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BRIEF ARTICLE

Cystatin C is a biomarker for predicting acute kidney injury in patients with acute-on-chronic liver failure

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Abstract

AIM: To investigate serum cystatin C level as an early biomarker for predicting acute kidney injury (AKI) in patients with acute-on-chronic liver failure (ACLF).

METHODS: Fifty-six consecutive patients with hepatitis B virus-related ACLF who had normal serum creatinine (Cr) level (< 1.2 mg/dL in men, or < 1.1 mg/dL in women) were enrolled in the Liver Failure Treatment and Research Center of Beijing 302 Hospital between August 2011 and October 2012. Thirty patients with chronic hepatitis B (CHB) and 30 healthy controls in the same study period were also included. Measurement of serum cystatin C (CysC) was performed by a particle-enhanced immunonephelometry assay using the BN Prospec nephelometer system. The ACLF patients were followed during their hospitalization period.

RESULTS: In the ACLF group, serum level of CysC was 1.1 ± 0.4 mg/L, which was significantly higher (P < 0.01) than those in the healthy controls (0.6 ± 0.3 mg/L) and CHB patients (0.7 ± 0.2 mg/L). During the hospitalization period, eight ACLF patients developed AKI. Logistic regression analysis indicated that CysC level was an independent risk factor for AKI development (odds ratio = 1.8; 95%CI: 1.4-2.3, P = 0.021). The cutoff value of serum CysC for prediction of AKI in ACLF patients was 1.21 mg/L. The baseline CysC-based estimated glomerular filtration rate ($eGFR_{CysC}$) was significantly lower than the creatinine-based eGFR ($eGFR_{CG}$ and $eGFR_{MDRD}$) in ACLF patients with AKI, suggesting that baseline $eGFR_{CysC}$ represented early renal function in ACLF patients while the Cr levels were still within the normal ranges.

CONCLUSION: Serum CysC provides early prediction of renal dysfunction in ACLF patients with a normal serum Cr level.

Key words: Acute-on-chronic liver failure; Cystatin C; Creatinine; Acute kidney injury; Prediction

Core tip: Severe renal dysfunction often occurs in patients with acute-on-chronic liver failure (ACLF) due to circulatory abnormalities and inflammation. New biomarkers with higher reliability and specificity for monitoring renal function are required. Fifty-six patients with ACLF and normal serum creatinine (Cr) were enrolled. Our results showed that patients who developed acute kidney injury during hospitalization had significantly higher basal serum cystatin C (CysC) levels.

CysC-based estimated glomerular filtration rate more accurately represented renal function in ACLF patients. CysC can be used as an early biomarker for detection of renal dysfunction in patients with ACLF before any increase in serum Cr is detected.

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INTRODUCTION

Acute-on-chronic liver failure (ACLF) encompasses patients with previously well-compensated liver disease in whom acute decompensation of liver function occurs because of a precipitating event[1]. In China, hepatitis B virus (HBV)-infected ACLF patients account for > 80% of ACLF patients, due to a high incidence of chronic HBV infection[2,3]. The progressive nature of ACLF affects many organ systems. Kidney dysfunction is a common complication of advanced liver disease and associated with a high mortality[4-6].

Acute tubular necrosis and hepatorenal syndrome (HRS) may account for the majority of cases of severe renal dysfunction in patients with ACLF due to underlying circulatory abnormalities and inflammation[4,7]. Recently, the Acute Kidney Injury Network (AKIN) proposed a new term for acute renal dysfunction, namely, acute kidney injury (AKI), which can represent the entire spectrum of acute renal dysfunction[8,9]. The definition of AKI is based on changes in serum creatinine (Cr). Unfortunately, Cr is an unreliable indicator during acute changes in kidney function because it is highly dependent on extrarenal factors during the estimation[10]. Serum Cr concentrations may not change until approximately 50% of kidney function has already been lost[11]. In addition, elevated serum bilirubin in ACLF patients can interfere with the measurement of serum Cr using the Jaffe method[12]. Therefore, a Cr-based estimation of the glomerular filtration rate (GFR) may overestimate renal function in patients with ACLF. Thus, new biomarkers with higher reliability and specificity for estimation of renal function are required.

Serum cystatin C (CysC) is currently being investigated for the prediction of AKI in patients with cardiac surgery[13], advanced liver diseases[14], and patients undergoing liver transplantation[15]. CysC is a ubiquitous protein that is freely filtered by the kidney and then metabolized by the tubules. Unlike Cr level, CysC level is independent of muscle mass, age or sex, and is not influenced by inflammatory conditions or malignancy[16,17]. CysC significantly outperforms both Cr and endogenous creatinine clearance rate and detects impairment of GFR earlier than Cr does[18]. Several reports have suggested that increased CysC levels are more sensitive for prediction of HRS development in patients with cirrhosis[14,19,20], but the data using CysC levels in ACLF patients are lacking.

The purposes of this study were to investigate whether serum CysC levels are increased in ACLF patients by comparing with chronic hepatitis B (CHB) patients and healthy controls, and to further determine whether CysC can be used as an early biomarker for predicting AKI in ACLF patients.

MATERIALS AND METHODS

Ethics

The protocol was approved by the Ethical Committee of Beijing 302 Hospital. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. Written informed consent was obtained from each patient before entering the study protocol.

Patients and controls

Fifty-six consecutive patients with HBV-related ACLF and normal serum creatinine level (male: < 1.2 mg/dL, female: < 1.1 mg/dL) were admitted to the Liver Failure Treatment and Research Center of Beijing 302 Hospital between August 2011 and October 2012. ACLF was diagnosed based on a recent increase in jaundice (serum total bilirubin > 171.0 μmol/L) and decreasing plasma prothrombin activity (< 40%)[21]. Thirty patients with CHB were enrolled during the same study period. CHB was diagnosed according to the criteria recommended by the Chinese Society of Infectious Diseases, and the Chinese Society of Hepatology[22]. Serum samples from 30 age- and sex-matched healthy volunteers were used to determine the normal values of the indicators. The ACLF patients were followed during their hospitalization. Patients with intrinsic renal disease, spontaneous bacterial peritonitis, sepsis or gastrointestinal bleeding at enrollment were excluded from the study.

Laboratory and clinical parameters

Consecutive serum samples from ACLF patients were collected upon admission and throughout hospitalization (every 3 d). The serum samples of healthy controls were collected when they came to the Health Examination Centre. The serum samples of CHB patients were collected on admission to our center. All samples were stored within 2 h at -20 ℃ until analysis. Biochemical tests, including blood urea nitrogen (BUN), sodium, albumin, and bilirubin, were routinely performed. Serum Cr levels were determined using the modified Jaffe method (Beckman, Hamburg, Germany). Serum CysC measurements were performed by the particle-enhanced immunonephelometry assay using the BN Prospec Nephelometer system (Dade Behring, Newark, DE, United States). The model for end-stage liver disease (MELD) score was

Table 1 Clinical characteristics of the study population at admission

Parameter	ACLF (*n* = 56)	CHB (*n* = 30)	Control (*n* = 30)
Male/female	40/16	21/9	14/6
Age (yr)	44 ± 11	40 ± 10	39 ± 8
Alanine aminotransferase (IU/L)	145 ± 189	71 ± 61	21 (10-31)
Total bilirubin (mg/dL)	20.2 ± 5.6	2.2 ± 1.3	0.7 ± 0.2
Albumin (g/L)	30.4 ± 4.8	33.5 ± 5.2	35.6 ± 4.9
BUN (mmol/L)	4.4 ± 2.1	4.1 ± 1.8	4.8 ± 1.5
Plasma sodium (mEq/L)	134.8 ± 4.5	135.6 ± 5.7	137.4 ± 3.8
Cr (mg/dL)	0.9 ± 0.1	0.8 ± 0.1	0.8 ± 0.1
CysC (mg/L)	1.1 ± 0.4	0.7 ± 0.2	0.6 ± 0.3
International normalized ratio	1.9 ± 0.4	1.1 ± 0.2	0.9 ± 0.1
HBV DNA log10 (IU/mL)	4.75 ± 2.11	6.21 ± 2.78	
Ishak score	ND	4 (3-5)[1]	
MELD score	24 ± 3	8 ± 4	

[1]Histopathological data from 20 chronic hepatitis B (CHB) patients. ND: Not determined; BUN: Blood urea nitrogen; Cr: Creatinine; CysC: Serum cystatin C; HBV: Hepatitis B virus; MELD: Model for end-stage liver disease.

calculated as: 3.8ln (total bilirubin in mg/dL) + 11.2ln (INR) + 9.6ln (Cr in mg/dL) + 6.4. In addition, two methods of Cr-based estimated GFR (eGFR) were used: (1) the formula of Cockcroft and Gault[23] (eGFR$_{CG}$); and (2) the modification of the diet in renal disease (MDRD) equation (eGFR$_{MDRD}$)[24]. CysC-based GFR estimation was calculated using the Hoek formula (eGFR$_{CysC-1}$)[25] and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (eGFR$_{CysC-2}$)[26].

AKI was diagnosed as follows[9]: an abrupt reduction in kidney function as manifested by an absolute increase in serum Cr by ⩾ 0.3 mg/dL, equivalent to a percentage increase in serum Cr by ⩾ 50% (⩾ 1.5 folds from baseline) without any evidence of pre-existing kidney disease.

Statistical analysis

The results are expressed as mean ± SD or the number of patients. Data processing was carried out using SPSS for Windows version 17.0 (SPSS, Chicago, IL, United States). Continuous variables were determined using Student's *t* test. Parameters with non-normal distribution were compared using the Mann-Whitney *U* test. Categorical data were compared by the χ^2 test. Spearman's correlation analysis was used to assess relationships between two parameters. Receiver operating characteristic curves (ROCs) were formed to detect sensitivity and specificity of CysC, Cr, BUN and serum sodium for predicting the development of AIK, using Medcalc 12.7.7 software. Multivariate analysis with logistic regression was used to determine independent factors. $P < 0.05$ was considered statistically significant.

RESULTS

Clinical characteristics of enrolled patients

A total of 86 patients with chronic HBV infection, including 56 with ACLF and 30 with CHB, and 30 healthy volunteers were enrolled in this study. The basal clinical characteristics of patients at admission are summarized in Table 1. Patients with ACLF comprised 40 men (71.4%) and 16 women (28.6%) with a mean age of 44 ± 11 years. The serum level of sodium in ACLF patients was 134.8 ± 4.5 mEq/L and hyponatremia (serum sodium level < 130 mEq/L) was documented in six patients (10.7%). The average level of Cr was 0.9 ± 0.1 mg/dL in ACLF patients. As shown in Table 1, the baseline serum level of CysC was 1.1 ± 0.4 mg/L in ACLF patients, which was significantly higher ($P < 0.01$) than those in CHB patients (0.7 ± 0.2 mg/L) and healthy controls (0.6 ± 0.3 mg/L). A moderate increase ($P > 0.05$) in CysC was found in CHB patients in comparison with healthy controls. Meanwhile, in ACLF patients, the serum CysC level showed a significant positive correlation with the MELD score ($r = 0.746$, $P < 0.001$) (Figure 1A). However, the serum CysC level was not correlated with the serum Cr level ($r = 0.193$, $P = 0.155$) (Figure 1B).

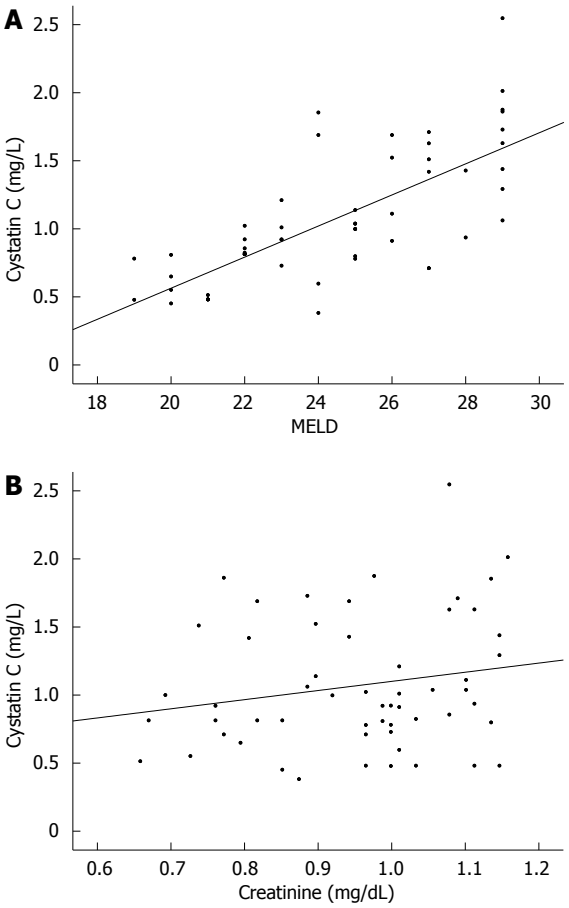

Figure 1 Scatter plots. A: Serum cystatin C (CysC) level *vs* model for end-stage liver disease (MELD) score; B: Serum CysC level *vs* serum creatinine (Cr) level.

Development of AKI

Patients with ACLF were followed during their hospitalization. The average hospitalization duration was 36 ± 10 d. During this period, eight (14.3%) of 56 patients developed AKI. The baseline clinical and laboratory charac-

Table 2 Comparison of baseline clinical characteristics in patients with or without acute kidney injury during hospitalization

Parameter	Without AKI (n = 48)	With AKI (n = 8)	P (univariate)	P (multivariate)	OR (95%CI)
Age (yr)	41 ± 9	55 ± 7	< 0.001		
Alanine aminotransferase (IU/L)	156 ± 158	62 ± 40	0.202		
Albumin (g/L)	30.1 ± 5.1	30.2 ± 2.1	0.965		
BUN (mmol/L)	4.2 ± 2.0	5.7 ± 1.1	0.065		
Sodium (mEq/L)	135.3 ± 4.2	132.1 ± 3.8	0.064		
Total bilirubin (mg/dL)	19.8 ± 5.6	21.3 ± 4.9	0.506		
Cr (mg/dL)	0.9 ± 0.1	1.0 ± 0.2	0.792		
International normalized ratio	1.9 ± 0.4	2.0 ± 0.3	0.367		
MELD score	24 ± 3	26 ± 2	0.094		
CysC (mg/L)	0.9 ± 0.3	1.8 ± 0.4	< 0.001	0.021	1.8 (1.4–2.3)

AKI: Acute kidney injury; BUN: Blood urea nitrogen; Cr: Creatinine; CysC: Serum cystatin C; MELD: Model for end-stage liver disease.

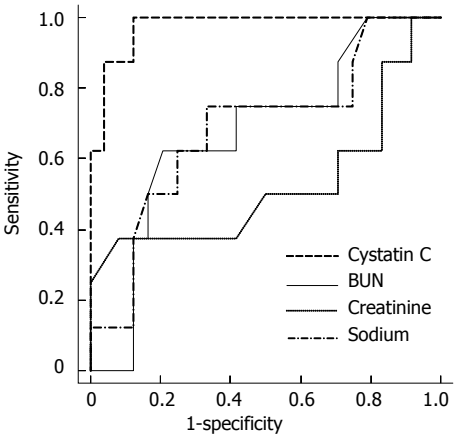

Figure 2 Receiver operating characteristic curve. Receiver operating characteristic curve analysis was performed to compare the efficacy of serum cystatin C, creatinine, blood urea nitrogen (BUN) and serum sodium level in predicting acute kidney injury.

teristics of patients with or without AKI are summarized in Table 2. Univariate analysis showed that patients who developed AKI were older (55 ± 7 years *vs* 41 ± 9 years, $P < 0.001$) and had a higher level of CysC (1.8 ± 0.4 mg/L *vs* 0.9 ± 0.3 mg/L, $P < 0.001$). The indicators (age, sodium, MELD score and CysC) which had $P < 0.1$ for patients with or without AKI were included in multivariate regression analysis. The results revealed that CysC level was the only independent predictive factor for the development of AKI in ACLF patients [odds ratio (OR) = 1.8; 95%CI: 1.4-2.3, $P = 0.021$].

ROC curve analysis was performed to compare the efficacy of CysC, Cr, BUN and serum sodium levels in predicting development of AKI during hospitalization (Figure 2). As shown in Table 3, the area under the curve (AUC) for CysC, Cr, BUN and serum sodium levels was 0.975, 0.526, 0.674 and 0.687, respectively. The results indicated that the AUC for CysC level had a better predictive value for development of AKI in ACLF patients ($P < 0.01$, DeLong's method for ROC curve comparison) in comparison with Cr, BUN and serum sodium. With an optimal cutoff value of 1.21 mg/L, the sensitivity and specificity of CysC for predicting the development of AKI were 100% and 87.5%, respectively ($P < 0.0001$).

Comparison of methods for estimating GFR using Cr- or CysC-based formulae

The methods for measuring eGFR included: Cr-based eGFR ($eGFR_{CG}$ and $eGFR_{MDRD}$), and CysC-based eGFRs ($eGFR_{CysC-1}$ and $eGFR_{CysC-2}$). These methods were compared between patients with or without AKI development (Figure 3). The four baseline eGFRs were not significantly different in patients without AKI (Figure 3A). In patients with AKI, baseline $eGFR_{CysC-1}$ when using the Hoek formula was 40.8 ± 9.7 mL/min, while the $eGFR_{CysC-2}$ from the Chronic Kidney Disease Epidemiology Collaboration equation was 40.3 ± 10.5 mL/min, which indicated a similar eGFR value using the two formulae. These two baseline $eGFR_{CysC}$ were significantly lower than $eGFR_{CG}$ (80.8 ± 19.6 mL/min, $P < 0.01$) and $eGFR_{MDRD}$ (79.8 ± 14.3 mL/min, $P < 0.01$) in patients with AKI (Figure 3A). The baseline $eGFR_{CysC-1}$ and $eGFR_{CysC-2}$ were significantly decreased in patients with AKI compared with those without AKI ($P < 0.001$). The baseline $eGFR_{CG}$ and $eGFR_{MDRD}$ were similar between patients with or without AKI. When AKI was diagnosed in ACLF patients, the $eGFR_{CG}$, $eGFR_{MDRD}$, $eGFR_{CysC-1}$ and $eGFR_{CysC-2}$ were 29 ± 3.3, 30.5 ± 5.1, 34.2 ± 5.7 and 33.3 ± 5.2 mL/min, respectively, suggesting no significant differences in the four eGFRs (Figure 3B). The results indicated that either Cr or CysC-based eGFRs reflected severe renal dysfunction when AKI occurred in ACLF patients. However, baseline $eGFR_{CysC}$ represented renal function of ACLF patients early during mild-to-moderate renal dysfunction, while the Cr levels were still within the normal ranges.

DISCUSSION

Patients with ACLF have immunological defects that are comparable to those in patients with sepsis. The clinical picture of both ACLF and septic shock is strikingly similar, and characterized by progressive vasodilatory shock and multiple organ failure[27]. Inflammation and oxidative stress also induce production of NO, which mediates the circulatory and renal disturbances of liver failure[28]. Recent reports from the European Association for the Study of the Liver (EASL) showed that the kidney failure

Table 3 Area under the curve for receiver operating characteristics and cutoff values for predicting acute kidney injury in acute-on-chronic liver failure patients

Parameter	Cutoff value	AUC (95%CI)	Sensitivity	Specificity	*P* value
CysC (mg/L)	1.21	0.974 (0.846-1.000)	100%	87.5%	< 0.0001
Cr (mg/dL)	1.1	0.526 (0.343-0.704)	37.5%	91.7%	0.828
BUN (mmol/L)	4.9	0.674 (0.487-0.829)	62.5%	79.2%	0.124
Serum sodium (mEq/L)	131	0.687 (0.500-0.839)	50%	87.5%	0.113

BUN: Blood urea nitrogen; Cr: Creatinine; CysC: Serum cystatin C; AUC: Area under the curve.

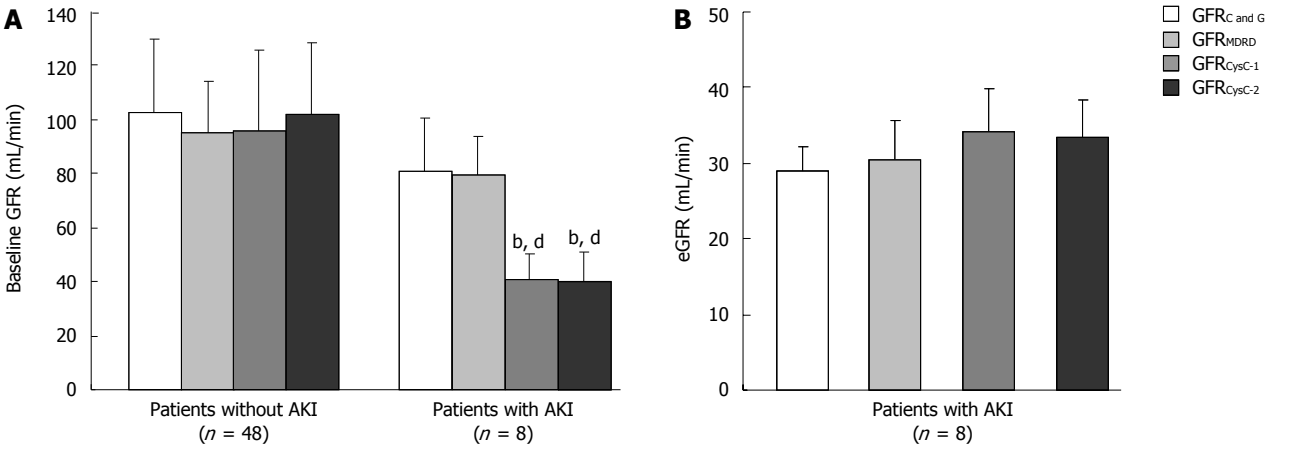

Figure 3 Performance of four equations for measuring estimated glomerular filtration rate in patients with acute-on-chronic liver failure. A: Baseline estimated glomerular filtration rate (eGFR) between patients with or without acute kidney injury (AKI); B: Comparison of four eGFR values in patients with AKI. $eGFR_{CG}$: The Cockcroft and Gault formula; $eGFR_{MDRD}$: The modification of the diet in renal disease equation; $eGFR_{CysC-1}$: Cystatin C-based Hoek estimate; $eGFR_{CysC-2}$: Chronic Kidney Disease Epidemiology Collaboration cystatin C equation. $^{b}P < 0.01$ *vs* GFR_{CysC} in patients without AKI; $^{d}P < 0.01$ *vs* e-GFR_{CG}, and e-GFR_{MDRD} in patients with AKI.

was clearly a risk factor for mortality in ACLF patients[6].

The progression of renal dysfunction in the presence of liver failure may be insidious and rapid or it may present as a mild or severe disturbance. Serum Cr is an easily measurable and widely used marker of renal function. However, Cr is an insensitive marker of kidney injury, and is usually maintained within the normal range until renal function is severely impaired, as in patients with cirrhosis and liver failure[29]. Several studies have reported that CysC is more useful for the assessment of renal function in patients with cirrhosis[14,19,20]. Assessment of CysC levels could be valuable in the early detection of renal dysfunction because they increase faster, as the GFR decreases, than do Cr levels[30]. However, data concerning CysC levels in ACLF patients are unavailable. All of the patients in the ACLF group had normal serum Cr level, with an average of 0.9 ± 0.1 mg/dL. Meanwhile, the average level of serum CysC was significantly higher in ACLF patients in comparison with healthy controls and CHB patients. Our results suggest that mild-to-moderate renal dysfunction may occur in ACLF patients who have a normal Cr level.

Patients with ACLF may have renal dysfunction other than HRS, due to the underlying circulatory abnormalities and sepsis[4,27,28]. Recently, the term AKI was proposed by AKIN, which may accurately represent the entire spectrum of acute renal dysfunction in ACLF patients. In our study, eight out of 56 ACLF patients (14.3%) developed AKI during hospitalization. Our results showed that CysC levels were significantly higher in patients who developed AKI during hospitalization. Our findings indicated that CysC could be used for the early detection of renal dysfunction in patients with ACLF before any increase in serum Cr levels is detected. Our multivariate analysis showed that age, Cr, sodium, and MELD score were not useful for predicting the development of AKI. The only independent predictive factor for AKI was CysC (OR = 1.8), which suggested that CysC represented renal function status more accurately in ACLF patients than did Cr. The results also indicated that CysC level might have accurately and rapidly reflected abnormalities in the renal handling of sodium and solute-free water before reduction in serum sodium level was detected. The diagnostic cutoff value of CysC for AKI prediction was 1.21 mg/L, which was different from that in cirrhosis patients reported previously[19,20].

It has been suggested that a Cr-based assessment of eGFR will overestimate the renal function in nonazotemic patients with cirrhosis and with moderate renal dysfunction (GFR < 60 mL/min)[31-33]. Two Cr-based and two CysC-based eGFR values were calculated in ACLF patients. The baseline Cr-based eGFR was similar in patients with or without AKI; however, baseline CysC-based eGFR was significantly lower in patients with AKI.

The results indicated that CysC-based eGFR was better in assessing kidney dysfunction in ACLF patients with a normal Cr level. In ACLF patients with an established diagnosis of AKI, both Cr-based and CysC-based eGFR were decreased to the same level, suggesting that these eGFR calculations were accurate in the case of severe renal dysfunction. Direct measurement of GFR using exogenous markers [Tc-99m diethylene-triamine-penta-acetic acid (DTPA) or inulin clearance] remains the standard for assessment of renal function[34,35]. Unfortunately, direct GFR assessment was not performed in our study because of the disease severity in ACLF patients. Demirtas *et al*[33] showed a correlation between CysC and 99mTc-DTPA clearance (r = -0.522, P = 0.006). They suggested that CysC assay, which has good analytical performance, could measure eGFR in patients with cirrhosis. That previous study, as well as our present study, suggests that CysC assay could replace Cr measurement for GFR assessment in patients with cirrhosis or ACLF.

In conclusion, CysC can be used as an early biomarker for the detection of renal dysfunction in patients with ACLF before any increase in the serum Cr levels can be detected. CysC-based eGFR calculation is more early represented renal function in ACLF patients during the period of mild-to-moderate renal dysfunction. The number size of patients for AKI development was small in this retrospective study. A prospective, large cohort study is ongoing in our research center to resolve this issue.

COMMENTS

Background

Kidney dysfunction is a common complication of advanced liver disease and associated with a high mortality. Serum creatinine (Cr) is an easily measurable and widely used marker of renal function. Unfortunately, Cr is an unreliable indicator during acute changes in kidney function because it highly depends on extrarenal factors such as muscle mass, gender, age and protein intake during the estimation. New biomarkers with higher reliability and specificity for estimation of renal function are required. Several reports have suggested that increased cystatin C levels are more sensitive for prediction of hepatorenal syndrome (HRS) development in patients with cirrhosis. However, data concerning serum cystatin C (CysC) levels in acute-on-chronic liver failure (ACLF) patients are unavailable.

Research frontiers

CysC is a ubiquitous protein that is freely filtered by the kidney and then metabolized by the tubules. Unlike Cr level, CysC level is independent of muscle mass, age or sex, and is not influenced by inflammatory conditions or malignancy. CysC detects impairment of glomerular filtration rate (GFR) earlier than Cr. The research hotspot is to investigate whether CysC can be used as an early biomarker for the detection of renal dysfunction in patients with ACLF before any increase in the serum Cr levels is detected.

Innovations and breakthroughs

Serum CysC is currently being investigated in the prediction of acute kidney injury (AKI) following cardiac surgery, advanced liver diseases, and undergoing liver transplantation, but the data using CysC levels in ACLF patients are lacking. Previous studies have reported that CysC was useful for the assessment of HRS in patients with cirrhosis. However, acute tubular necrosis and HRS may account for the majority of cases of severe renal dysfunction in patients with ACLF due to underlying circulatory abnormalities and inflammation. AKI which can represent the entire spectrum of acute renal dysfunction in ACLF patients was introduced in this paper.

Applications

CysC can be used as an early biomarker for the detection of renal dysfunction in patients with ACLF before any increase in the serum Cr levels. CysC-based eGFR more early represented renal function of ACLF patients during the period of mild-to-moderate renal dysfunction.

Terminology

AKI: a abrupt reduction in kidney function manifested by an absolute increase in serum creatinine by 0.3 mg/dL or more, equivalent to a percentage increase in serum creatinine by 50% or more (≥ 1.5 folds from baseline) without any evidence of preexisting kidney disease.

Peer review

The authors presented the finding that, in case of acute-on-chronic liver failure, the predictive performance of serum CysC and eGFR calculated from CysC is superior to that of serum creatinine and the other parameters. The prospective observation is excellent. The data collected in this study contribute to our understanding of common rule in the ACLF.

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