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***Original Research Article***

# COMPARISON STUDY OF CYSTATIN C & CREATININE-BASED GFR FORMULAS WITH 51CR-EDTA CLEARANCE IN PATIENTS WITH CIRRHOSIS

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**Abstract:** *This study aimed to compare cystatin C and Creatinine based GFR equations with 51Cr-EDTA clearance as the gold standard in cirrhotic patients. A prospective study was conducted in the Hepatology & Medicine Departments of Tertiary Care Hospitals. A total of 140 patients were included in the study. 66 cirrhotic patients correlated with cystatin C with creatinine and 74 patients correlating 51Cr-EDTA glomerular filtration rate to adjustments of diet in renal disease and Larsson and Hoek formulas for Cystatin C were selected for the study. Bland-Altman plots and concordance correlation coefficients were used to evaluate agreements. The correlation between cystatin C and bilirubin was poor, and the correlation between bilirubin and creatinine was strong. The medium values of creatinine and cystatin C were greater in a group with a GFR of more than 70 ml (27 patients), and their difference was significant (p <0.0001). The new GFR obtained by the creatinine formula was more accurate than GFR obtained by the cystatin C formula. With a 50% change in GFR, the creatinine formula provided a 90% GFR estimate. CysC formulas are not better for estimating glomerular filtration rate than creatinine formulas.*

**Keywords:** Cystatin C, Cirrhosis, Glomerular Filtration Rate, Creatinine

## Introduction

Renal failure strongly predicts mortality in liver failure and cirrhosis patients, especially in serious complications like severe sepsis and post-orthotopic liver transplant(Pool et al., 2018). Serum creatinine is the indicator of kidney function, i.e., glomerular filtration rate. However, the creatinine measurement is unreliable. Various studies used different methods to measure creatinine, and the values differed significantly (Pundir et al., 2019). In addition, a discrepancy has also been reported between laboratory values that measured creatinine by the same method (Verna et al., 2020).

However, the most commonly used formulas for estimating renal function are Cockcroft-Gault and Modification of Diet in Renal Disease use several adjustments to variables like age, sex, ethnicity, and body weight (Palacio-Lacambra et al., 2018). A study was conducted to evaluate the accuracy of these formulas, keeping 25I-iothalamate clearance as a reference. The MDRD formula showed greater accuracy than the CG formula, but its concordance with the reference standard was less than reported in other populations (Gonwa et al., 2004).

Renal function can be accurately assessed by inulin clearance and chromium-51 EDTA, Iodine 125-Iothalamate, and 99m Tc-diethylene-triamine-pentaacetate. Although inulin clearance is the gold standard, chromium-51 EDTA is the best substitution for this method.

Serum cystatin C is a more accurate indicator of kidney function than creatinine in diseases like cirrhosis, as it is independent of age, sex, and bodily components. Therefore, several equations based upon Cys-C have been derived that measure renal function in patients without hepatic disorder. Although these formulas were more effective than the creatinine-based equations, they do not have a strong correlation to direct methods of estimating renal function. Larsson et al. and Hoek et al. reported a significant difference between GFR values by Cys C formulas and inulin clearance.

CysC is a predictor of the stage of liver disease in cirrhotic patients. An elevated CysC value in such

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patients indicates increased production, inflammation, fibrosis, decline in kidney function, or both.

This study compared cystatin C and Creatinine based GFR equations with $^{51}$Cr-EDTA clearance as the gold standard in cirrhotic patients.

## Methodology

A prospective cohort study was conducted in the Hepatology & Medicine Departments of Tertiary Care Hospitals. A total of 140 patients, 66 cirrhotic patients correlating cystatin C with creatinine and 74 cirrhotic patients scheduled for liver transplant correlating $^{51}$Cr-EDTA glomerular filtration rate to adjustments of diet in renal disease and Larsson and Hoek formulas for Cystatin C were selected for the study. All the patients provided informed consent to participate in the study. The ethical committee of the hospital approved the study design.

All the clinical and biochemical data were noted in liver transplant patients at the time of $^{51}$Cr-EDTA. MELD and CPT scores were calculated. Imaging and histological data were used to diagnose ascites, hepatocellular carcinoma, cirrhosis, and encephalopathy.

We used four methods to measure serum creatinine in the first cohort: O'Leary modified Jaffe method, compensated kinetic Jaffe method, enzymatic creatinine lab test, and standard kinetic Jaffe method. Serum cystatin C was evaluated by immunonephelometry.

In the second cohort, cJCr and ECr methods were used to measure creatinine and CysC when bilirubin was less than 171 µmol/L. C51Cr-EDTA was done by blood collection after tracer administration for 6 hours with a two-hour difference. Slope -intercept technique was used to calculate GFR, adjusting body surface area and fast exponentiation.

The four variable MDRD formulas were used to calculate creatinine-based GFR, and Hoek and Larsson's formulas were used for CysC-based GFR calculation.

Data was evaluated by Medcalc software. Mean and standard deviation expressed parametric quantitative variables, and the median expressed non-parametric variables. Unpaired t-tests were performed to compare parametric data, and Mann-Whitney's test was performed for non-parametric data. Pearson's correlation was used to analyze parametric correlation, and Spearman was used to assess non-parametric data. Bland-Altman plots and concordance correlation coefficients were used to evaluate agreements. A probability value of less than 0.05 was considered significant.

## Results

A total of 66 cirrhotic patients were included, and 256 samples were collected. Median INR was 1.9 and bilirubin was 167 µmol/L.Median serum Cystatin C was 1.20. There was a reasonable correlation between Cystatin C and creatinine measurement methods ($p<0.001$) (Table I).

The creatinine measurement methods were further divided regarding ascending bilirubin levels. 90 samples (35.4%) had a 100-199 µmol/L bilirubin level. The medium values of the groups are shown in Table II. The comparison of cystatin C values in samples with more than 400 µmol/L with other groups was significant. However, the correlation between cystatin C and bilirubin was poor, and the correlation between bilirubin and creatinine was strong, showing that the increase in Cystatin C with increase in bilirubin was due to renal function and not cirrhosis.

In the second cohort of 74 cirrhotic patients, the mean MELD was 13 ± 6.5, and $^{51}$Cr EDTa was 82.6 ± 31.6/min/1.73m$^2$. The medium values of creatinine and cystatin C were greater in a group with a GFR of more than 70 ml (27 patients), and their difference was significant ($p <0.0001$) (Table III).

These patients were also divided with respect to the CPT stage. There was a significant difference between creatinine, GFR and cystatin C measurements as measured by Larsson, $^{51}$Cr-EDTa and Hoek and MDRD (Table IV).

According to Bland-Altman analysis, both creatine and cystatin C formulas were more accurate than Hoek, Larsson, and MDRD equations. However, the new GFR obtained by the creatinine formula was more accurate than GFR obtained by the cystatin C formula. With a 50% change in GFR, the creatinine formula provided a 90% GFR estimate (Table V).

**Table I: Patient characteristics of cirrhotic patients and samples**

| Characteristics | Cirrhotic patients (n=66) | Samples (n=256) |
|---|---|---|
| **Age** | 52 (27-93) | |
| **Gender** | | |
| **Female** | 26 (39.3%) | |
| **Male** | 40 (60.6%) | |
| **Etiology of liver disease** | | |
| **Alcohol** | 5 (7.5%) | |
| **Hepatitis B or C** | 25 (37.8%) | |

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| | | |
|---|---|---|
| **Autoimmune** | 2 (3%) | |
| **NASH** | 10 (15.1%) | |
| **Primary biliary cirrhosis/ Primary sclerosing cholangitis** | 12 (18.1%) | |
| **Other** | 12 (18.1%) | |
| **MELD** | | 25 (8-44) |
| **INR** | | 1.9 (1-9) |
| **Bilirubin** | | 167 (9-914) |
| **mJCr** | | 111 (60-1.39) |
| **cJCr** | | 82 (37-1.44) |
| **ECr** | | 75 (36-1.15) |
| **JCr** | | 95 (41-1.31) |
| **Serum cystatin C** | | 1.20 (0.32-4.85) |

**Table II: Medium values of serum creatinine and Cystatin C**

| | **mJCr** | **cJCr** | **ECr** | **JCr** | **CysC** |
|---|---|---|---|---|---|
| **Bilirubin <100 (n=61)** | 85 (60-160) | 73 (37-172) | 67 (36-159) | 80 (50-161) | 1.0 (0.4-2.7) |
| **Bilirubin ≥100 and <200 (n=90)** | 101 (74-405) | 78 (40-440) | 74 (38-457) | 93 (41-417) | 1.0 (0.6-3.8) |
| **Bilirubin ≥200 and <400 (n=56)** | 130 (83-295) | 82 (40-290) | 80 (36-257) | 95 (57-285) | 1.16 (0.5-3.2) |
| **Bilirubin ≥400 (n=49)** | 175 (103-1281) | 107 (47-1340) | 92 (37-1147) | 120 (68-1214) | 1.40 (0.6-5.0) |
| **P** | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 |

**Table III: Characteristics of cirrhotic patients candidates for liver transplant**

| | **Total (n=74)** | **GFR >70 (n= 47)** | **GFR <70 (n=27)** | **P-Value** |
|---|---|---|---|---|
| **Age** | 50 (10.1) | 50 (10.5) | 51 (9.6) | 0.5 |
| **Weight** | 78 (14.1) | 77.5 (13.3) | 79 (17.5) | 0.4 |
| **Height** | 171 (9) | 171 (9) | 170 (9) | 0.4 |
| **Body surface area** | 27.5 (5.5) | 1.94 (0.20) | 1.20 (0.3) | 0.1 |
| **CPT score** | 9.3 (2.5) | 9.2 (2.7) | 9.5 (2.2) | 0.4 |
| **MELD score** | 13 (6.5) | 11.4 (5.3) | 16.5 (6.3) | 0.0002 |
| **Creatinine** | 68.5 (29-235) | 65 (29-91) | 110 (54-235) | <0.0001 |
| **CyS C** | 0.92 (0.41-3.0) | 0.91 (0.4-1.2) | 1.21 (0.7-3.0) | <0.0001 |
| **C51Cr-EDTA** | 82.6 (31.6) | 101 (18.4) | 48.8 (18.5) | |
| **Severe ascites** | 18 (24.3%) | 8 (17%) | 11 (40%) | 0.4 |
| **Severe Encephalopathy** | 9 (12.1%) | 7 (14.8%) | 3 (11.1%) | 0.3 |
| **Bilirubin** | 39 (7-958) | 55 (7-278) | 36 (7-958) | 0.1 |
| **AST** | 70.5 (18-267) | 77 (28-267) | 57 (18-223) | 0.01 |
| **ALT** | 50.5 (12-509) | 59 (16-226) | 39 (12-509) | 0.01 |
| **Albumin** | 34.9 (6.0) | 34.6 (6.3) | 35.1 (5.5) | 0.4 |
| **Prothrombin time** | 19.1 (13-40) | 19.1 (13-40) | 20 (14-26) | 0.7 |
| **INR** | 1.9 (1.0-3.5) | 1.9 (1.0-3.5) | 1.9 (1-2.5) | 0.7 |
| **CRP** | 6.4 (1-81) | 9 (1-81) | 5.5 (1-65) | 0.2 |
| **Platelets** | 98.2 (22-918) | 93.2 (34-918) | 121 (22-329) | 0.06 |

**Table IV: GFR formulas with regard to the CPT stage**

| | **CPT class A** | **CPT class B** | **CPT class C** | **P-Value** |
|---|---|---|---|---|
| **CyS C** | 0.87 (0.52-3.0) | 1.06 (0.43-2.72) | 0.89 (0.42-1.32) | 0.4 |
| **Creatinine** | 70.4 (49-235) | 68 (41-229) | 69 (29-151) | 0.5 |

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| | | | | |
|---|---|---|---|---|
| **C51Cr-EDTA** | 85.6 (39) | 84.2 (33) | 77.5 (22.3) | 0.3 |
| **MDRD** | 97.4 (36.5) | 96 (37.1) | 111 (49.2) | 0.5 |
| **Larsson** | 90.1 (42.2) | 106 (54.3) | 108 (45) | 0.3 |
| **Hoek** | 85.1 (34.2) | 96.3 (42.4) | 98.1 (32.9) | 0.3 |

**Table IV: GFR estimates with adjustments in measured 51CR-EDTA**

| GFR estimates | 10% change | 30% change | 50% change |
|---|---|---|---|
| **New Cr eGFR** | 40% | 80% | 90% |
| **New CysC eGFR** | 35% | 76% | 85% |
| **MDRD** | 39% | 65% | 83% |
| **Hoek** | 35% | 70% | 80% |

## Discussion

We included two cohorts of cirrhotic patients. In the first cohort, serum cystatin values were compared with the four creatinine measurement methods, and in the second cohort, the new GFR values obtained by creatinine and cystatin values were compared.

There was a poor correlation between bilirubin and cystatin; a strong correlation was observed with creatinine. Another study also reported that hyperbilirubinemia <700 µmol/L did not influence the correlation between bilirubin and cystatin C measurement of GFR(Pottel et al., 2023). As observed in other studies, this relationship also remained insignificant with changes in the CPT stage (da Silva Selistre et al., 2019; Inker et al., 2021; Pottel et al., 2021).

As compared to $^{51}$Cr-EDTA, both creatinine and cystatin C performed very well; however, the CPT score made the creatinine GFR more accurate, and the presence of ascites added to the accuracy of cystatin GFR. The female gender influenced the creatinine formula, but the cystatin formula remained unchanged (Allen et al., 2018; Sealock et al., 2022). Hence, the creatinine formula had the highest accuracy compared to MDRD, Hoek, Larsson, and cystatin formulas.

The multi-variable MDRD formula has been formulated from non-liver disease patients, but its accuracy was validated in only one cohort of cirrhotic patients(Yoo et al., 2019). Similarly, the cystatin C formulas were formulated from patients without liver disease (glomerulopathy, diabetes, and vasculitis) but only validated in 44 cirrhotic patients (Pöge et al., 2006).

In our patients, 51Cr-EDTA performed the worst compared to Hoek, Larsson, MDRD, and cystatin formulas. The Hoek and cystatin formulas were better than Larsson, which was better and less biased than MDRD. However, MDRD had a greater precision than Hoek and Larsson's formulas.

A similar study was conducted, which compared creatinine and cystatin C formulas, keeping inulin clearance as a reference (Singapura et al., 2021). The CPT score was comparable to ours, but bilirubin was lower than our study (29 vs 39 µmol/L), and creatinine was higher than our subjects (94.5 vs 68.5 µmol/L). All the formulas performed well, but cystatin formulas were more precise than creatinine formulas. However, for variable percentages of GFR, the accuracies were low, i.e., 20.5% at 50%, which is lower than our study (90% and 85%). Gonwa et al. reported similar values to our study (Gonwa et al., 2004).

Our study has some limitations. We included a limited number of patients in both cohorts; a large cohort can reveal better results. Additionally, the gold standard in our study has not been widely evaluated in ascites patients.

## Conclusion

CysC formulas are not better for estimating glomerular filtration rate than creatinine formulas.

## Conflict of interest

The authors declared absence of conflict of interest.

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