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ORIGINAL ARTICLE

Cystatin C and interleukin-6 for prognosticating patients with acute decompensation of cirrhosis

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Key words
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Abstract

Background and Aim: Systemic inflammation and organ dysfunction/failure can complicate acute decompensation (AD) of cirrhosis with progression to acute-on-chronic liver failure (ACLF), leading to increased mortality. There are few studies on serum biomarkers predicting renal dysfunction (RD) or ACLF in AD. Serum cystatin C (CysC) and interleukin-6 (IL-6) were evaluated for predicting RD, ACLF, and mortality in AD patients.

Methods: Consecutive AD patients seen from January 2018 to June 2019 were included. IL-6 and CysC were measured in serum at the time of index presentation. Patients were followed for 90 days or until primary (development of RD) or secondary outcomes (development of ACLF or mortality). Multivariate analysis was performed to find whether CysC and IL-6 can independently predict primary and secondary outcomes.

Results: A total of 124 patients were screened; 88 patients were included. On follow up, 22 (27.3%) developed RD, 11 (11/57, 19.3%) developed ACLF, and 21 (24%) died. The CysC predicted RD (odds ratio [OR] 7.97, 95% confidence interval [CI] 2.70–23.53, $P = 0.001$) and ACLF (OR 5.486, 95% CI 1.456–20.6, $P = 0.012$) development. IL-6 was not an independent predictor of RD ($P = 0.315$), ACLF ($P = 0.168$), and mortality ($P = 0.225$).

Conclusion: Serum CysC can predict the development of RD and ACLF in patients of cirrhosis with AD.

Introduction

Patients with cirrhosis can develop acute decompensation (AD) either due to progressive liver injury or due to superimposed acute hepatic insult. Patients with AD have good short-term prognosis with a 28-day mortality of 1.9%, but in those who develop acute-on-chronic liver failure (ACLF), the 28-day mortality increases to 30%.[1] The most common organ dysfunction/failure in ACLF is renal; traditionally, renal failure has been defined as increase in serum creatinine (Sr. Cr) of ≥50% from baseline to a final value >1.5 mg/dL.[2] Despite recent changes in the definition of acute kidney injury (AKI), the Sr. Cr of 1.5 mg/dL is still important as the short-term mortality in patients whose peak Sr. Cr does not exceed 1.5 mg/dL parallels the mortality of those without AKI, and regression also occurs frequently in them without any intervention.[3]

However, in patients with cirrhosis, Sr. Cr overestimates the glomerular filtration rate (GFR) as its synthesis is reduced due to muscle wasting and decreased protein intake.[4,5] In addition, Sr. Cr is not very sensitive in detecting small changes of the GFR, which is important in the diagnosis of early renal dysfunction (RD).

Cystatin C (CysC) is a 122-amino acid, 13-kDa protein and a member of the family of cysteine proteinase inhibitors, is expressed in the all nucleated cells, and is produced at a constant rate.[6] Serum CysC is promising biomarker to estimate GFR and diagnose AKI early as CysC levels increase before an increase in Sr. Cr.[7] It correlates well with the gold-standard method of GFR estimation, such as diethylenetriamine pentaacetate scan or iohexol-based clearance.[8] In addition, the estimated GFR based on CysC-based formulas is more accurate than Cr-based formulas.[9] Moreover, CysC is less affected than Sr. Cr by factors like muscle wasting, reduced protein diet, and high bilirubin levels.[5,10]

IL-6 is a proinflammatory cytokine and has been used as a biomarker to predict mortality in patients with cirrhosis. A study showed that IL-6 predicted 90-day mortality and was comparable to model of end-stage liver disease (MELD)-Sodium(Na) for predicting mortality in end-stage liver disease (ESLD) patients.[11] IL-6 in a single retrospective study including AD patients predicted the development of ACLF independently; however, it was not a robust marker for predicting ACLF development, and it did not predict mortality in a later study as well.[12]

In the present study, we have evaluated serum CysC and interleukin-6 (IL-6) in patients of cirrhosis presenting with AD in order to predict the RD, ACLF and mortality up to 90 days.

Methods

This was a prospective observational study conducted at the Department of Gastroenterology, Govind Ballabh Pant Institute of Postgraduate Medical Education and Research, New Delhi, India, from January 2018 to July 2019. Ethical approval was obtained from the institutional ethics committee.

Study population. Consecutive cirrhosis patients presenting with new-onset AD were evaluated for enrolment in the study. Patients with stable decompensated liver disease, hepatocellular carcinoma, extrahepatic malignancy, pregnancy, expected survival less than 5 days, comorbidities—chronic kidney disease, congestive heart failure, and HIV—and age >65 years and <18 years were excluded. All patients were offered liver transplant as the treatment option. Those who declined were enrolled in the study after obtaining duly informed consent.

Patients evaluation. All patients underwent baseline investigations including hemogram, coagulation profile, renal function test, liver function test, ultrasound abdomen, upper gastrointestinal endoscopy, ascitic fluid analysis, work up for etiology of acute and chronic liver disease, and cultures for evaluation of suspected infection as required. Standard treatment protocol was followed for all patients as per their clinical requirements. The patients were evaluated on a daily basis during hospitalization until the time of discharge and, after discharge, were followed up at weekly intervals for 1 month and then monthly for 90 days. The patients were followed up during hospitalization and after discharge for the development of RD, ACLF, or death. For the patients who did not present for follow up, survival status was confirmed through phone contact.

Liver cirrhosis was diagnosed based on the combination of conventional clinical, biochemical, endoscopic, and imaging criteria. The new-onset AD of cirrhosis, ACLF, and RD were defined as per the CANONIC study.[1] The AD of cirrhosis was defined as acute development of one or more major complications of liver disease (i.e. recent onset ascites [grade 2/3], hepatic encephalopathy (HE), gastrointestinal hemorrhage, bacterial infections). RD was defined as Sr. Cr ≥1.5 mg/dL, and ACLF was categorized into three grades of severity[1]:

1. ACLF grade 1: Included three subgroups: (i) patients with renal failure; (ii) single failure of the liver, coagulation, circulation, or respiration who had an Sr. Cr ranging from 1.5 to 1.9 mg/dL and/or mild to moderate HE; and (iii) cerebral failure and SR. Cr of 1.5–1.9 mg/dL.
2. ACLF grade 2: Includes patients with two organ failures.
3. ACLF grade 3: Includes patients with three organ failures or more.

Organ failures (OF) were diagnosed as per Chronic Liver Failure Consortium (CLIF-C) OF score: liver failure serum bilirubin of ≥12 mg/dL, kidney failure creatinine of ≥2 mg/dL (or renal replacement therapy), coagulation failure International Normalised Ratio (INR) of ≥2.5, and/or a platelet count of ≤20 × 109/L. Circulatory failure when vasopressors were used to maintain Mean Arterial Pressure (MAP) and respiratory failure when the patient received mechanical ventilation (not due to HE-induced coma) or PaO_2/FiO_2 were ≤200 or an SpO_2 to FiO_2 ratio of ≤200; cerebral failure was measured as West Haven HE grades III and IV.[1]

Serum CysC and IL-6 were measured in the blood sample collected at the time of index presentation. The blood samples after collection were sent immediately to the laboratory for appropriate processing and storage at −80°C. The levels of CysC were measured by immunoturbidimetry assay using a fully automated autoanalyzer (ROCHE c501, Hitachi by Roche diagnostics) with commercially available kits (Roche Diagnostics Pvt. Ltd., Germany), and the levels of IL-6 were measured by Enzyme-Linked Immunosorbent Assay (ELISA) using diaclone IL-6 ELISA kits.

Statistical analysis. Data processing was performed using SPSS software version23. Quantitative variables were expressed as mean and SD or median and interquartile range (IQR) wherever appropriate, while categorical/qualitative variables were expressed as proportions. Quantitative variables were compared by using the student *t* test or the Mann–Whitney *U* test. Categorical variables were expressed as proportions and compared using the chi-square test/Fisher's exact test. Multivariate logistic regression analyses for independent variables with statistically significant results on univariate analyses were carried out to predict RD, ACLF, and mortality. The accuracy of prediction of RD, ACLF, and mortality was measured by estimating the area under the curve of the receiver-operating characteristics (ROC). The ROC analyses were performed to determine the best cut-off value of CysC and IL-6 for predicting the development of RD, ACLF, and 90-day mortality. Tests were considered statistically significant at a two-sided *P* value of <0.05.

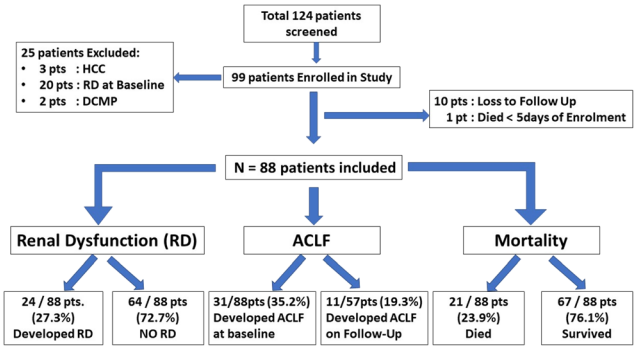

Figure 1 Study population.

Results

Overall, 124 patients of AD were evaluated during study period; 88 AD patients were included in the study, while 36 patients were excluded (Fig. 1).

Baseline characteristics of the study population at enrolment. The mean age of patients was 44 ± 11 years, and 61 (69%) patients were males. The most common etiology

of cirrhosis was alcohol-related liver disease (n = 38, 43%), hepatitis B virus (HCV) (n = 15, 17%), hepatitis C virus (HBV) (n = 12, 13.6%), cryptogenic cirrhosis (n = 8, 9.1%), non-alcoholic steatohepatitis-related cirrhosis (n = 8, 9%), autoimmune hepatitis (n = 3, 3.4%), HBV–HCV coinfection (n = 2, 2.3%), Budd-Chiari syndrome (n = 1, 1%), and primary biliary cholangitis (n = 1, 1%). The clinical presentation was new-onset ascites (n = 72, 82%), jaundice (n = 46, 52%), gastrointestinal bleeding (n = 33, 38%), and HE (n = 16, 18%). The mean MELD score at time of presentation was 20 ± 6.7, with 34 (38.6%) patients in the Child-Turcotte Pugh (CTP-B) category and 47 (53.4%) patients in CTP-C category (Table 1).

The baseline serum CysC and IL-6 for predicting renal dysfunction on follow-up. A total of 88 AD patients had no RD at time of index presentation, of which 24 (27.3%) patients developed RD on follow-up. The median creatinine-based estimated Glomerular Filtration Rate (eGFR) in patients without RD on follow-up was 98 mL/min (IQR, 78–117.2), while the median cystatin-based eGFR was 64.5 mL/min (IQR, 47.7–79) (P = <0.0001). In patients who developed RD on follow-up, median creatinine-based eGFR was 95 mL/min (IQR, 80.7–108), while the median cystatin-based eGFR was 37.5 mL/min (IQR, 29.2–44.7) (P = <0.0001). The median baseline CysC levels in patients who did not develop RD on follow-up was 1.2 mg/L (IQR, 1.02–1.40) and in those who developed RD was 1.8 mg/L (IQR, 1.50–2.14) (P = 0.001) (Table 2). The median baseline serum IL-6 levels in patients who did not develop RD was 5.81 pg/mL (IQR, 7.25–23.82), and in those who developed RD, it was 15.01 pg/mL (IQR, 13.42–86.85) (P = 0.001).On multivariate analysis, CysC predicted RD (odds ratio [OR] 7.97, 95% confidence interval [CI]: 2.70–23.53, P = 0.001); however, IL-6 did not predict RD (OR 1.01 [95% CI: 0.99–1.01], P = 0.315) (Table 3). The Area Under Recevier Operating Characteristic (AUROC) of baseline serum CysC for predicting RD was 0.82 (95% CI, 0.72–0.91) (P = 0.001) (Fig. 2). The serum CysC cut-off level of 1.45 mg/L had a sensitivity of 83% and specificity of 77%, a positive predictive value (PPV) of 60%, and a negative predictive value (NPV) of 92% with diagnostic accuracy of 78.4% for predicting RD.

Table 1 Baseline characteristics at enrolment

Characteristics (n = 88)	Parameters
Hemoglobin (g/dL) (mean, SD)	8.54 ± 2.38
TLC (per mm^3) (median, interquartile range [IQR])	6200 (4577–9882)
Platelet count (per mm^3) (median, IQR)	90 000 (62250–129 750)
Bilirubin (mg/dL) (median, IQR)	3.65 (1.25–12.17)
INR	1.62 ± 0.56
Aspartate aminotransferase (IU/L) (median, IQR)	78 (49–135)
Alanine aminotransferase (IU/L) (median, IQR)	45 (28–92)
Serum creatinine (mg/dL)	0.9 (0.7–1.1)
Serum sodium (mEq/L) (mean, SD)	133 ± 5.81
Child pugh turcotte (CTP)	
CTP B	34 (38.6%)
CTP C	47 (53.4%)
Model of end-stage liver disease score (mean, SD)	20 ± 6.7
Acute-on-chronic liver failure (ACLF) at baseline	31(35.22%)
Grade 1 ACLF	15 (17.04%)
Grade 2 ACLF	13 (14.77%)
Grade 3 ACLF	3 (3.41%)
Spontaneous bacterial peritonitis	11/69 (16%)
Sr CysC (mg/L) (median, IQR)	1.3 (1.1–1.8)
SrIL-6 (pg/mL) (median, IQR)	15.55 (7.92–39.15)

The baseline serum CysC and IL-6 for predicting ACLF on follow-up. A total of 57 patients with no ACLF at index presentation were included for predicting ACLF on follow-up. On follow-up, 11 patients (19.3%) developed ACLF. The grades of ACLF were Grade 1 ACLF (n = 8, 72.7%), Grade 2 ACLF (n = 2, 18.1%), and Grade 3 ACLF (n = 1, 9.1%). The median CLIF-OF score for patients who developed ACLF was 9 (IQR 9–10). The age, gender, etiology of liver disease, MELD score, and CTP score at baseline were not significantly different between patients who did not develop ACLF and those who developed ACLF (Table 2).

The baseline median serum CysC levels were 1.10 mg/L (IQR, 0.97–1.35) in patients without ACLF on follow-up and 1.7 mg/L (IQR, 1.4–1.9) in patients who developed ACLF (P = 0.009) (Table 2). The baseline IL-6 levels were 10.8 pg/mL (IQR, 7.15–17.2) in patients with no ACLF on follow-up and 21.1 pg/mL (IQR, 10.5–56.2) in patients who developed ACLF (P = 0.04). On multivariate analysis, CysC predicted ACLF (OR 5.48, 95% CI, 1.45–20.6) (P = 0.012), while IL-6 did not predict ACLF development (OR 1.035, 95% CI: 1.005–1.006, P = 0.23) (Table 3). The AUROC of baseline CysC levels for predicting ACLF was 0.89 (95% CI, 0.80–0.98) (P = 0.001) (Fig. 3). The serum CysC cut-off level of 1.35 mg/L had a sensitivity of 91%, specificity of 76%, PPV of 53%, and NPV of 97% with diagnostic accuracy of 80% for predicting ACLF.

The baseline serum CysC and IL-6 for predicting mortality on follow-up. A total of 21 (23.8%) patients died during the 90-day follow-up. The patients with alcohol as etiology and those with jaundice at presentation and ACLF were associated with higher mortality. The serum bilirubin, Total Leukocyte Count (TLC), INR, CTP score, and MELD score were significantly higher in patients who died (Table 2). The median CysC levels were 2 mg/L (IQR 1.10–1.60) in patients who survived and 1.9 mg/L (IQR 1.25–2.30) in patients who died on follow-up (P = 0.004) (Table 2). The median IL-6 levels were 12.5 pg/mL (IQR 7.2–21.4) in patients who survived and 56.01 pg/mL (IQR 21.35–79.75) in patients who died on follow-up (P = 0.001).On multivariate analysis, both CysC (OR 2.01, 95% CI 0.55–7.34, P = 0.29) and IL-6 (OR 1.01, 95% CI 0.996–1.02, P = 0.21) did not predict mortality (Table 3).

Discussion

The present study evaluates the role of serum CysC and IL-6 in prognosticating patients presenting with AD of cirrhosis.

Table 2 Baseline characteristics of patients who developed renal dysfunction, acute-on-chronic liver failure (ACLF), and survived or died on follow-up

Characteristics	No renal dysfunction (RD) (n = 64)	RD (n = 24)	P value	No ACLF (n = 46)	ACLF (n = 11)	P value	Survived (n = 67)	Died (n = 21)	P value
Age (years)	43.8 ± 11.5	46.83 ± 10.83	0.30	45.9 ± 11	48 ± 11	0.68	45 ± 10.9	43.24 ± 12.8	0.537
Gender (males, %)	43 (67.18%)	18 (75%)	0.481	28 (60.9%)	9 (81.81%)	0.21	44 (65.67%)	17 (80.95%)	0.18
TLC (per mm^3) (median, interquartile range [IQR])	5650 (4500–9500)	7590 (5200–11 400)	0.110	5050 (4075–9175)	9600 (4600–13 000)	0.067	5600 (4500–9500)	9500 (5700–12 250)	0.008
Creatinine (mg/dL)	0.86 ± 0.26	0.94 ± 0.20	0.287	0.95 (0.8–1.1)	0.90 (0.7–1.1)	0.671	0.882 ± 0.25	0.87 ± 0.29	0.91
Bilirubin mg/dL) (median, IQR)	2.45 (1.1–10.27)	6.3 (1.42–13.65)	0.165	1.7 (0.8–4.2)	2.1 (1.2–9.2)	0.122	2.7 (0.9–7.3)	13.2 (1.91–19.5)	0.004
Albumin (g/dL) (mean, SD)	2.84 ± 0.53	2.68 ± 0.47	0.197	2.8 ± 0.49	2.6 ± 0.57	0.246	2.8 ± 0.48	2.5 ± 0.56	0.013
INR	1.6 ± 0.60	1.65 ± 0.43	0.195	1.37 ± 0.256	1.5 ± 0.38	0.314	1.56 ± 0.54	1.79 ± 0.49	0.044
Sodium (mEq/L)	133 ± 5.86	132 ± 5.59	0.248	134 ± 5	133 ± 5.5	0.427	133 ± 5.3	132 ± 7.1	0.59
Model of end-stage liver disease (MELD)	19.39 ± 6.5	21.83 ± 6.87	0.169	16.2 ± 5	16.85 ± 5.2	0.76	19.1 ± 6.4	23 ± 7.02	0.029
CTP B	26 (40.6%)	7 (29.2%)	0.328	23 (50%)	5 (45.5%)	0.79	27 (40.3%)	6 (28.6%)	0.33
CTP C	32 (50%)	16 (66.7%)	0.16	16 (34.7%)	6 (54.5%)	0.22	33 (49.3%)	15 (71.4%)	0.07
Sr CysC (mg/L) (median, IQR)	1.2 (1.02–1.40)	1.8 (1.5–2.14)	0.001	1.10 (0.97–1.35)	1.7 (1.4–1.9)	0.009	1.2 (1.10–1.60)	1.9 (1.25–2.30)	0.004
Sr IL-6 (pg/mL) (median, IQR)	5.81 (7.25–23.82)	15.01 (13.42–86.85)	0.001	10.8 (7.15–17.2)	21.1 (10.5–56.2)	0.041	12.5 (7.2–21.4)	56.01 (21.35–79.75)	0.001

In the CANONIC study, patients with AD who developed ACLF had a 28-day mortality of 33%. Patients with RD/renal failure had higher mortality (18.6%) than nonrenal OF (10–13.9%).[1] Thus, it becomes important to find predictors of RD/renal failure and ACLF in patients presenting with AD of cirrhosis.

In the present study, 24 (27.3%) patients developed RD, 11 patients (19.3%) developed ACLF on follow-up, and 21 patients (23.8%) died. A similar study by Markwardt *et al.* included 429 (31.9%) of 1343 AD patients of the CANONIC study, evaluated the role of serum CysC and Neutrophil Gelatinase-Associated Lipocalin (NGAL) in AD patients and showed that CysC can predict RD, ACLF, and mortality, while NGAL only predicted mortality.[13] Gender distribution, severity of liver disease (MELD score), and proportion of ACLF patients at presentation were comparable (35.7 *vs* 35.2%) with the above study; however, new onset RD on follow-up was higher (27.3 *vs* 14%).[13] They showed that CysC of 1.5 mg/L predicted development of RD with sensitivity (63.0%) and specificity (73.5%).[13] In the present study, serum CysC cut-off levels of 1.45 mg/L predicted the development of RD with a higher sensitivity of 86% and similar specificity of 77%. As CysC is a ubiquitous protein and is freely filtered by kidneys, its levels remain unaltered by age, gender, or inflammatory conditions. As patients of cirrhosis can have RD despite normal creatinine levels, there is high propensity of progressive

Table 3 Multivariate logistic regression analysis for predicting renal dysfunction (RD), acute-on-chronic liver failure (ACLF), and mortality

Variable	Odds ratio (95% CI)	P value
RD		
Cystatin C	7.97 (2.70–23.53)	0.001
IL-6	1.01 (0.99–1.01)	0.315
ACLF		
Cystatin C	5.486 (1.456–20.6)	0.012
IL-6	1.035 (1.005–1.066)	0.168
Mortality		
Cystatin C	2.01 (0.55–7.34)	0.29
IL-6	1.01 (0.996–1.02)	0.21

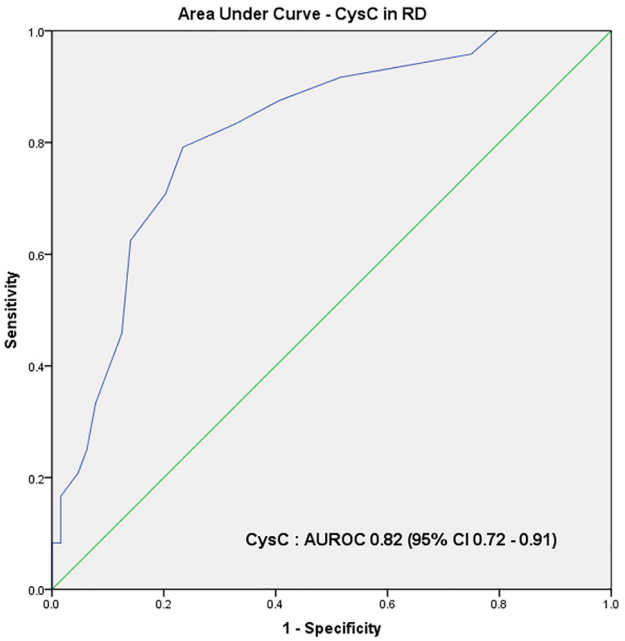

Figure 2 Area under curve—Cystatin C in renal dysfunction.

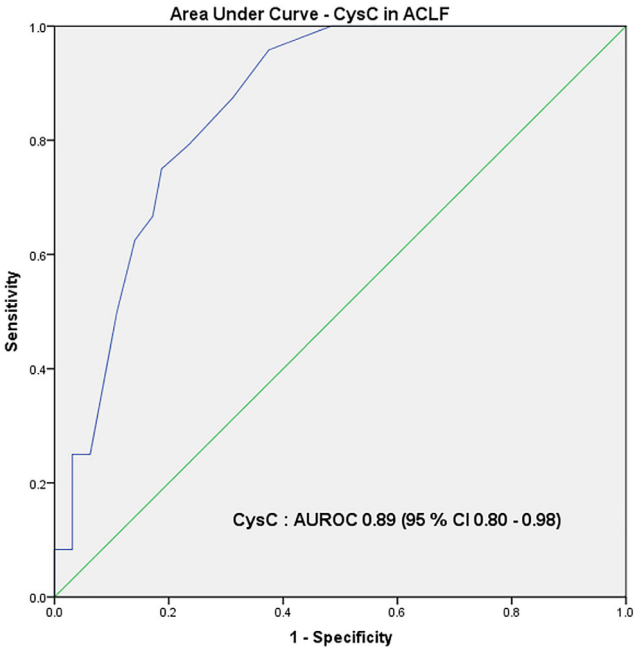

Figure 3 Area under curve—Cystatin C in acute-on-chronic liver failure.

renal compromise with increasing hepatic dysfunction or when there is acute liver injury. Thus, apart from being a marker of AKI, elevated serum CysC levels can predict the development of RD in AD.

New-onset ACLF during follow-up was 19.3% in our study, comparable to 11% (112/1040 patients) in the CANONIC study, but much lower (33%, 69/209 patients) than the previous study.[13] This variation may be due to heterogeneity between study populations and selection of only a subset of patients in the latter study.[13] The baseline CysC cut-off levels of ≥1.35 mg/L predicted ACLF on follow-up with high sensitivity and specificity. The occurrence of ACLF is associated with significant alteration in circulatory hemodynamics, and this compromises the renal functions; thus, CysC might be helpful in predicting ACLF in patients with AD. Recently, Mauro *et al*. showed that CysC levels ≥1.5 mg/L predicted ACLF in decompensated cirrhotic patients awaiting liver transplant.[14]

The levels of IL-6 at baseline in the present study were significantly higher in patients who developed ACLF and RD on follow-up than those without; however, IL-6 did not predict the development of ACLF and RD. Trebicka *et al*. showed serum IL-6 to be useful in predicting ACLF among AD patients; however, they also included patients with nonrenal OF and isolated renal or cerebral dysfunction in AD patients.[12] In fact, in the same study, AD patients with non-OF and renal or cerebral dysfunction had very low-grade systemic inflammation. Similarly, Clara *et al*. found a direct relationship between grades of ACLF and intensity of systemic inflammation indicated by levels of cytokine (i.e. IL-6, IL-8) elevation.[15] Thus, one possible reason why IL-6 failed to predict ACLF in the present study might be because AD patients at time of presentation might have had very low-grade systemic inflammation. This assumption is further strengthened by Sole *et al*. as they found that levels of IL-6 were not significantly different in patients of AD with or without ACLF.[16]

Markwardt *et al*. have shown that both CysC and NGAL predicted 90-day mortality among AD patients with reasonably good accuracy.[13] Serum CysC and IL-6 in the present study were significantly higher in those who died; however, neither predicted the mortality among AD patients. Such variable results might be due to the smaller study sample size and the majority of patients with developed Grade I ACLF having lower risk of mortality. The role of IL-6 in predicting mortality among AD patients has shown disparate results. Trebicka *et al*. found that IL-6 did not predict 28-day mortality.[12] However, Fischer *et al*. found that IL-6 was an independent predictor of 90-day mortality in AD patients.[17] The reasons for variability of IL-6 in predicting mortality are not clear, and one postulated reason is that patients presenting with first episode of AD probably have lesser immune activation and immune dysregulation, causing lesser elevation in IL-6 levels. Previously, Jin *et al*. showed that chronic IL-6 elevation sensitizes the liver cells to injury and death, contributing to the increased likelihood of liver failure and mortality, emphasizing that persistent elevations of IL-6 with ongoing systemic inflammation are associated with poor outcome.[18]

The strengths of our study are that it was a prospective study in a real-life scenario and evaluated both CysC (marker of RD) and IL-6 (marker of inflammation) together for prognosticating AD patients. This study highlights the role of biomarkers in predicting vital events like RD in the natural history of cirrhosis and paves the way for the development of targeted renoprotective interventions to help prevent such events. Our study had limitations; it had a small sample size, and the correlation of CysC with any of the gold-standard methods of GFR estimation was not carried out.

In conclusion, in the present study, in patients of AD of cirrhosis, baseline levels of serum CysC were useful in predicting RD and ACLF. However, IL-6 was not useful in predicting RD, ACLF, and mortality. The role of serum CysC as a biomarker for predicting the adverse outcomes in patients of cirrhosis with AD can be explored further.

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