP, spontaneous bacterial peritonitis; sCr, serum creatinine; sHR, subdistribution hazard ratios.

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Conflicts of interest

Dr. Naga Chalasani has ongoing paid consulting activities (or had in preceding 12 months) with Abbvie, Madrigal, Foresite, Galectin, Zydus, and Boehringer-Ingelheim, Altimmune. These consulting activities are generally in the areas of non-alcoholic fatty liver disease and drug hepatotoxicity. Dr. Chalasani receives research grant support from Exact Sciences, DSM, and Galectin Therapeutics where his institution receives the funding. He has equity interest in RestUp, a healthcare staffing start-up company Remaining authors have no disclosures to report. None of the aforementioned disclosures are related to the study.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Study Concept and Design: KRP and ESO. Data Analysis: KRP, MA, JES, and ESO. Manuscript Preparation: KRP and ESO. Critical Manuscript Review: All authors.

Data availability statement

The data that support the findings of this study are available from Cerner Health Facts. Restrictions apply to the availability of this data, which was used under license for this study. Data is available from Dr. Ananth Grama and Mr. Mobasshir Naved with the permission of Cerner Health Facts. Data in Health Facts is extracted directly from the electronic medical records from hospitals in which Cerner has a data use agreement. Encounters may include pharmacy, clinical and microbiology laboratory, admission, and billing information from affiliated patient care locations. All admissions, medication orders and dispensing, laboratory orders and specimens are date and time stamped, providing a temporal relationship between treatment patterns and clinical information. Cerner Corporation has established Health Insurance Portability and Accountability Act-compliant operating policies to establish de-identification for Health Facts. No data is reproduced from other sources.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2022.02.009.

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