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Incidence, Risk Factors, and Outcomes of Transition of Acute Kidney Injury to Chronic Kidney Disease in Cirrhosis: A Prospective Cohort Study

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Transition to chronic kidney disease (CKD) after an episode of acute kidney injury (AKI) is known in patients without cirrhosis. We studied the incidence and risk factors for development of CKD in patients with cirrhosis. Competing risk analysis was performed to identify risk factors for CKD development. Of 818 patients with cirrhosis (age, 50.4 ± 11.8 years; 84% males; Model for End-Stage Liver Disease [MELD], 19.9 ± 9.9), 36% had AKI at enrollment, 27% had previous AKI, and 61% developed new episodes of AKI during the follow-up period. CKD developed in 269 (33%) patients. Serum cystatin C (CysC; subdistribution hazard ratio [SHR], 1.58; 1.07-2.33), episodes of previous AKI (SHR, 1.26; 1.02-1.56), and AKI stage at enrollment (no AKI [SHR, 1] vs. stage 1 [SHR, 3.28; 1.30-8.25] vs. stage 2 [SHR, 4.33; 1.76-10.66] vs. stage 3 [SHR, 4.5; 1.59-12.73]) were identified as baseline risk factors for CKD development. On time-varying competing risk analysis, MELD (SHR, 1.01; 1.00-1.03), number of AKI episodes (SHR, 1.25; 1.15-1.37), and CysC (SHR, 1.38; 1.01-1.89) predicted CKD development. Development of CKD was associated with higher risk of death. Reduction in glomerular filtration rate (GFR) not meeting CKD criteria was observed in 66% of patients with cirrhosis, more so in those with previous AKI episodes and a high CysC level and MELD score. Renal histology, available in 55 patients, showed tubulointerstitial injury in 86%, cholemic nephrosis in 29%, and glomerular changes in 38%. *Conclusion:* Almost two-thirds of patients with cirrhosis develop episodes of AKI and reduction in GFR; one-third progress to CKD, resulting in adverse outcomes. Higher MELD and CysC levels and number of AKI episodes predict development of CKD in patients with cirrhosis. (Hepatology 2020;71:1009-1022).

Acute kidney injury (AKI) is observed in approximately 20% of patients with cirrhosis and is an ominous complication.[1] Approximately two-thirds of AKI episodes in patients with cirrhosis are functional or volume responsive and reversible.[1] With an increase in the severity of liver disease, the incidence of AKI increases, with higher risk of developing hepatorenal syndrome (HRS), a severe form of renal dysfunction characterized by decrease in cardiac output and enhanced renal vasoconstriction.[1] Patients with cirrhosis remain prone to develop repeated episodes of AKI or HRS

Abbreviations: AKI, acute kidney injury; ATN, acute tubular necrosis; CI, confidence interval; CKD, chronic kidney disease; CTP, Child-Turcotte-Pugh; CysC, cystatin C; (e)GFR, (estimated) glomerular filtration rate; HRS, hepatorenal syndrome; IgA, immunoglobulin A; IHC, immunohistochemistry; INR, international normalized ratio; MDRD6, Modification of Diet in Renal Disease 6; MELD, Model for End-Stage Liver Disease; NDRD, nondiabetic renal disease; OR, odds ratio; ROC, receiver operating characteristic; sCr, serum creatinine; SHR, subdistribution hazard ratio.

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because the factors that predispose to AKI usually continue to persist until these patients undergo liver transplantation.[2]

Studies in populations without cirrhosis have suggested that AKI is a risk factor for transition to chronic kidney disease (CKD) secondary to nephron loss and hyperfiltration, vascular insufficiency, and maladaptive repair mechanisms, which cause incomplete recovery and transition to CKD.[3,4] Classically, a complex interaction has been known to exist between AKI and CKD: Patients with AKI are predisposed to develop CKD, and the presence of underlying CKD increases the risk of AKI.[4] This is because, with each AKI episode, there is loss of functional nephrons, which compromises the "renal reserve" that classically regulates the autoregulatory response of the kidney to the precipitating insult, resulting in AKI.[5] It has been well documented, in animal models of inflammation or ischemia-related AKI, that the recovery process after AKI is associated with interstitial fibrosis rather than regeneration, predisposing these patients to CKD.[6] The association is determined largely by the status of recovery after the AKI episode,[7]severity of the AKI episode, as well as etiology, that is, presence of acute tubular necrosis (ATN).[7] Apart from these, studies in patients without cirrhosis evaluating the progression of AKI to CKD have also highlighted baseline estimated glomerular filtration rate (eGFR) and serum albumin as significant risk factors for CKD development.[8] In patients with advanced cirrhosis, renal histological changes suggestive of structural kidney damage were observed in more than one-half of patients despite the absence of abnormalities in urinalysis or markers of renal impairment.[9] However, in this study, the exact mechanisms of development of CKD were not evaluated. The influence of the number of previous AKI episodes, etiology of AKI, severity of the episode(s), and/or status of recovery after AKI on CKD development are not known. The role of biomarkers predictive of CKD development has also not been studied. We have recently reported on the utility of cystatin C (CysC) as a marker of renal reserve and risk of future AKI in a large cohort of 531 patients with cirrhosis followed for a year. However, whether CysC can also predict development of CKD needs to be explored.[10,11]

We therefore aimed to prospectively study the incidence and risk factors for development of CKD in patients with cirrhosis. We evaluated the role of CysC as a potential biomarker and AKI as a risk factor for CKD development in these patients.

Patients and Methods

This was a prospective cohort study. Patients visiting the outpatient clinic or admitted as inpatients in the Department of Hepatology from August 2013 to February 2015 at the Institute of Liver and Biliary Sciences were screened and enrolled. The protocol was approved by Institutional ethics committee (IEC/IRB No. 39/10). Written informed consent was obtained from each patient. Consecutive patients with cirrhosis with or without AKI were included and followed. For all these patients, serum CysC was done at the time of enrollment. Patients were excluded for the following reasons: aged <18 or >70 years, preexisting CKD, obstructive uropathy, hepatocellular carcinoma, advanced coexisting cardiopulmonary diseases, pregnancy, absence of available baseline serum creatinine (sCr), extrahepatic

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malignancy, urinary tract infection, and already meeting the criteria for structural AKI. The primary outcome of the study was development of CKD.

All enrolled patients with cirrhosis were followed at least once every 3 months. At each visit (outpatient), a routine urine microscopy and liver and kidney function tests were performed, and AKI episodes were recorded. Calculation of the estimated glomerular filtration rate (eGFR) was performed using the creatinine-based equation by Modification of Diet in Renal Disease 6 (MDRD6). In patients with AKI, the number of AKI episodes was recorded, including the severity and duration of each episode.

KIDNEY BIOPSY

In patients who had an abnormal urine microscopy or renal function tests suggestive of structural kidney damage, a transjugular/ultrasound-guided kidney biopsy was done; these patients gave informed consent and had acceptable coagulation parameters. Postmortem kidney biopsies were collected whenever feasible. The biopsies were done to understand the nature and degree of structural kidney injury, but were not taken as a criterion for the diagnosis of CKD.

CysC

Serum CysC was done at enrollment for all patients with cirrhosis.

STRUCTURAL AKI

Structural AKI was defined with abnormal urinalysis; presence of proteinuria (>500 mg/day) or microhematuria (>50 red blood cells per high-power field); or presence of granular casts with abnormal findings on renal ultrasonography or kidney biopsies (wherever feasible).[12]

CKD

CKD was defined if the patient met the following criteria.[12]

Functional criteria included persistent reduction in eGFR <60 mL/min/1.73 m^2 by MDRD6 for more than 3 months. Structural criteria included persistently abnormal urine microscopy (as defined for structural AKI) for more than 3 months.

For details of methods, including other definitions, please see Supporting Methods.

STATISTICAL ANALYSIS

Descriptive statistics for categorical variables are presented in the form of frequencies and percentages. For continuous variables, descriptive statistics are presented in the form of mean ± SD. In the case of skewed continuous variables, descriptive statistics are presented in the form of median (Q1-Q3), where Q1 and Q3 refer to the first and third quartiles, respectively.

Competing risk survival analysis by the Fine and Gray method, with liver transplant and mortality as competing events for CKD development, was used separately with (1) only baseline variables and (2) baseline variables that are time invariant and time-varying variables that were recorded at least once every 3 months on follow-up to identify risk factors for development of CKD. When data are available only at one time point or when all the explanatory variables are time invariant, it is appropriate to use static variables to explain the outcome. But when information on time-varying explanatory variables is collected during the follow-up period, using such variables as time-varying explanatory variables in the regression model is more robust.[13] Therefore, we also performed the time-varying competing risk analysis to understand the effects of time-varying covariates on CKD development in our study.

For all enrolled patients, details of eGFR, bilirubin, international normalized ratio (INR), sCr, albumin and sodium, leukocyte counts, number of episodes of AKI, and severity and duration of AKI were recorded at least once every 3 months, which were subsequently used in time-varying competing risk analysis. Nonparametric estimates of cumulative incidence of CKD (i.e., the cumulative probability of CKD development) were provided. Gray's test was used to compare equality of cumulative incidence functions across different categories of each considered factor. Cut-off values for different variables for graphical depiction of competing risk analysis were obtained using the receiver operating characteristic (ROC) curves. eGFR was calculated using the MDRD6 equation as $170\times (\text{Serum creatinine})^{-0.999} \times (\text{Age})^{-0.176} \times (0.762$ if patient is female) $\times (1.180$ if black) $\times (\text{Blood Urea Nitrogen})^{-0.170} \times (\text{Albumin})^{0.318}$

Repeated-measure analysis followed by post-hoc comparison by the least significant difference method was performed to assess for change in GFR over time. Log transformation was applied wherever the data were skewed.

Nonparametric survival estimates were obtained using the Kaplan-Meier method, and survival curves were compared using the log-rank test. Cox regression was used to identify factors associated with survival of patients, with CKD as one of the factors. Binary logistic regression analysis was done to identify predictors of GFR reduction. Variables found significant at $P < 0.1$ in univariate analysis were considered for multivariate analysis. Highly correlated variables were not considered for multivariate analysis. All tests were two-tailed, and a P value of <0.05 was considered significant. Competing risk survival analysis was performed using the SAS University Edition. The remainder of the analysis was performed by using SPSS (version 22; IBM Corp., Armonk, NY) and Stata software (version 13; StataCorp LP, College Station, TX).

Results

BASELINE CHARACTERISTICS OF THE STUDY COHORT

Of the 1,109 patients screened, 818 were enrolled into the study (Supporting Fig. S1). Mean age of the cohort was 50.4 ± 11.6 years; 687 (84%) were male, and alcohol was the predominant etiology of liver disease in 402 (49%). Mean Model for End-Stage Liver Disease (MELD) score was 19.9 ± 9.9. Mean sCr and CysC at enrollment were 1.3 ± 1.2 and 1.64 ± 0.9 mg/L, respectively (Table 1). Baseline eGFR of patients was 79.2 (63.4-107.7) mL/min/m^2. Of all patients, 112 (14%) had diabetes and 21 (3%) had hypertension. Previous AKI was noted in 226 (27.6%) patients, and AKI at enrollment was observed in 293 (35.8%) patients (stage 1, 139 [47.6%]; stage 2, 77 [26.2%]; stage 3, 77 [26.2%]). Levels of CysC (mg/L) at enrollment were higher in patients with previous AKI (2.06 ± 0.98 vs. 1.45 ± 0.78; $P < 0.001$) and those with AKI (2.11 ± 1.02 vs. 1.35 ± 0.65; $P < 0.001$).

INCIDENCE AND SPECTRUM OF AKI ON FOLLOW-UP

A total of 501 patients had at least one episode of AKI on follow-up (range, one to six episodes). Of these, 121 (24%) had one episode, 330 (66%) had two, 37 (7.4%) had three, 8 (1.6%) had four, and 5 had more than four episodes of AKI. As a result,

TABLE 1. Baseline Characteristics of the Study Cohort

Variable	Total Cohort (n = 818)
Age (years)	50.4 ± 11.6
Sex (males)	687 (83.9)
Etiology of cirrhosis	
Alcohol	402 (49.1)
Viral	103 (12.6)
Other	313 (38.3)
Diabetes mellitus	112 (13.7)
Hypertension	21 (2.6)
CTP score	9.4 ± 2.3
MELD score	19.9 ± 9.9
Ascites	
Absent	92 (11.2)
Grade 1	142 (17.4)
Grade 2 or 3	584 (71.4)
Hepatic encephalopathy	153 (18.7)
Active alcohol use	101 (12.5)
Sepsis	344 (42.1)
Beta-blocker therapy	252 (30.8)
Norfloxacin	266 (32.5)
Diuretics	736 (90)
eGFR (MDRD6; mL/min/m^2)	79.2 (63.4-107.7)
Serum sodium (mEq/L)	133.4 ± 6.6
Hemoglobin (g/dL)	10.2 ± 2.2
Total leukocyte counts (×10^3 cells/mm^3)	7.4 (5-12)
Total bilirubin (mg/dL)	9.4 ± 11.3
Albumin (g/dL)	2.6 ± 0.7
INR (sec)	1.83 ± 0.94
AKI stage at enrollment	
0	525 (64.2)
1	139 (17)
2	77 (9.4)
3	77 (9.4)
Baseline sCr (mg/dL)	0.85 ± 0.26
CysC (at enrollment; mg/L)	1.64 ± 0.89
sCr at enrollment (mg/dL)	1.3 ± 1.2
Previous AKI (in last 3 months)	226 (27.6)
Episodes of previous AKI	
1	147 (65)
2	77 (34.1)
3	2 (0.9)
AKI cause	
Prerenal (vol. resp.)	145 (49.5)
HRS	56 (19.1)
ATN	92 (31.4)
Duration of AKI (days)	9.6 ± 2.4

Data presented as mean (SD) or median (IQR) and frequency (percentage).
The details of severity, cause, and duration of AKI have been shown for patients with AKI at enrollment.
Abbreviation: vol. resp, volume responsive.

there were a total of 950 episodes of AKIs among study participants, giving an incidence rate of 0.12 (95% confidence interval [CI], 0.11-0.13) episodes per person-month follow-up. Patients with previous AKI and those with AKI at enrollment had a significantly higher incidence rate of AKI on follow-up than patients without previous AKI (0.28 [0.26-0.31] vs. 0.08 [0.07-0.09]; $P < 0.001$) and patients having no AKI at enrollment (0.26 [0.24-0.29] vs. 0.07 [0.06-0.07]; $P < 0.001$), respectively.

Cause of AKI was prerenal in 266 patients (53%), HRS in 82 (16%), and ATN in the remaining 153 (31%). Of 501 patients who developed AKI, 180 (35.9%) had complete, 173 (34.5%) had partial, and 148 (29.5%) had no renal recovery at last assessment. Peak AKI stage reached was stage 1 in 185 patients (36.9%), stage 2 in 107 (21.4%), and stage 3 in 209 (41.7%), with mean peak sCr of 2.1 ± 1.4 mg/dL and peak duration of AKI 10.3 ± 2.1 days.

DEVELOPMENT OF CKD

CKD developed in 269 (32.8%) patients. Among them, median time to development of CKD was 173 days (interquartile range [IQR], 90-294). In these patients, median urine protein (g/day) was 0.69 (0.38-1.51), median spot urinary sodium was 35 mEq (11-70), and 74 patients (28%) had presence of granular casts. In patients diagnosed with CKD, 52 (19.3%) never had an AKI episode. Of the remaining 217 patients, 57 (26.2%) had complete, 87 (40%) had partial, and 73 (33.6%) had no renal recovery after the last AKI episode. This suggests that almost one-third of patients develop CKD despite having complete recovery after the AKI episode. Development of CKD was associated with worse outcomes and was an independent predictor of mortality (1.38; 1.07-1.79; Supporting Table S1; Supporting Fig. S2).

RISK FACTORS PREDICTING CKD DEVELOPMENT

Baseline Risk Factors for CKD Development

UNIVARIATE COMPETING RISK ANALYSIS

On univariate analysis, patient age and sex did not confer a higher risk of CKD development (Table 2). Use of diuretics was associated with higher risk (subdistribution hazard ratio [SHR], 1.52; 95% CI, 0.96-2.40) at 10% level of significance. However, a statistically significant effect was not observed with norfloxacin and beta-blockers. Etiology of liver disease was also not associated with CKD development as was active alcohol use. Severity of liver disease as assessed by high MELD (SHR, 1.40; 1.12-1.73), but not Child-Turcotte-Pugh (CTP), score predicted a higher risk of CKD development. The possible reason could be the inclusion of creatinine, which could reflect AKI effect as a component of MELD, but not CTP, score. Interestingly, ascites grade 2 or 3 were associated with higher risk of CKD. Similarly, lower serum albumin (SHR, 0.82; 0.70-0.96) and higher leukocyte counts (SHR, 1.11; 0.93-1.33) predicted higher risk of CKD. Comorbid diseases, that is, presence of diabetes (SHR, 1.39; 1.03-1.88) and hypertension (SHR, 1.85; 1.06-3.21), were also associated with CKD development in patients with cirrhosis. Serum CysC levels at the time of enrollment (SHR, 2.03; 1.58-2.62) and baseline eGFR values (0.44; 0.32-0.60) predicted development of CKD. Furthermore, previous AKI (SHR, 2.79; 2.21-3.51) and number of episodes of previous AKI (SHR, 1.68; 1.47-1.92) were important risk factors for CKD development. Impact of severity (AKI stage), cause, and duration of AKI was evaluated on CKD development. It was interesting to observe a higher risk of CKD with respect to the cause of AKI, with highest risk for ATN as compared to HRS, prerenal volume-responsive AKI, and no AKI. Similarly, a higher severity of AKI stage at enrollment and prolonged duration were associated with higher risk of CKD development on follow-up.

MULTIVARIATE COMPETING RISK ANALYSIS

Variables significant at 10% level of significance (i.e., $P < 0.1$) in the univariate regression analyses were considered for multivariate analysis avoiding multicollinearity (Table 2). On multivariate competing risk analysis, serum CysC (SHR, 1.58; 1.07-2.33), number of episodes of previous AKI (SHR, 1.26; 1.02-1.56) and severity of AKI, that is, the stage of AKI at enrollment with respect to no AKI, were identified as significant and independent risk factors for CKD development (no AKI [SHR, 1] vs. stage 1 [SHR, 3.28; 1.30-8.25] vs. stage 2 [SHR, 4.33; 1.76-10.66] vs. stage 3 [SHR, 4.5; 1.59-12.73]).

TABLE 2. Baseline Risk Factors for CKD Incidence Using Competing Risk Survival Analysis (n = 818)

Variable	Crude SHR	95% CI	*P* Value	Adjusted SHR	95% CI	*P* Value
Age (years)	1.01	1.00-1.02	0.11			
Sex (males)	0.94	0.68-1.30	0.71			
Etiology of cirrhosis						
Alcohol	1					
Viral	0.87	0.67-1.13	0.30			
Other	1.26	0.92-1.73	0.16			
Diabetes mellitus	1.39	1.03-1.88	0.05	1.08	0.78-1.50	0.63
Hypertension	1.85	1.06-3.21	0.04	1.01	0.55-1.87	0.98
CTP score	1.01	0.96-1.06	0.123			
MELD score	1.40	1.12-1.73	<0.001	0.99	0.97-1.01	0.16
Hepatic encephalopathy	1.01	0.73-1.39	0.56			
Ascites						
Absent	1					
Grade 1	1.38	0.90-2.13	0.14	0.86	0.32-2.35	0.78
Grade 2 or 3	1.67	1.04-2.68	0.033	0.63	0.24-1.70	0.37
Active alcohol use	1.1	0.76-1.61	0.61			
Sepsis	0.41	0.13-1.25	0.115			
Beta-blockers	0.84	0.66-1.07	0.15			
Norfloxacin use	1.01	0.79-1.29	0.96			
Diuretic use	1.52	0.96-2.40	0.08	1.72	0.58-5.08	0.32
eGFR (MDRD6)* (mL/min/m^2)	0.44	0.32-0.60	<0.001	0.80	0.56-1.17	0.25
Serum sodium (mEq/L)	1.00	0.98-1.02	0.71			
Total leukocyte counts* ($\times 10^3/mm^3$)	1.11	0.93-1.33	0.02	1.11	0.90-1.38	0.37
Total bilirubin* (mg/dL)	0.96	0.87-1.07	0.28			
Albumin (g/dL)	0.82	0.70-0.96	0.001			
INR* (sec)	1.05	0.79-1.39	0.08			
Baseline sCr* (mg/dL)	1.82	1.28-2.58	0.001			
sCr at enrollment* (mg/dL)	1.84	1.53-2.21	<0.001			
CysC (at enrollment)* (mg/L)	2.03	1.58-2.62	<0.001	1.58	1.07-2.33	0.02
Previous AKI	2.79	2.21-3.51	<0.001			
Episodes of previous AKI	1.68	1.47-1.92	<0.001	1.26	1.02-1.56	0.03
AKI cause at enrollment						
No AKI	1					
Prerenal (vol. resp.)	1.89	1.20-2.99	<0.001			
HRS	2.14	1.55-2.96	0.005			
ATN	4.67	3.36-6.49	<0.001			
AKI stage at enrollment						
0	1			1		
1	2.28	1.71-3.03	<0.001	3.28	1.30-8.25	0.012
2	2.98	2.14-4.16	<0.001	4.33	1.76-10.66	0.001
3	2.93	2.00-4.27	<0.001	4.50	1.59-12.73	0.005
Duration of AKI (days)	1.08	1.06-1.11	<0.001	0.93	0.85-1.02	0.13

Data presented as crude and adjusted SHR and their 95% CIs.
*Log-transformed variables.
Variables significant at $P < 0.1$ were considered for multivariate analysis.
Though serum creatinine is significant, it is not included in the multivariate model because it is included as a component of MELD. Similarly, albumin was not included because it is a component of eGFR. The cause of AKI and AKI stage at admission were collinear because the sum of dummy variables of AKI cause is equal to the sum of dummy variables of AKI stage; therefore, AKI cause was not included in the multivariate analysis. Previous AKI and the number of episodes of previous AKI were collinear; therefore, only episodes of previous AKI (as a continuous variable) were included in multivariate analysis.
Abbreviation: vol. resp, volume responsive.

TABLE 3. Time-Varying Competing Risk Analysis for Development of CKD (n = 818)

Variable	Crude SHR	95% CI	*P* Value	Adjusted SHR	95% CI	*P* Value
Age (years)	1.01	1.00-1.02	0.11			—
Sex (males)	0.94	0.68-1.30	0.71			—
Etiology of cirrhosis						
Alcohol	1					
Viral	0.87	0.67-1.13	0.30			—
Other	1.26	0.92-1.73	0.16			—
Diabetes mellitus	1.39	1.03-1.88	0.05	1.19	0.85-1.67	0.32
Hypertension	1.85	1.06-3.21	0.04	1.31	0.72-2.38	0.38
CTP score	1.01	0.96-1.06	0.123			
MELD score	1.02	1.01-1.03	<0.001	1.01	1.00-1.03	0.03
Ascites						
Absent	1			1		
Grade 1	1.38	0.90-2.13	0.14	1.25	0.45-3.43	0.67
Grade 2 or 3	1.67	1.04-2.68	0.03	0.71	0.27-1.92	0.51
Active alcohol use	1.1	0.76-1.61	0.61			
Sepsis	0.41	0.13- 1.25	0.12			
Beta-blockers	0.84	0.66-1.07	0.15			
Norfloxacin use	1.01	0.79-1.29	0.96			
Diuretic use	1.52	0.96-2.40	0.08	1.27	0.43-3.73	0.67
CysC* (at enrollment; mg/L)	2.03	1.58-2.62	<0.001	1.38	1.01-1.89	0.04
Serum sodium† (mEq/L)	2.37	0.22-25.51	0.48			
Total leukocyte counts*† ($\times 10^3/mm^3$)	1.32	1.14-1.54	<0.001	1.05	0.85-1.29	0.68
Total bilirubin*† (mg/dL)	1.06	0.96-1.17	0.25			
INR*† (sec)	1.50	1.18-1.90	0.001			
Albumin† (g/dL)	0.81	0.69-0.96	0.017			
sCr*† (mg/dL)	1.76	1.51-2.06	<0.001			
No. of AKI episodes†	1.33	1.24-1.43	<0.001	1.25	1.15-1.37	<0.001
Duration of AKI†	1.01	1.01-1.02	<0.001			
Severity of AKI†						
Stages 0 and 1	1					
Stages 2 and 3	1.98	1.28-3.08	<0.001	1.01	0.63-1.62	0.95

Data presented as crude and adjusted SHR, 95% CIs.
*Log-transformed variables.
†MELD, serum bilirubin, INR, sCr, serum sodium, leukocyte counts, serum albumin, number of episodes of AKI, and duration and severity of AKI have been considered as time-varying covariates in uni- and multivariate analysis.
Number of AKI episodes is the sum of the number of previous AKI episodes, AKI status at enrollment, and the number of AKI episodes during the follow-up. Variables significant at $P < 0.1$ were considered for multivariate analysis.
Though serum creatinine and INR were significant, they were not included in the multivariate model because they are included as a component of MELD. Similarly, albumin was not included because it is a component of eGFR, and eGFR was not included because it was used to define development of CKD. Severity of AKI stage was considered as a binary variable (stages 0 and 1 vs. stages 2 and 3) because there were technical problems in considering variables with more than two categories in the time-varying competing risk analysis. Furthermore, severity of AKI stage and duration were highly related because patients with severe AKI had prolonged duration; therefore, only severity of AKI stage was included in the multivariate analysis.

Time-Varying Competing Risk Analysis for Identification of Risk Factors for CKD Development

UNIVARIATE TIME-VARYING COMPETING RISK ANALYSIS

Factors that can change over time and on which information was collected over the follow-up period were included as time-varying covariates in the competing risk survival analysis in this section (Table 3). Development of new AKI episodes and duration and severity of AKI were considered as time-varying covariates for predicting the risk of CKD development. Similarly, MELD and its individual components (serum bilirubin, creatinine, and INR), serum albumin, sodium, and leukocyte counts were used as time-varying covariates for predicting the risk of

TABLE 4. Predictors of Decline in GFR: Binary Logistic Regression Analysis (n = 549)

Variable	*P* Value	Crude OR	95% CI	*P* Value	Adjusted OR (95% CI) Model 1	*P* Value	Adjusted OR (95% CI) Model 2
Age (years)	0.27	1.01	0.99-1.03				
Sex (males)	0.04	1.6	1.01-2.54	0.11	1.53 (0.91-2.58)	0.17	1.44 (0.86-2.41)
Etiology of cirrhosis							
Alcohol		1			1		
Viral	0.07	1.41	0.97-2.05	0.90	0.97 (0.63-1.50)	0.76	0.94 (0.61-1.44)
Other	0.58	1.19	0.65-2.17	0.84	1.07 (0.56-2.04)	0.94	1.03 (0.54-1.96)
Diabetes mellitus	0.14	1.54	0.89-2.75				
Hypertension	0.15	4.67	0.59-37.1				
CTP score	<0.001	1.14	1.06-1.23				
MELD score	<0.001	1.06	1.04-1.08	0.001	1.05 (1.02-1.07)	0.09	1.02 (0.10-1.05)
Ascites							
Absent		1					
Grade 1	0.67	1.15	0.61-2.18				
Grade 2 or 3	0.13	1.50	0.89-2.51				
Active alcohol use	0.54	1.19	0.69-2.05				
Beta-blockers	0.47	0.87	0.6-1.27				
Sepsis	0.57	2.32	0.5-3.32				
Norfloxacin use	0.75	1.06	0.73-1.56				
Diuretics	0.34	1.30	0.76-2.23				
CysC at enrollment* (mg/L)	<0.001	2.57	1.68-3.93	0.05	1.92 (0.99-3.74)	0.18	1.56 (0.81-2.99)
Serum sodium (mEq/L)	0.92	0.99	0.97-1.07				
Total leukocyte counts* ($\times 10^3/mm^3$)	0.13	1.24	0.94-1.64				
Albumin (g/dL)	0.11	0.82	0.64-1.05				
INR (sec)	0.11	1.18	0.96-1.45				
Baseline sCr (mg/dL)	0.001	2.46	1.47-4.12				
sCr at enrollment (mg/dL)	0.006	1.38	1.10-1.74				
Previous AKI	0.04	1.64	1.01-2.67				
Episodes of previous AKI	0.03	1.42	1.02-1.98	0.56	1.2 (0.65-2.21)		
No. of AKI episodes	<0.001	1.61	1.38-1.88			<0.001	1.35 (1.11-1.64)
AKI stage at enrollment							
0		1			1		
1	0.48	1.21	0.71-2.05	0.46	2.58 (0.21-31.5)		
2	0.08	2.08	0.92-4.67	0.24	4.78 (0.36-63.3)		
3	0.002	6.72	2.03-22.26†	0.12	9.68 (0.97-166.30)†		
Duration of AKI (days)	0.02	1.05	1.01-1.09	0.18	0.85 (0.68-1.07)		

*Log transformed.
Logistic regression results are presented as crude and adjusted ORs and their 95% CIs.
Variables significant at $P < 0.1$ in univariate analysis were considered for multivariate analysis. In model 1, all baseline factors that were significant at univariate analysis were considered in the multivariate analysis except sCr, which even though significant was not included in the multivariate model because it is a component of the MELD score. Similarly, previous AKI, which is collinear to episodes of previous AKI, and CTP score, which is collinear to the MELD score, were not considered in the multivariate analysis.
In model 2, the number of AKI episodes (which is the sum of the number of previous AKI episodes, AKI status at enrollment, and the number AKI episodes during the follow-up) was used in place of the number of previous AKI episodes. Because duration of AKI episodes at enrollment is highly correlated with the number of AKI episodes, duration was not considered in the multivariate analysis.
†Wide CI attributed to small sample size in the corresponding category.

CKD development. eGFR was recorded as a time-varying covariate, but was not considered as a risk factor for CKD because it was used for defining CKD. Data on use and discontinuation of diuretics, beta-blockers, antibiotic use during AKI episodes, and active alcohol use were not recorded on follow-up visits, and therefore these were not analyzed as time-varying factors in the context of CKD development, alongside other baseline

factors that are either time invariant (such as sex, etiology, and comorbid diseases) or on which we do not have subsequent information after baseline (CysC). On univariate competing risk analysis, a higher CKD risk was noted with increase in the number of AKI episodes (SHR, 1.33; 1.24-1.43), increase in MELD (SHR, 1.02; 1.01-1.03), decline in serum albumin (SHR, 0.81; 0.69-0.96), and increase in leukocyte counts (SHR, 1.32; 1.14-1.54). Similarly, a prolonged duration of AKI (SHR, 1.01; 1.01-1.02) and higher severity of AKI stage on follow-up were also predictive of increased risk of CKD development.

MULTIVARIATE TIME-VARYING COMPETING RISK ANALYSIS

On multivariate analysis, increasing MELD (SHR, 1.01; 1-1.03) and number of AKI episodes (SHR, 1.38; 1.01-1.89) and higher CysC at enrollment (SHR, 1.38; 1.01-1.89) were identified as independent risk factors for CKD development after adjusting for the other factors (Fig. 1; Supporting Table S2).

CHANGE IN GFR WITH RESPECT TO AKI AND CKD

A significant reduction of GFR with time was noted for patients who developed either AKI or CKD ($P < 0.001$). Interestingly, a significant reduction in GFR was also noted for patients who did not develop AKI or CKD on follow-up ($P < 0.001$); however, the reduction was significantly higher in patients with AKI as compared to no AKI ($P = 0.001$) and patients who developed CKD as compared to no CKD ($P = 0.001$; (Fig. 2; Supporting Table S3).

Predictors of GFR Reduction in Absence of CKD

There were 364 of 549 (66.3%) patients who had reduction in GFR, but did not meet the criteria for CKD. Of these, 103 (28.3%) had previous AKI. Interestingly, the majority of patients with GFR reduction on follow-up had previous AKI (77 [21.2%]

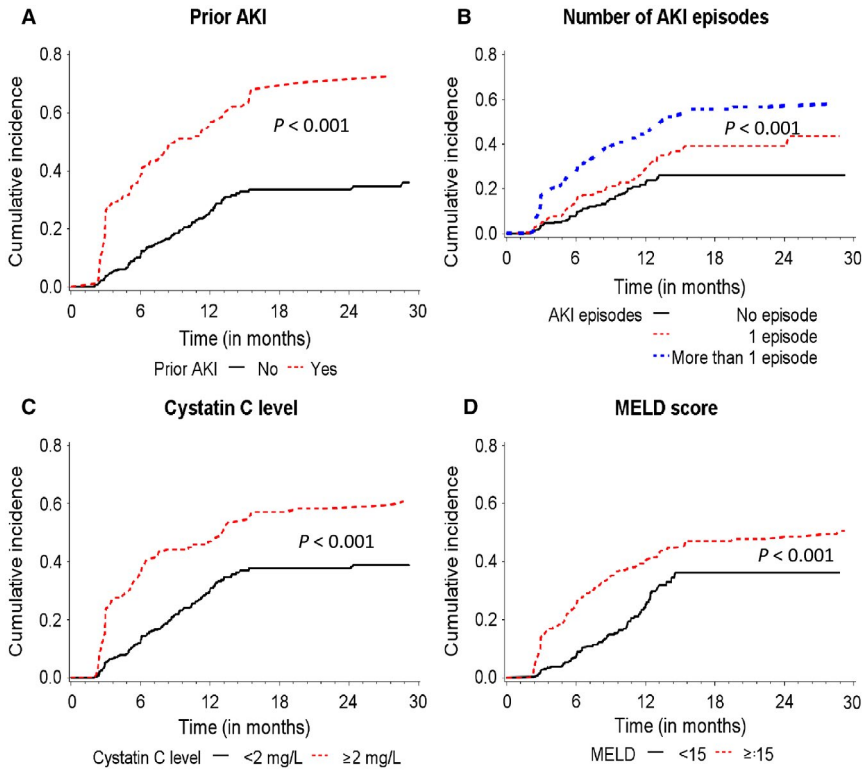

FIG. 1. Nonparametric estimates of incidence of CKD by (A) previous AKI status, (B) number of AKI episodes, (C) cystatin C at enrollment, and (D) MELD score at enrollment. Note: Result of Gray's Test for Equality of Cumulative Incidence Functions across different categories was provided in the form of *P* value. Cut-off point for MELD was derived using ROC curve analysis. Number of AKI episodes is the sum of the number of prior AKI episodes, AKI status enrolment, and the number of AKI episodes during the follow-up period.

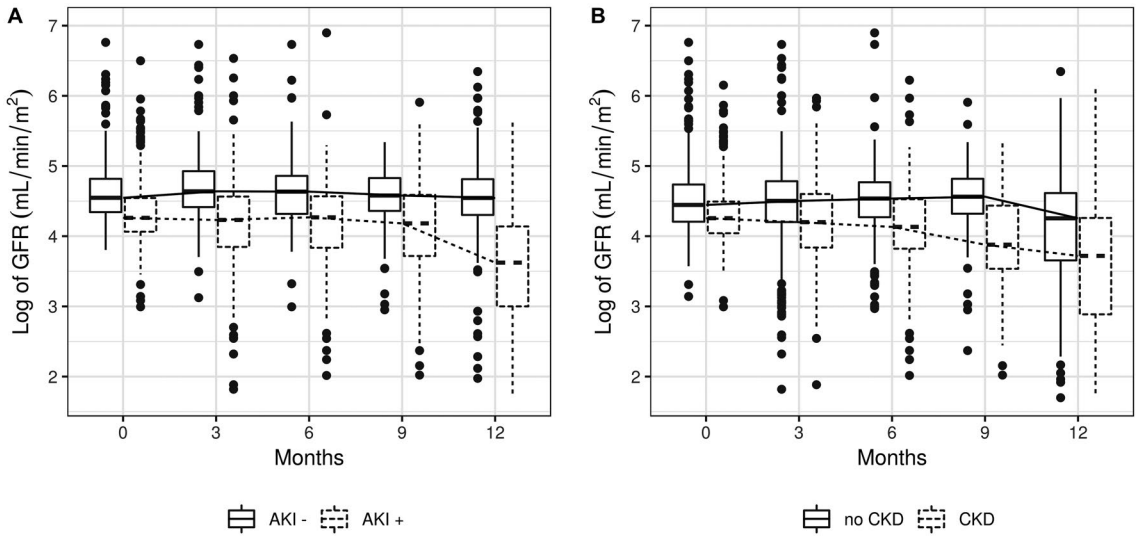

FIG. 2. Box plot depicting changes in estimated GFR with time in two groups. In each graph, the *y*-axis denotes log-transformed eGFR (in mL/min/m^2), and the *x*-axis denotes follow-up time in months. (A) Stratification based on status of AKI, that is, no AKI versus AKI. (B) Stratification based on CKD, that is, no CKD versus CKD.

vs. 26 [14.1%]; $P = 0.045$) and also had a significantly higher CysC (mg/L) at enrollment (1.64 ± 0.92 vs. 1.29 ± 0.52; $P < 0.001$) as compared to patients without GFR reduction, respectively. On follow-up, mean number of AKI episodes was also higher (1.17 ± 1.1 vs. 0.52 ± 0.85; $P < 0.001$) in this group. Of these, 45 (12.4%) had one, 164 (45%) had two, 15 had three, and 1 patient each had four and five episodes of AKI.

On univariate logistic regression analysis, apart from CysC and number of previous AKI episodes, male sex, severity, and duration of AKI at enrollment, and higher liver disease severity scores (MELD and CTP) were significant factors for GFR reduction. On multivariate analysis, CysC (odds ratio [OR], 1.92; 0.99-3.74) and higher MELD (OR, 1.05; 1.02-1.07) were independent predictors of GFR reduction in patients with cirrhosis (model 1). When the cumulative number of AKI episodes was controlled in the model in place of the number of previous AKI episodes, both the above factors lost their significance, whereas the cumulative number of AKI episodes became a significant predictor of GFR decline (OR, 1.35; 1.11-1.64; model 2, Table 4).

SPECTRUM OF RENAL HISTOLOGICAL CHANGES IN PATIENTS WITH CIRRHOSIS

Kidney biopsies were performed in 105 patients; of these, 65 (63%) were postmortem. Of the postmortem biopsies, 50 were suboptimal, leaving 55 adequate renal biopsies. Histological changes were suggestive of structural kidney changes in all biopsied patients. The majority of biopsied patients with cirrhosis had features of acute or chronic tubulointerstitial injury. Of these, a total of 47 (85.5%) cases had acute tubulointerstitial injury (ATN, 17; interstitial inflammation, 10; osmotic nephrosis, 4; ATN and cholemic nephrosis, 16 [29.1%]). Chronic tubulointerstitial nephritis with mild-to-moderate interstitial fibrosis and foci of tubular atrophy was recorded in 11 cases (Fig. 3). Glomerular diseases were noted in 21 (38.2%) cases; immunoglobulin A (IgA) nephropathy in 8; mesangioproliferative disease in 5; membranoproliferative glomerulonephritis in 4; membranous nephropathy in 2; and hypertensive nephrosclerosis in another 2 patients. Vascular pathologies of fibrous intimal hyperplasia, arteriolar hyalinosis, and arteriolosclerosis were recorded in 11 (20%) cases.

Acute renal dysfunction with changes of acute tubulointerstitial nephritis was common in alcohol-related liver disease (24 of 47; 51%). Interestingly, a sizable proportion of patients with cirrhosis with diabetes (11 of 12) had nondiabetic renal disease (NDRD) in the form of tubulointerstitial changes. Patients with tubulointerstitial changes on biopsies more frequently had previous AKI or sepsis-related AKI. Of patients with previous AKI, 17 (94%) had tubulointerstitial changes, whereas only 4 (22%) had

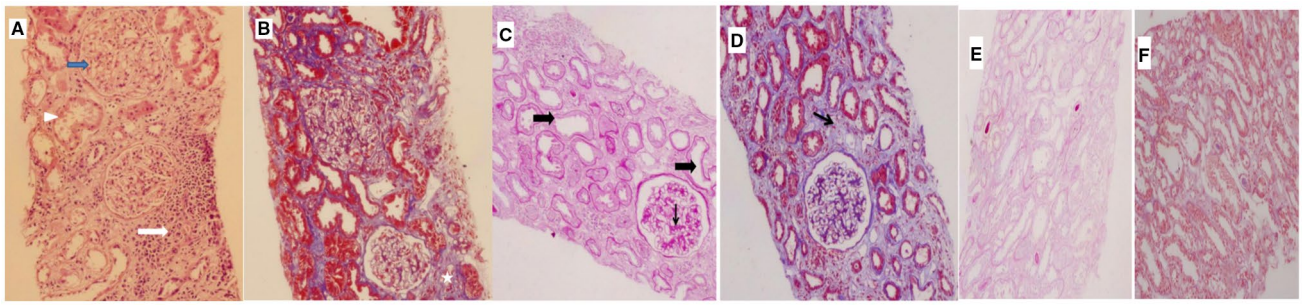

FIG. 3. (A) Blue arrow: normal glomeruli; white triangle: features of acute tubular necrosis; white arrow: interstitial inflammation. (B) White star: minimal interstitial fibrosis. (C) Broad arrow: features of ATN; small arrow: proliferative glomerulonephritis. (D) Arrow: minimal interstitial fibrosis. (E) Acute tubule necrosis. (F) No interstitial inflammation or fibrosis.

glomerular changes. In patients with sepsis-associated AKI (n = 18), majority had ATN (n = 11) and the remaining patients had cholemic nephrosis (n = 7).

MECHANISTIC BASIS OF STRUCTURAL KIDNEY DAMAGE IN PATIENTS WITH CIRRHOSIS

Immunohistochemistry (IHC) of adequate kidney biopsies was performed for cleaved caspase 3 (to identify the apoptotic changes in tubules) and activated complement C3a and C5a (Fig. 4). It was interesting to see that 20 of 47 (42.5%) patients had positive IHC for cleaved caspase 3, signifying the apoptotic changes in the tubules along with histological findings of tubular necrosis. Furthermore, of the 21 patients with glomerular changes, 17 (80.9%) had activated complement cascade C3a and 5a that suggest the proliferative glomerulopathy attributed to activated complement against immune complexes, which are known, for example, IgA in IgA nephropathy and immunoglobulin G and immunoglobulin M in mesangio- and membranoproliferative glomerulopathies. This signifies excessive immune-complex–associated glomerular changes in patients with cirrhosis.

Discussion

This is a large, prospective cohort study evaluating the impact of AKI on transition to CKD in patients with cirrhosis. The results of our study clearly demonstrate that almost one-third of patients with advanced cirrhosis develop CKD. Higher CysC, liver disease severity, and number of AKI episodes predict CKD development. Apart from this, we observed a significant decline in eGFR with time in patients with cirrhosis, more so in those who had developed AKI. The number of AKI episodes, CysC, and a high MELD score were associated with this observed decline. This signifies that there is a gradual reduction in renal reserve in the form of decline in GFR in cirrhosis, which is exacerbated by an episode of AKI. A high MELD score may, in fact, reflect changes in sCr as an effect of AKI to predict the observed decline in GFR. CysC can be considered a useful biomarker of renal reserve because it predicted development of CKD. Histological changes in the form of acute or chronic tubulointerstitial nephritis were the most common findings noted on kidney biopsies in patients with cirrhosis. These changes were more common in patients with alcoholism with previous AKI and sepsis. Presence of apoptotic pathology in renal tubules and immune-complex–mediated glomerular damage were the key findings on IHC staining in kidney biopsies.

Almost two-thirds of patients with cirrhosis do develop AKI, with an incidence of 1.89 episodes per patient. Among all patients who developed AKI, one-fourth had at least one episode during a follow-up of 1 year, whereas the majority developed more than one episode of AKI. Furthermore, consistent with previous reports, nearly one-third (35.9%) achieved complete recovery, a nearly equal proportion had partial recovery, and the remaining patients had no renal recovery.[1] It was observed that the number of AKI episodes was significantly associated with progression to CKD, and this risk increased with the number of AKI episodes.

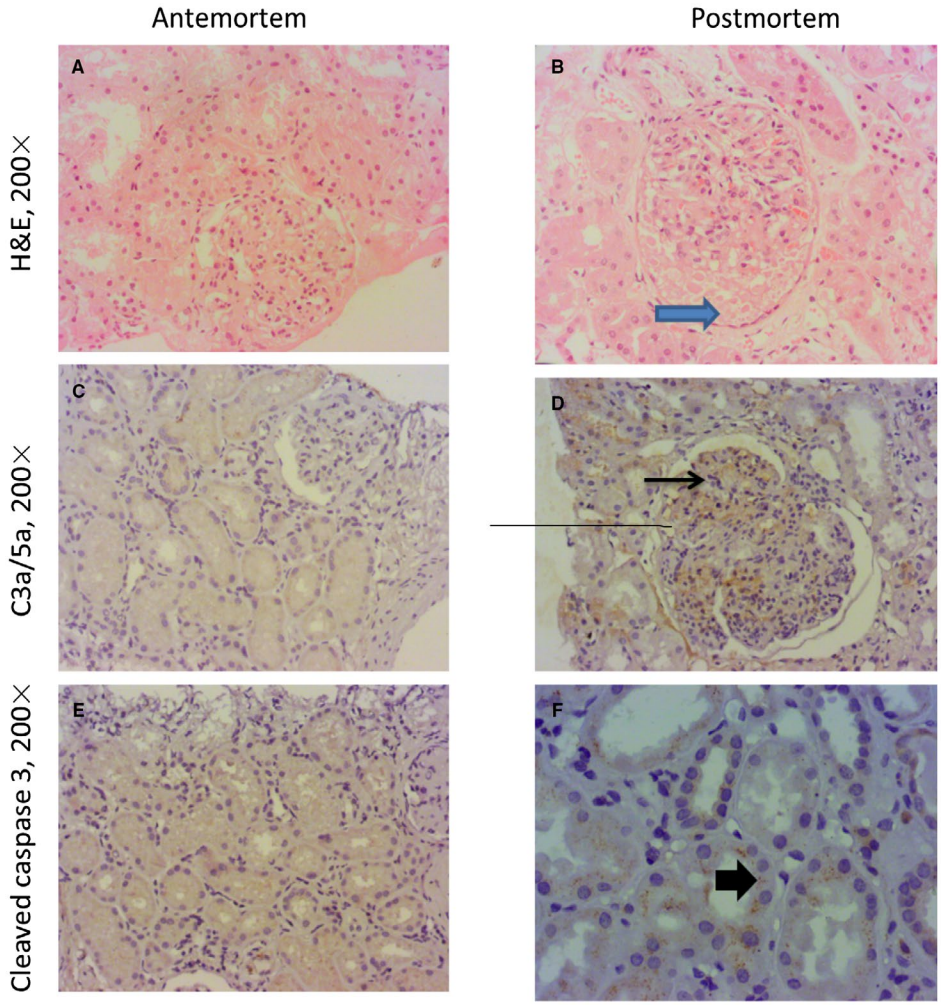

FIG. 4. Kidney biopsy. (A,B) Glomeruli (200×; hematoxylin and eosin [H&E]). (B) Collapsed capillary loops in a glomerulus. (C,D) Differential expression of complements system components in (D) proliferative glomerulonephritis. (E,F) Comparative expression of cleaved caspase in damaged tubular cells (more prominent in [F]); all images 200×.

This can be explained by the fact that, with each AKI episode, there is a loss of functional nephrons, which compromises the renal functional reserve. A concomitant decline in eGFR with time was also noted in patients with AKI as compared to patients with no AKI. Similarly, a strong effect of the number of AKI episodes was noted on decline in GFR in these patients.

Studies in patients without cirrhosis have well documented that, even if patients recover from an AKI episode and have normal sCr and GFR, considerable loss of nephrons and renal functional reserve occurs, predisposing these patients not only to future episodes of AKI, but also increased susceptibility to the precipitant minor insults, causing severe damage to the kidneys.[5-7] Consistent with these findings, we have reported that AKI itself predisposes a patient with cirrhosis to future episodes of AKI.[10] All attempts should therefore be made to prevent repeated episodes of AKI because these are detrimental for the kidneys and may also necessitate a simultaneous liver-kidney transplant if this remains unabated by leading to CKD. It can be argued that eGFR is a derived value and may not be appropriate for understanding the functional variations in the kidney after AKI. However, eGFR still remains the most readily available method for estimating renal functions. In addition to the number of AKI episodes, the other factors that contributed to CKD development included the

time for which the AKI persists and the severity and cause of AKI. As reported for patients without cirrhosis, the risk for CKD development was highest for patients with severe stage 3 AKI and those with ATN.[7] The severity of AKI and AKI cause were collinear. Similarly, duration was closely related to severity because patients with severe AKI also had prolonged duration. Therefore, these factors could not be considered together in the same multivariate model in the time-varying analysis. Interestingly, severity was identified as an independent predictor of CKD development in the baseline model, but not in the time-varying analysis. It is quite possible that patients with multiple episodes of severe AKI would probably have died before development of CKD. Undoubtedly, careful monitoring and aggressive management is required for patients with severe AKI or with ATN to prevent development of CKD.

The role of biomarkers in understanding the natural course and progression of AKI in patients with cirrhosis needs to be understood. We previously reported the role of CysC in predicting AKI as well as mortality in patients with cirrhosis.[10] In the current investigation, we found CysC as an accurate biomarker to predict the risk of progression to CKD and mortality. Levels of CysC also predicted decline in GFR in patients with cirrhosis. Interestingly, in the multivariate model 1 for predicting GFR reduction in patients who did not develop CKD, MELD and CysC were significant after controlling for the number of previous AKI episodes. However, when the cumulative number of AKI episodes (which was the sum of the number of previous AKI episodes, AKI at enrollment, and number AKI episodes during the follow-up) was controlled in the model (model 2) in place of previous AKI episodes, MELD and CysC lost their significance, whereas the cumulative number of AKI episodes had a statistically significant effect on CKD development. This may indicate a robust effect of the number of AKI episodes when compared to MELD and CysC on GFR decline. As a matter of fact, it is also quite possible that the follow-up data of CysC in context of CKD development as well as GFR decline could have further strengthened its utility as a biomarker, which, however, was not performed in the current study.

Comorbid diseases, such as diabetes mellitus and hypertension, were recognis\zed as significant risk factors on univariate, but not multivariate, analysis. Presence of diabetes is the most common cause of CKD. The impact of duration of diabetes and glycemic control was, however, not evaluated as a time-varying covariate in the current study. Leukocyte counts can be considered as a crude marker of systemic inflammation or infection in patients with cirrhosis and were significantly associated with risk of CKD development on univariate analysis; however, further studies with evaluation of C-reactive protein, procalcitonin, and other cytokines are needed to evaluate the impact of systemic inflammation on risk of CKD development. We also propose studying other biomarkers, such as urine neutrophil gelatinase-associated lipocalin and interleukin-1B, in this context.

The data of kidney biopsies showed interesting findings. A sizable proportion of diabetics with cirrhosis in the current study had NDRD in the form of tubulointerstitial nephritis on kidney biopsies. It has been reported that a considerable proportion of diabetics could actually have NDRDs or diabetic nephropathy plus NDRDs.[14] The tubulointerstitial changes in diabetic nephropathy are thought to be related to the renal microvasculature alterations, and it is generally held that they are attributed to chronic ischemia or hypoxia.[14] IHC studies of the kidney biopsies showed apoptotic pathology in the renal tubules. The outcome of renal tubular injury could be apoptosis of epithelial cells with mild injury and necrosis if the insult is severe.[15] AKI is characterized by tubular cell injury and death (necrosis, apoptosis), which trigger endothelial activation and inflammatory cell recruitment.[16] In an animal model, it has been reported that cirrhosis itself induces apoptosis in renal tissue by increase in intracellular reactive oxygen species and DNA damage.[17] Therefore, it is quite possible that repeated minor insults to the kidney in a patient with cirrhosis, along with a chronic state of ongoing inflammation, causes reduction in GFR, leading to development of CKD. These changes could accelerate in patients who have recurrent AKI or AKI that is severe and prolonged.

The strengths of our study are inclusion of the largest cohort of patients with cirrhosis with a reasonable and comprehensive follow-up for natural history of AKI. Our large study has also assessed the utility of serum CysC as a biomarker for prediction of CKD in cirrhosis. We also propose to study the impact of CKD development on CysC on follow-up, which would add weight to its utility as a renal biomarker. However, the

role of CysC needs to be evaluated with a more reliable direct method of GFR measurement. Although renal biopsies were not envisaged in the initial study design, it would have been better to have more biopsies and compared the structural damage with CysC and GFR. However, this limitation cannot be overcome because of the risk of complications and ethical considerations in performing a renal biopsy in patients with advanced cirrhosis attributed to the presence of coagulopathy and ascites. It is also quite possible that there may be patients who would have already developed CKD and may not have manifested on microscopic urinalysis or reduction in GFR because the diagnosis was not biopsy proven in all these patients. Estimation of GFR by the MDRD6 equation for the diagnosis of CKD may also be fraught with limitation, particularly in patients with cirrhosis. However, considering an extremely large cohort of patients that were enrolled in the current study, it was impractical to perform repeated GFR measurement by any of the gold-standard methods.

In summary, this is a large cohort study evaluating the impact of AKI on transition to CKD and the utility of CysC as a measure of renal reserve and biomarker for CKD development in patients with cirrhosis. Our results clearly indicate that AKI predisposes to development of CKD in cirrhosis and necessitates prompt and aggressive management of AKI in these patients. It would go a long way to improve the outcomes of patients with cirrhosis if attempts are made to prevent recurrent AKI episodes during their management.

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REFERENCES

1) Angeli P, Gines P, Wong F, Bernardi M, Boyer TD, Gerbes A, et al. Diagnosis and management of acute kidney injury inpatients with cirrhosis: revised consensus recommendations of the International Club of Ascites. Gut 2015;64:531-537.
2) Maiwall R, Sarin SK, Moreau R. Acute kidney injury in acute on chronic liver failure. Hepatol Int 2016;10:245-257.
3) Finkenstaedt JT, Merrill JP. Renal function after recovery from acute renal failure. N Engl J Med 1956;254:1023-1026.
4) Pannu N. Bidirectional relationships between acute kidney injury and chronic kidney disease. Curr Opin Nephrol Hypertens 2013;22:351-356.
5) Sharma A, Mucino MJ, Ronco C. Renal functional reserve and renal recovery after acute kidney injury. Nephron Clin Pract 2014;127:94-100.
6) D'hoore E, Neirynck N, Schepers E, Vanholder R, Verbeke F, Van Thielen M, et al. Chronic kidney disease progression is mainly associated with non-recovery of acute kidney injury. J Nephrol 2015;28:709-716.
7) Lo LJ, Go AS, Chertow GM, Mc Collough CE, Fan D, Ordonez JD, et al. Dialysis-requiring acute renal failure increases the risk of progressive chronic kidney disease. Kidney Int 2009;76:893-899.
8) Ishani A, Xue JL, Himmelfarb J, Eggers PW, Kimmel PL, Molitoris BA, et al. Acute kidney injury increases risk of ESRD among elderly. J Am Soc Nephrol 2009;20:223-228.
9) Trawalé JM, Paradis V, Rautou PE, Francoz C, Escolano S, Salleé M, et al. The spectrum of renal lesions in patients with cirrhosis: a clinicopathological study. Liver Int 2010;30:725-732.
10) Maiwall R, Kumar A, Bhardwaj A, Kumar G, Bhadoria AS, Sarin SK. Cystatin C predicts acute kidney injury and mortality in cirrhotics: a prospective cohort study. Liver Int 2018;38:654-664.
11) Maiwall R, Kumar S, Chandel SS, Kumar G, Rastogi A, Bihari C, et al. AKI in patients with acute on chronic liver failure is different from acute decompensation of cirrhosis. Hepatol Int 2015;9:627-639.
12) Barry R, James MT. Guidelines for classification of acute kidney diseases and disorders. Nephron 2015;131:221-226.
13) Allison PD. Survival Analysis Using SAS: A Practical Guide. Cary, NC: SAS Institute; 2010.
14) Kritmetapak K, Anutrakulchai S, Pongchaiyakul C, Puapairoj A. Clinical and pathological characteristics of non-diabetic renal disease in type 2 diabetes, patients. Clin Kidney J 2018;11:342-347.
15) Ueda N, Shah SV. Tubular cell damage in acute renal failure: apoptosis, necrosis, or both. Nephrol Dial Transplant 2000;15:318-323.
16) Francoz C, Nadim MK, Durand F. Kidney biomarkers in cirrhosis. J Hepatol 2016;65:809-824.
17) Silveira KC, Viau CM, Colares JR, Saffi J, Marroni NP, Porawski M. Cirrhosis induces apoptosis in renal tissue through intracellular oxidative stress. Arq Gastroenterol 2015;52:65-71.

Supporting Information

Additional Supporting Information may be found at onlinelibrary.wiley.com/doi/10.1002/hep.30859/suppinfo.