RESEARCH ARTICLE

Evaluation of serum Cystatin C as a reliable marker of renal dysfunction in chronic liver disease

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Abstract

Objective: To compare the reliability of serum cystatin C and serum creatinine in assessing renal dysfunction among chronic liver disease patients.

Method: The cross-sectional study was conducted from May 1, 2023, to January 30, 2024, at the Jinnah Postgraduate Medical Centre, Karachi, in collaboration with the University of Karachi and the Bahria University of Health Sciences, Karachi. The sample comprised healthy controls in group A, chronic liver disease patients Child-Pugh class A in group B, chronic liver disease Child-Pugh class B in group C, and chronic liver disease Child-Pugh class C in group D. Baseline demographic data was collected, and blood samples were analysed for liver and renal function tests. Serum cystatin C and creatinine levels were measured, and the ratio between the two was calculated to assess renal impairment. Data was analysed using SPSS 25.

Results: Of the 200 participants, 108(54%) were females and 92(46%) were males. Mean serum cystatin C levels increased significantly across Child-Pugh classes (0.7mg/L in controls vs 1.13mg/L in class A, 1.46mg/L in class B, and 1.53mg/L in class C; $p<0.01$). Serum creatinine levels also showed an increase (0.69mg/dL in controls vs 0.90mg/dL, 0.97mg/dL, and 0.99mg/dL respectively; $p<0.01$), though the rise was less consistent across patient groups. Blood urea nitrogen levels demonstrated a marked progressive increase from control to class C ($p<0.01$). Renal impairment was significantly associated with worsening Child-Pugh class ($p<0.01$).

Conclusion: Serum cystatin C was a more reliable marker of renal impairment than serum creatinine in chronic liver disease and correlated with disease severity, supporting its use in early detection.

Key Words: Cystatin C, Creatinine, Liver disease, Renal insufficiency, Glomerular filtration rate.

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Introduction

Chronic liver disease (CLD) is a major global health burden, with viral hepatitis, alcohol-associated liver disease, and non-alcoholic fatty liver disease (NAFLD) being the leading contributors.[1] Hepatitis B virus (HBV) and hepatitis C virus (HCV) infections remain important aetiological factors, as persistent viral replication leads to progressive hepatic inflammation, fibrosis, and cirrhosis if untreated.[1] Despite advancements in antiviral therapy, these infections frequently remain clinically silent for years, resulting in delayed diagnosis once significant liver injury has already occurred.[2]

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In addition to viral hepatitis, NAFLD has emerged as the fastest-growing cause of CLD worldwide. Its prevalence parallels the global rise in obesity and metabolic syndrome, and it now affects approximately one-quarter of the world's population, with particularly high rates in Western countries.[3] The disease spectrum ranges from simple steatosis to non-alcoholic steatohepatitis (NASH), which may progress to fibrosis, cirrhosis and hepatocellular carcinoma (HCC).

Assessment of liver disease severity commonly relies on the Child-Pugh scoring system, originally developed by Child and Turcotte, and later modified by Pugh et al. This scoring tool incorporates five clinical and laboratory parameters — serum bilirubin, serum albumin, prothrombin time (PT)/international normalised ratio (INR), ascites, and hepatic encephalopathy — to classify patients into Child-Pugh classes A, B and C.[4,5] These classes reflect increasing severity of hepatic dysfunction and help guide clinical decision-making.

Renal impairment is a well-recognised complication of advanced liver disease. Haemodynamic changes, including marked splanchnic vasodilation, reduced effective arterial blood volume, and activation of the

renin-angiotensin-aldosterone system (RAAS) and sympathetic nervous system, ultimately lead to renal vasoconstriction and impaired glomerular filtration.[6] Hepatorenal syndrome (HRS), a severe form of renal dysfunction, is characterised by profound renal vasoconstriction in the absence of intrinsic structural kidney injury, and is associated with high morbidity and mortality.[7]

Acute kidney injury (AKI) in cirrhotic patients may result from hypovolaemia, infection or nephrotoxic exposures. Standardised definitions and staging — such as those proposed by the Acute Kidney Injury Network (AKIN) and the Kidney Disease: Improving Global Outcomes (KDIGO) group — have improved early detection and management.[8] Chronic kidney disease (CKD) in the context of cirrhosis remains less clearly defined, but generally represents a spectrum of gradually progressive renal dysfunction that worsens with advancing liver disease severity.

Given the strong interplay between hepatic and renal dysfunction, accurate assessment of renal function in CLD is essential. Traditional markers, like serum creatinine (Cr) may be unreliable in cirrhosis due to reduced muscle mass, altered tubular secretion, and assay interference. Cystatin C (Cys C), a low-molecular-weight protein freely filtered by the glomerulus, has emerged as a more reliable biomarker of renal impairment in cirrhotic patients.[9]

The current study was planned to compare the reliability of serum Cys C and serum Cr in assessing renal dysfunction among CLD patients.

Patients and Methods

The analytical, cross-sectional study was conducted from May 1, 2023, to January 30, 2024, at the Jinnah Postgraduate Medical Centre (JPMC), Karachi, in collaboration with the University of Karachi. All biochemical analyses were performed at the Multidisciplinary Research Laboratory of the Bahria University of Health Sciences (BUHS), Karachi.

After approval from the institutional ethics committee, the sample size was calculated using the formula applicable to the comparison of two means[10]:

$$n = (2\sigma^2 (Z_{\alpha/2} + Z_{\beta})^2) / ((\mu_1 - \mu_2)^2)$$

The sample was raised using non-probability consecutive sampling technique. The sample comprised healthy controls in group A, CLD Child-Pugh class A patients in group B, CLD Child-Pugh class B patients in group C, and CLD Child-Pugh class C patients in group D. Controls were healthy adults accompanying patients at the outpatient clinics who volunteered for screening and were found to have normal physical examination, ultrasound and laboratory parameters. The controls were not individually matched to cases. The patients included were those with a confirmed CLD diagnosis and Child-Pugh classification based on the standard scoring system, which includes serum bilirubin, serum albumin, PT/INR, ascites and hepatic encephalopathy. Scores of 5-6 indicated class A, 7-9 indicated class B and 10-15 indicated class C.[4,5] Only patients with ultrasound-confirmed cirrhosis were included in the three patient groups. Those having other significant comorbidities, such as uncontrolled diabetes or CKD unrelated to the liver disease, and those aged <18 years were excluded.

After taking informed consent from all the subjects, data was noted, including age, gender, body weight, systolic blood pressure (SBP) and diastolic blood pressure (DBP). Also noted was detailed patient history to establish the duration of the liver disease and hepatitis status. Clinical assessment was also carried out, including abdominal palpation, to check for the degree of hepatosplenomegaly and the degree of ascites.

Venous blood samples were drawn from all the participants after 12-hour fasting. The blood samples taken were subjected to liver function test (LFT) and renal function test (RFT) analysis. RFTs included blood urea nitrogen (BUN), serum Cr, and Cys C. Glycated haemoglobin (HbA1c) was measured to exclude patients with uncontrolled diabetes, which could confound renal function results. Renal impairment index on the basis of Cr/Cys C ratio was calculated to determine the degree of kidney damage.

Data was analysed using SPSS 25. Baseline and biochemical characteristics were summarised using descriptive statistics. For continuous variables, mean ± standard deviation was used, while categorical variables were presented as frequencies and percentages. The relationships between categorical variables were tested using the Pearson chi-square test, while intergroup mean values were compared using one-way analysis of variance (ANOVA_. $P<0.05$ was considered significant.

Results

Of the 200 patients, 108(54%) were females and 92(46%) were males (Table 1). There were 50(25%) subjects in group A with mean age 37.46±9.09 years, 50(25%) in group B with mean age 42.32±12.24 years, 50(25%) in group C with mean age 44.36±11.29 years, and 50(25%) in group D with mean age 45.70±10.24 years. In group B, 31(62%) patients had HCV, 40(20%) had mild ascites, and 25(50%) demonstrated early renal impairment. In group

Table-1: Baseline characteristics of the study groups.

Variables		Control Group n=50		Class A Child Pugh n =50		Class B Child Pugh n =50		Class C Child Pugh n =50		p-value
		n	%	n	%	n	%	N	%	
Gender	Female	26	52.0	29	58.0	27	54.0	26	52.0	0.99
	Male	24	48.0	21	42.0	23	46.0	24	48.0	
Ultrasound	Cirrhosis	0	0.0	50	100.0	50	100.0	50	100.0	<0.01*
	Normal	50	100.0	0	0.0	0	0.0	0	0.0	
Hepatitis	Normal	50	100.0	0	0.0	0	0.0	0	0.0	<0.01*
	Hepatitis B	0	0.0	19	38.0	19	38.0	21	42.0	
	Hepatitis C	0	0.0	31	62.0	31	62.0	29	58.0	
Ascites	Control	50	100.0	0	0.0	0	0.0	0	0.0	<0.01*
	Slight	0	0.0	10	20.0	46	92.0	36	72.0	
	Moderate	0	0.0	0	0.0	4	8.0	14	28.0	
	Absent	0	0.0	40	80.0	0	0.0	0	0.0	
RenalImpairment	No (GFR ≥90 mL/min)	50	100.0	21	42.0	11	22.0	8	16.0	<0.01*
	Early (GFR 60–89 mL/min)	0	0.0	25	50.0	25	50.0	28	56.0	
	Advanced (GFR 30–59 mL/min)	0	0.0	4	8.0	14	28.0	14	28.0	

*p<0.05 was considered statistically significant using Pearson Chi Square test

Table-2: Mean comparison of physical parameters and glycated haemoglobin (HbA1c).

Variables	Control Group		Class A Child Pugh		Class B Child Pugh		Class C Child Pugh		p-value
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
Age (years)	37.46	9.09	42.32	12.24	44.36	11.29	45.70	10.24	<0.01*
Weight (kg)	76.24	10.35	72.40	8.16	71.58	5.93	73.10	6.63	0.56
Duration(years)	.	.	1.26	1.04	2.3	1.85	2.65	2.04	0.95
SBP	116.00	8.04	118.00	9.21	120.00	10.12	110.00	15.04	0.99
DBP	74.38	5.28	76.38	7.26	77.38	10.26	70.38	6.26	0.96
HbA1c	5.43	0.41	5.32	0.30	5.51	0.33	5.51	0.31	0.98

*p<0.05 was considered statistically significant using one way ANOVA SBP: Systolic blood pressure, DBP: Diastolic blood pressure, SD: standard deviation.

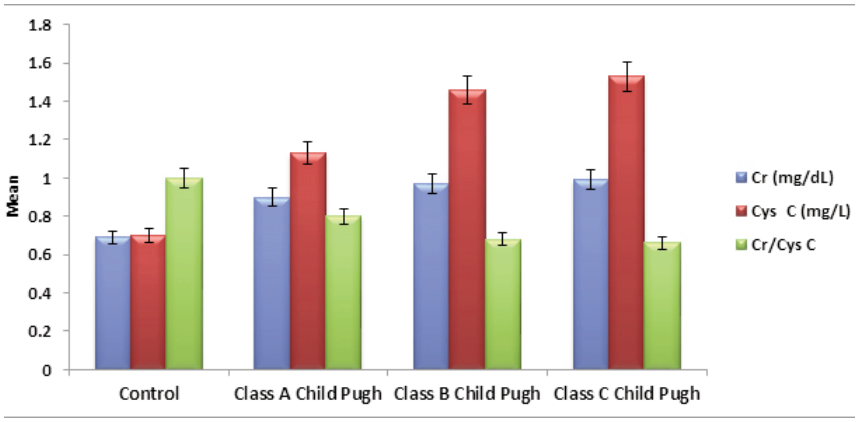

Figure-1: Mean comparison of blood urea nitrogen (BUN), creatinine (Cr) and cystatin C Sys C).

C, 46(92%) patients presented with ascites, while in group D, 36(72%) had ascites and 28(56%) had renal impairment. Overall, ultrasound findings, including the presence of hepatitis, ascites and renal impairment, were significantly associated across the study groups (p<0.05) (Table 1).

There was a significant difference in age among the groups (p<0.01), with post-hoc analysis confirming that the difference was relevant to group A, C and D. No significant differences were observed in body weight, HbA1c and the duration in number of years since the CLD diagnosis (p>0.05) (Table 2).

The mean serum creatinine

levels increased progressively from the control group to Child-Pugh class C patients, rising from approximately 0.69 mg/dL in controls to 0.90 mg/dL in class A, 0.97 mg/dL in class B, and 0.99 mg/dL in class C. A more pronounced increase was observed in serum cystatin C levels, which rose from approximately 0.70 mg/L in controls to 1.13 mg/L in class A, 1.46 mg/L in class B, and 1.53 mg/L in class C. In contrast, the Cr/Cys C ratio demonstrated a progressive decline across the study groups, decreasing from approximately 1.00 in controls to 0.80 in class A, 0.68 in class B, and 0.65 in class C. (Figure).

Discussion

The study highlights the potential of Cys C as a marker that is more sensitive and specific than any available RFTs in the patients studied, particularly relating to the different classes of hepatic complication.

The gender distribution across the study groups was relatively balanced, with females constituting slightly over half of the participants in every group. All the patients had ultrasound-confirmed cirrhosis, which was an inclusion requirement and not a component of the Child-Pugh scoring system. This significant association ($p<0.01$) underscores progressive liver damage in CLD patients. This is consistent with earlier findings.[11]

HCV was present in 58% to 62%, and hepatitis B in 38% to 42% across the current patient groups. The variation in bilirubin, albumin and INR values was consistent with increasing Child-Pugh severity, although these laboratory parameters were used exclusively for scoring, and were not presented as separate outcome variables. Mild ascites occurred in 92% of class B, 20% of class A, and 72% of class C cases, with moderate ascites in class B (8%) and class C (28%). The difference of ascites' severity among the groups was significant ($p<0.01$), providing evidence of the deterioration of liver function with disease progression. These results are consistent with those of Francoz et al.[12]

Early renal impairment was seen in 50% of class A and B, and 56% of class C patients, while advanced impairment occurred in 8% of class A and 28% of class B and C patients. These results are consistent with other studies.[13] The increased amount of renal impairment seen in more advanced liver disease processes is probably explained by the fact that cirrhosis is a progressive disease that in turn worsens renal dysfunction via portal hypertensive, systemic inflammation and renal perfusion impairment. These factors increase the likelihood of renal impairment as the liver disease worsens, reinforcing the connection between cirrhosis and declining kidney function.[13]

Mean age also differed significantly from one group to the other ($p<0.01$) in a way that depicted the progressive nature of CLD in the current study. Although minor variations were observed in weight, SBP, DBP and HbA1c across the groups, these differences were not statistically significant, and, therefore, did not act as confounding variables in the assessment of renal function markers.

The study revealed a significant and steady rise in the Cys C levels with increasing Child-Pugh class, highlighting an advanced degree of renal impairment attributable to deteriorating liver functions. The mean Cys C levels in the current study were 1.13mg/L in Child-Pugh class A, 1.46mg/L in class B and 1.53mg/L in class C patients compared to 0.7mg/L in the control group ($p<0.01$). These findings aligned with previous studies that highlighted the superiority of Cys C in identifying early renal insufficiency in cirrhotic patients, even when serum Cr levels were within normal ranges.[10,14,15]

Comparatively, serum Cr levels also increased with the severity of liver disease, but were less consistent in the current study. The mean serum Cr levels were 0.90mg/dL in class A, 0.97mg/dL in class B, and 0.99mg/dL in class C patients, and all were significantly higher than the control group's mean of 0.69mg/dL ($p<0.01$). However, the variations in Cys C were more pronounced and consistent, supporting its use as a superior biomarker.

The significant differences in Cys C levels across the study groups highlight its potential clinical utility. Early detection of renal impairment is crucial in managing CLD patients, as timely interventions can prevent the progression to severe renal failure, including HRS, which has a high mortality rate. The use of Cys C in routine clinical practice could lead to earlier identification of disease and better treatment of renal impairment in these individuals. This is consistent with previous studies which emphasised the utility of Cys C in the early identification of renal impairment in subjects with end-stage hepatic disease.[16-18]

Despite the promising findings, the current study has limitations. First, the sample size was relatively modest, which may have limited the generalisability of the results to a broader population of CLD patients. Larger, multicentre studies are needed to validate the current findings across different demographic and clinical settings. Second, the study design was cross-sectional, preventing the assessment of longitudinal changes in renal function markers over time. A prospective study could better establish the predictive value of serum Cys C in monitoring renal dysfunction progression. Additionally, other potential confounding factors, such as medication

use, comorbidities and variations in hydration status, were not extensively analysed, which may have influenced renal function parameters. All biomarkers were measured at a single time-point at enrolment, and no longitudinal follow-up was conducted. Duration since diagnosis was recorded, but was not used as a time-to-event variable. Body mass index (BMI) could not be calculated because height measurements were not recorded during data collection, and, as such, weight was used as the available anthropometric parameter. Besides, only overall ANOVA levels of significance have been presented because pairwise comparisons could not be accommodated due to editorial restrictions related to space and number tables. Although LFT components (bilirubin, albumin, INR) were used for Child–Pugh scoring, they were not included as separate table outputs to comply with relevant limits.

Longitudinal studies are recommended in order to help assess the predictive value of serum Cys C over time and its role in tracking renal function deterioration in CLD patients. Additionally, integrating biomarker panels that include Cys C alongside inflammatory markers and renal perfusion indicators could enhance early detection and risk stratification for renal impairment in cirrhotic patients. Exploring the cost-effectiveness and feasibility of incorporating Cys C testing into routine clinical practice would also be beneficial. Furthermore, interventional studies evaluating the impact of early Cys C-based renal function monitoring on patient outcomes and treatment strategies, particularly in preventing complications like HRS, could provide valuable insights into its clinical utility.

Conclusion

Serum Cys C was found to be a sensitive and reliable biomarker for assessing renal dysfunction in CLD patients, outperforming serum Cr. Its strong correlation with liver disease severity suggested potential for improving clinical evaluations and treatment decisions.

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Conflict of Interest: None.

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AUTHORS' CONTRIBUTIONS:

AB: Supervision and Final approval.
MF: Data analysis and interpretation.
SR: Drafting, writing, biochemical analysis, running of kits and bench work.
SK: Data collection.
AMJ: Clinical supervision.
AZ: Biochemical analysis of biomarkers and Bench work.