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Serum Cystatin C Unmasks Renal Dysfunction in Cirrhosis and Performs Better in GFR Estimation

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Abstract

Aims: i) To measure Glomerular Filtration Rate (mGFR) using ^{99}Tc DTPA in patients with Child Pugh C cirrhosis and normal serum creatinine levels.

ii) To compare the performance of creatinine and cystatin C-based equations (eGFRs) to ^{99}TcDTPA GFR in the same group.

Materials and Methods: We selected a group of 65 consecutive patients with advanced liver cirrhosis and apparently normal renal function by serum creatinine alone. Patients with confounding and reversible factors were excluded. Demographic data, blood, urine and imaging tests along with simultaneous measurement of serum creatinine and cystatin C were analyzed. The GFR was measured by ^{99}Tc DTPA scintigraphy (mGFR) in 41 patients. We compared the performance of Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI-Creatinine, CKD-EPI-Cystatin C and CKD-EPI-Creatinine-Cystatin C) and MDRD equations for bias (mean difference), precision (root mean square error) and accuracy (P10 and P30). Bland-Altman plots were used to show the agreement of eGFR and mGFR.

Results: Sixty one percent of patients had significant renal dysfunction (GFR ≤ 60 ml/min/1.73 m^2) by ^{99}TcDTPA in our study. Three patients were already in stage 4 CKD despite normal serum creatinine values. Cystatin C-based equations estimated the mGFR better compared to creatinine based equations. CKD-EPI-Creatinine-Cystatin C combined equation had the least bias (-2.3), superior precision (7.1), highest P30 accuracy (78%), good sensitivity (87.5%) and best specificity (96%) in our study.

Discussion: Creatinine based GFR estimation is fallacious in cirrhosis. Cystatin C and equations based on it may be worthwhile in liver disease.

Conclusions: i) Two-thirds of patients with cirrhosis had significant renal impairment despite normal serum creatinine. Isolated serum creatinine values are misleading in cirrhosis.

ii) Cystatin C unmasks renal dysfunction in these patients. CKD-EPI-Creatinine-Cystatin C equation showed the best correlation and accuracy with ^{99}TcDTPA GFR in our study.

Keywords: Cystatin C; Cirrhosis; Glomerular filtration rate; ^{99}TcDTPA

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Introduction

Renal function is an important predictor of outcome in advanced stages of liver cirrhosis [1]. Cirrhotic patients are susceptible to reversible as well as chronic kidney dysfunction because of altered haemodynamics, volume shifts and comorbidities. Sustained intrarenal vasoconstriction secondary to circulatory dysfunction results in progressive decline of glomerular filtration rate and chronic kidney disease [2].

Serum creatinine measurement and thereby GFR estimation is faulty in cirrhosis due to: (1) defective synthesis of creatine [3], the precursor of creatinine in liver [4], (2) poor muscle mass and malnutrition [5], (3) higher volume of distribution and (4) assay interference due to Jaffe positive compounds like bilirubin. Deceptively low creatinine values (<1 mg/dl) may mask significant decline in GFR. Accurate GFR estimation is necessary to avoid over dosage of drugs and to plan early Renal Replacement Therapy (RRT) in the event of complications. There is a need to accurately diagnose and manage renal impairment coexistent with cirrhosis to improve outcomes. KDIGO 2012 clinical practice guideline suggests using additional tests in specific circumstances when

Table 1: Equations used in the study.

Formula	Full Expression
Modification of Diet in Renal Disease equation (MDRD)	MDRD (ml/min/1.73 m^2) = 175 × $(Pcr)^{-1.154}$ × age $(years)^{-0.203}$ × 0.742 (if female) × 1.21 (if black)
CKD-EPI Creatinine equation (2009)	CKD-EPI-Cr (ml/min/1.73 m^2) = 141 × min $(Pcr/k, 1)^{\alpha}$ × max $(Pcr/k, 1)^{-1.209}$ × 0.993^{age}
CKD-EPI-Cr	(× 1.018 if female | × 1.159 if black) k is 0.7 for females and 0.9 for males α is -0.329 for females and -0.411 for males " min" is the minimum of PCr/k or 1 and "max" the maximum of PCr/k or 1
CKD-EPI Creatinine Cystatin C equation (2012)	CKD-EPI-Cr-CysC (ml/min/1.73 m^2) = 135 × min $(Pcr/k, 1)^{\alpha}$ × max $(Pcr/k, 1)^{-0.601}$ × min (CysC/0.8, 1)$^{-0.375}$ × max (CysC/0.8, 1)$^{-0.711}$ × 0.995^{age}
CKD-EPI-Cr-CysC	(× 0.969 if female | × 1.08 if black) k is 0.7 for females and 0.9 for males α is -0.248 for females and -0.207 for males "min" is the minimum of PCr/k or 1 or the minimum of CysC/0.8 or 1 and "max"
CKD-EPI Cystatin C equation (2012)	CKD-EPI-CysC (ml/min/1.73 m^2) = 133 × min (CysC/0.8, 1)$^{-0.499}$ × max (CysC/0.8, 1)$^{-1.328}$ × 0.996^{age}
CKD-EPI-CysC	(× 0.932 if female) "min" indicates the minimum of CysC/0.8 or 1 and "max" the maximum of CysC/0.8 or 1.
MELD Score	MELD = 10 × [0.957 × Ln(PCr)+0.378 × Ln(Total Bilirubin)+1.12 × Ln(INR)+0.643] (Laboratory values <1 mg/dl were rounded up to 1)

eGFR based on serum creatinine is unreliable [6]. The gold standard method for GFR measurement is urinary clearance of inulin during a continuous intravenous infusion. ^{99}Tc DTPA scintigraphy is a less cumbersome, non-invasive and easily available alternative method to inulin clearance that provides a close approximate for measured GFR (mGFR) in clinical studies [6]. Studies have reported that cystatin C-based GFR estimation is more accurate in cirrhosis than methods based solely on serum creatinine. Serum cystatin C is less influenced by most of the above limitations of creatinine in liver disease [7] (Figure 1). Cystatin C is independent of muscle mass, age and sex, so that the same reference interval applies to the whole population [8]. Drawbacks of cystatin C are that it can be influenced by inflammation, infection and volume of distribution changes which are prevalent in the setting of cirrhosis. Whether cystatin C-based equations are reliable and can obviate the need for isotopic GFR measurements is still a matter of debate.

The purpose of this study was to evaluate the diagnostic superiority of cystatin C based eGFRs in patients with Child Pugh C stage liver cirrhosis using measured GFR by ^{99}Tc DTPA [9,10].

Materials and Methods

Study population

The study was performed at a tertiary care centre in South India between March 2018 to September 2018. We included 65 patients with Child Pugh C cirrhosis between 18 to 55 years of age with serum creatinine less than 1 mg/dl.

Table 2: GFR categories of all 41 patients as per ^{99}TcDTPA mGFR.

GFR category	GFR (in ml/min/1.73 m^2)	Number of patients (total=41)	Percentage
G1	≥ 90	0	0
G2	60-89	16	39%
G3a	45-59	12	29.20%
G3b	30-44	10	24.30%
G4	15-29	3	7.30%
G5	<15	0	0

The following patients were excluded from the study group:

1. Patients with diabetes, hypertension, family history of chronic kidney disease and those with acute kidney injury or hepatorenal syndrome.

2. Patients with dehydration, upper gastrointestinal bleed, sepsis, spontaneous bacterial peritonitis, tense ascites, aggressive paracentesis, acute liver decompensation in the previous month or suspicion of hepatocellular carcinoma.

3. Patients with recent decline in urine output, proteinuria, active urinary sediments or imaging abnormalities of the kidneys.

4. Patients with thyroid disease and usage of NSAID, aminoglycosides, trimethoprim or indigenous medicines.

Data regarding baseline demographic characteristics were collected. Model for End Stage Liver Disease (MELD) scores were

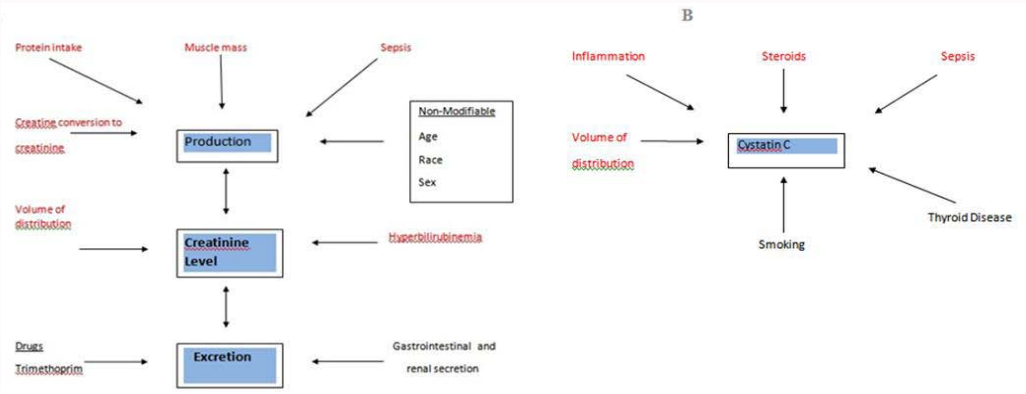

Figure 1: (A) Factors influencing creatinine and cystatin C levels in cirrhosis. (B) Factors that are most significant are highlighted in red.

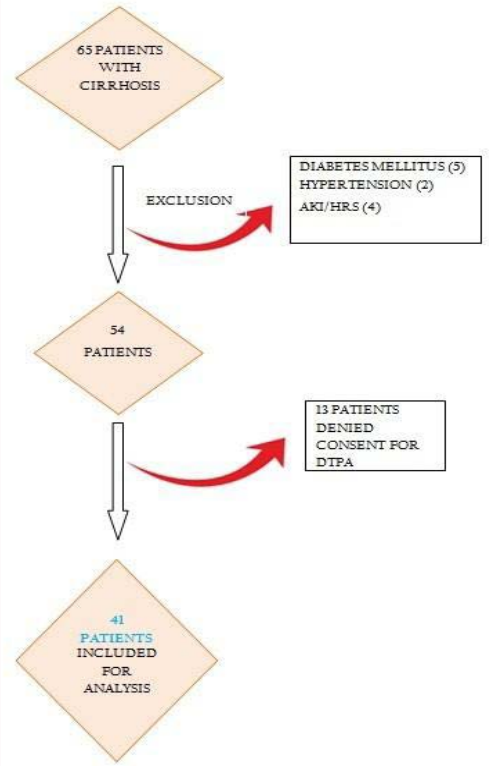

Figure 2: Patient selection.

calculated for all patients (Table 1). Simultaneous plasma samples for creatinine and cystatin C were collected and ^{99}Tc DTPA renal dynamic scintigraphy was done in 41 patients with informed consent. The study was approved by the institutional ethics committee.

Patient selection

Patient selection is in Figure 2.

Measurement of plasma creatinine (Pcr) and plasma cystatin C (PcysC): Serum creatinine was measured by kinetic Jaffe's method, using an automated biochemical analyzer (Roche Cobas c311) and commercially available assay kits by the same manufacturer. This assay uses "rate-blanking" to minimize interference by bilirubin. A correction factor is built-in for non-specific reactions due to pseudo-creatinine chromogens like proteins and ketones. The assay was standardized against IDMS. The detection limit was 0.17 mg/dl.

Normal reference interval of creatinine:

- Adult Males: 62 µmol/L to 106 µmol/L (0.7 mg/dl to 1.2 mg/dl)
- Females: 44 µmol/L to 80 µmol/L (0.5 mg/dl to 0.9 mg/dl)

Serum cystatin C was measured by a Particle-Enhanced Turbidimetric Immunoassay (PETIA) with a commercially available reagent set (Proton Biological, India) and read using semi-autoanalyzer (Biosystem BTS-350). The detection limit was 0.1 mg/L. The intra- and interassay coefficient of variation (CV's; n=20) determined at 1.71 mg/L were <1.12% and <2.01% at 3.54 mg/L. Cystatin C measuring range was 0.2 mg/L to 8.0 mg/L.

Normal reference interval of cystatin C: 0.56 mg/L to 1.25 mg/L (as per package insert).

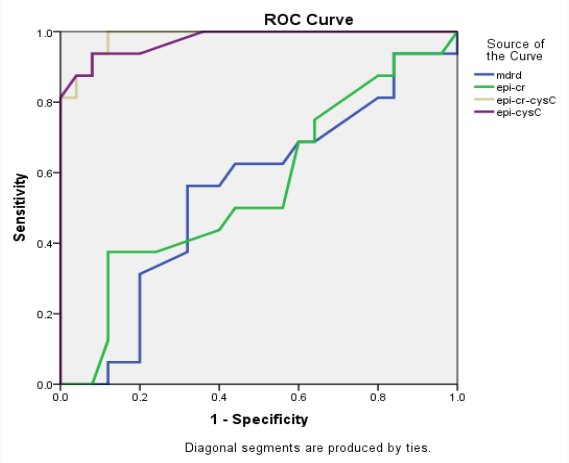

Figure 3: ROC plot of all eGFR equations.

mGFR measurement

mGFR was measured by ^{99}Tc DTPA renal scintigraphy using revised Gates equation as below.

% Renal DTPA uptake= $\{((RK-RB)/e^{-\mu RD}) + ((LK-LB)/e^{-\mu RD})\} \times 100$/injected counts

Revised gates equation:

Revised GFR (ml/min) = (%renal uptake × 11.7773)-0.7354

Where RK is the number of counts from the right kidney, RB is the number of counts in the right kidney background, RD is the renal depth of the right kidney (in centimeters), LK is the number of counts from the left kidney, LB is the number of counts from the left kidney background, LD is the renal depth of the left kidney (in centimeters), and µ is the attenuation coefficient of Tc-99m in soft tissue (0.153/cm).

eGFR estimation

All estimated GFRs were calculated using standardized formulae given in Table 1.

Statistical analysis

The parameters for assessment of eGFR equations in comparison to mGFR were based on Kidney Disease Improving Global Outcomes (KDIGO) and national kidney foundation Kidney Disease Outcome Quality Initiative (K/DOQI) practice guidelines [11].

1. Bivariate correlation between eGFR and mGFR was tested by Pearson's correlation coefficient (r). Lin's Concordance Correlation Coefficient (CCC) was also calculated.

2. Bias, precision and accuracy of each eGFR equation was calculated. Bias (mean mGFR-eGFR) and precision was calculated by Root Mean Square Error (RMSE) between eGFR and mGFR values. Accuracy was measured as percentage of eGFRs varying by <10% (P10) and <30% (P30) from the corresponding mGFR value.

3. Receiver Operating Characteristic (ROC) plots were constructed and sensitivity and specificity at the cut-off value 60 ml/min/1.73 m^2 were calculated based on Area Under the Curve (AUC).

4. Bland-Altman plot was used to analyze agreement between eGFR and mGFR.

Table 3: Baseline Demographics of 41 patients analysed according to MELD severity of liver disease.

Patient Characteristics	All patients (n= 41)	MELD<20 (n=17)	MELD ≥ 20 (n=24)	Significance
Age - Median (IQR) in years	45 (40-54)	45 (40-54.5)	47.5 (40-54.5)	NS
Men: Women	M 39; F 2	M 17; F 0	M 22; F 2	
Height-Mean ± SD in cms	163.34 (7.1)	164 (6.2)	162.4 (7.6)	NS
Weight - Mean ± SD in Kg	60.8 (10.9)	61.3 (7.9)	60.5 (12.8)	NS
BMI -Mean ± SD in kg/m^2	22.72 ± 3.3	22.54 ± 2.16	22.84 ± 3.94	NS
BSA -Mean ± SD in m^2	1.65 ± 0.17	1.67 ± 0.14	1.67 ± 0.14	NS
SBP Median (IQR) in mmHg	120 (110-130)	120 (110-130)	120 (110-130)	NS
DBP Median (IQR) in mmHg	70 (70-80)	70 (70-80)	80 (70-80)	NS
Bilirubin - Median (IQR) in mg	4.4 (2.55-7.3)	1.6 (0.95-3.85)	6.8 (3.7-8.75)	Significant (p<0.05)
Sr Albumin - Median (IQR) in mg	3.2 (2.9-3.9)	3.0 (2.9-3.65)	3.4 (2.9-4.0)	NS
INR - Median (IQR)	1.9 (1.65-2.3)	1.8 (1.65-2.0)	2.1 (1.6-2.3)	NS
Platelet - Median (IQR) in lakhs	1.3 (0.92-2.0)	1.3 (1.2-1.95)	1.3 (0.56-2.07)	NS
Cr - Median (IQR) in mg/dl	0.9 (0.8-0.9)	0.8 (0.8-0.9)	0.9 (0.8-0.9)	NS
Cys-C -Median (IQR) in mg/L	2.2 (1.5-2.5)	1.9 (1.3-2.3)	2.3 (1.5-2.65)	Significant (p<0.05)
Measured GFR(mGFR) - Mean ± SD; in ml/min/1.73 m^2	55.22 ± 16.4	60.7 ± 15	51.3 ± 16.5	NS
MDRD- Mean ± SD in ml/min/1.73 m^2	97.8 ± 16.9	102.24 ± 16.3	94.75 ± 16.9	NS
CKD-EPI-Cr- Mean ± SD; in ml/min/1.73 m^2	103.07 ± 10.3	106.2 ± 8.3	100.9 ± 11.15	NS
CKD-EPI-Cr-CysC - Mean ± SD; in ml/min/1.73 m^2	57.56 ± 14.8	63.3 ± 15	53.5 ± 13.5	NS
CKD-EPI-CysC - Mean ± SD; in ml/min/1.73 m^2	36.1 ± 17.2	41.76 ± 18.4	32.08 ± 15.36	NS

BMI: Body Mass Index; BSA: Body Surface Area (Dubois); SBP: Systolic BP; DBP: Diastolic BP

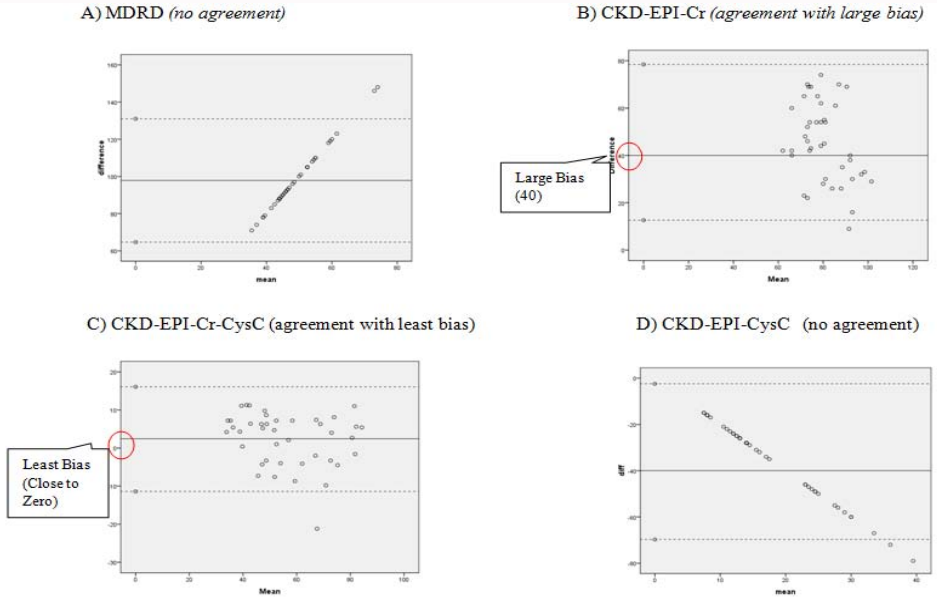

Figure 4: Bland-Altman plots showing, for each formula, the estimated GFR minus the measured GFR, bias (in ml/min/1.73 m^2) in function of the measured GFR (Tc DTPA in ml/min/1.73 m^2) as reference standard in the whole population. The solid line represents the mean ratio. The broken lines represent the 95% limits of agreement (± 1.96 × standard deviation).

Statistical software used was SPSS for Windows (Version 23) and R studio. p value less than 0.05 was taken as significant.

Results

Patients

^{99}Tc DTPA values of all patients according to GFR category is shown in Table 2. Sixty one percentages of patients had GFR ≤ 60 ml/min/1.73 m^2 signifying moderate to severe renal dysfunction. Three patients had GFR <30 ml/min/1.73 m^2. The baseline characteristics of 41 patients are shown in Table 3. Thirty nine subjects were males (95%). The mean MELD score was 20.8 signifying advanced cirrhosis and 59% of patients had MELD score more than 20. Mean measured GFR of 41 patients was 55.2 ± 16.4 ml/min/1.73 m^2 (Mean ± SD). The mean mGFR values were lower among those with MELD score ≥ 20 (51.3 ± 16.5 ml/min/1.73 m^2) *vs.* MELD <20 (60.7 ± 15 ml/min/1.73 m^2), though it is not statistically significant. The median cystatin C values also differed between both MELD groups and this was statistically significant (p<0.05).

Table 4: Performance parameters of GFR predicting equations in the whole population and according to MELD scores.

Performance Criteria	Mean DTPA GFR	MDRD	CKD-EPI-Cr	CKD-EPI-Cr-CysC	CKD-EPI-CysC
All patients (n=41)					
eGFR		97.8 ± 16.9	103.07 ± 10.3	57.56 ± 14.8	36.1 ± 17.2
Correlation (r)	**55.2 ± 16.4**	0.04	0.18	0.9[s]	0.87[s]
CCC (95% CI)		0.04 (-0.02,0.34)	0.17 (-0.13,0.46)	0.9 (0.827,0.947)	0.86 (0.76,0.92)
P30 (%)		2.4	0	78	36.5
P10 (%)		0	0	31.7	19.5
MELD <20 (n =17)					
eGFR		102.24 ± 16.3	106.2 ± 8.3	63.3 ± 15	41.76 ± 18.4
Correlation(r)	**60.7 ± 15**	0.002	-0.04	0.87[s]	0.84[s]
P30 (%)		0	0	76.4	47
P10 (%)		0	0	35.2	29.4
MELD ≥ 20 (n=24)					
eGFR		94.75 ± 16.9	100.9 ± 11.15	53.5 ± 13.5	32.08 ± 15.36
Correlation(r)	**51.3 ± 16.5**	-0.02	0.19	0.92[s]	0.88[s]
P30 (%)		0	0	83.3	25
P10 (%)		0	0	54.1	20.8

r: Pearson's Correlation Coefficient; CCC: Lin's Concordance Correlation Coefficient; 95% CI: Confidence Intervals; P105 and P30%: Proportion of Estimates Falling Within the Interval mGFR ± 10% and mGFR ± 30%; superscript s: statistical significance

Correlation, sensitivity and specificity

Pearson's correlation coefficient showed strong positive correlation between CKD-EPI-Creatinine-CysC (r=0.9), CKD-EPI-CysC (r=0.87) equations and measured GFR (p<0.001). Lin's Concordance Correlation Coefficient (CCC) confirmed these results (Table 4). The positive correlation between these variables was consistent independent of MELD scores. ROC curves of eGFRs were constructed (Figure 3). CKD-EPI-Creatinine-CysC and CKD-EPI-CysC had the best performance with highest Area under the Curve (AUC). Among the two equations, CKD-EPI-Creatinine-CysC had superior sensitivity (87.5%) and specificity (96%) whereas CKD-EPI-Cystatin C had poor sensitivity (31.3%) in spite of 100% specificity (Table 5). eGFRs based solely on creatinine, MDRD and CKD-EPI-Cr had the least AUC (0.546 and 0.559 respectively).

Bias, precision, accuracy and Bland Altman agreement

Mean bias was least (-2.3) and precision calculated as root mean square of error was also lowest (7.1) for CKD-EPI-Creatinine-CysC equation (Table 6). P30 accuracy of CKD-EPI-Creatinine-CysC eGFR was 78% in the entire population and improved to 83.3% in the group with higher MELD score. The same equation showed the best agreement with mGFR on Bland-Altman plot (Figure 4).

Discussion

Renal failure worsens the prognosis of patients with liver cirrhosis and contributes to a 7-fold rise in mortality [12]. Serum creatinine is included in MELD scoring system to prioritise patients for liver transplant worldwide [13]. In a study of 70 cirrhosis patients, Omar et al. [14] demonstrated that creatinine based eGFRs overestimate renal function and have poor sensitivity and specificity (MDRD; 72.7%, 54.2% and CKD-EPI-Cr; 77.3%, 55.2% respectively). GFR measurements by Haddadin have shown superior diagnostic accuracy of Cystatin C-based equations over others comparing with ^{99}Tc DTPA GFR in cirrhosis. Although inulin is the gold standard for GFR measurement, ^{99}Tc DTPA scintigraphy is a reasonably accurate, easily available and practical alternative to measure GFR. ^{99}Tc DTPA has been employed as reference GFR by Omar et al. [14] (70 patients) and Kim et al. [18] (89 patients) in patients with cirrhosis. The findings of these studies are in line with Western reports using inulin [15], iohexol [16], 51Cr EDTA [17] and justifies the usage of ^{99}Tc DTPA as a close approximate of mGFR in resource limited settings.

The present study was a single centre experience at a tertiary care centre catering to predominantly South Indian population. All patients had serum creatinine values <1 mg/dl. Unlike similar studies performed in Western countries [14,19], alcohol was the most common etiology for liver cirrhosis and viral hepatitis contributed only 12% to the total. The mean measured GFR (55.22 ml/min/1.73 m^2) was lower than that reported in similar papers. Sixty one percentage of patients were categorized to moderate and severe renal dysfunction (GFR <60 ml/min/1.73 m^2). The GFR ranged between 28 ml/min/1.73 m^2 to 55 ml/min/1.73 m^2 in this low GFR group. Nearly seven percent patients had stage 4 CKD. This finding highlight that significant renal failure is not uncommon in advanced cirrhosis even with a normal creatinine. The magnitude of under-recognized renal dysfunction in this population is alarming and has therapeutic implications for the treating physician. Mean mGFR was lower (51.3 ± 16.5 ml/min/1.73 m^2) in the subgroup with higher MELD scores. Similar findings were reported by Souza et al. [15] who classified patients by the degree of ascites. Those cirrhotics with refractory ascites had statistically significant lower mGFR values in his population (59 ml/min/1.73 m^2 *vs*. 83 ml/min/1.73 m^2). In our study, while serum creatinine was less than 1 mg/dl in both MELD groups median serum cystatin C values were significantly higher in the group with higher MELD scores

Table 5: Performance of formulas at GFR 60 ml/min/1.73 m^2, sensitivity and specificity based on ROC.

GFR predicting equation	AUC	Sensitivity	Specificity	P value
MDRD	0.55	100%	0	0.621
CKD-EPI-Cr	0.56	100%	0	0.53
CKD-EPI-Cr-CysC	0.99	87.50%	96%	<0.001
CKD-EPI-CysC	0.98	31.30%	100%	<0.001

Table 6: Precision and bias of all equations in the population.

GFR predicting equation	Bias (in ml/min/1.73 m^2)	Precision (in ml/min/1.73 m^2) by RMSE	Ability to correctly predict patients GFR above or below 60 ml/min/1.73 m^2
MDRD	-34.3	25.37	37.80%
CKD-EPI-Cr	-47.85	17.73	39%
CKD-EPI-Cr-CysC	-2.3	7.1	93.30%
CKD-EPI-CysC	19.1	8.7	100%

CKD-EPI-Cr-CysC had least bias, least root mean square error i.e. best precision. CKD-EPI-CysC equation was precise but had a large bias.

(2.3 mg/L *vs.* 1.9 mg/L; p<0.05). Lower mGFR and higher cystatin C in this subgroup, confirms the results of Ustundang et al. [20] that cystatin C levels correlate with GFR in each stage of liver failure and has diagnostic advantage in cirrhosis.

Creatinine based equations, MDRD and CKD-EPI-Cr consistently overestimated renal function. These equations had poor P10 and P30 accuracy and large bias. Discriminative ability at 60 ml/min GFR for MDRD and CKD-EPI-Cr were abysmal (37.8% and 39% respectively). These results match the conclusions of previous studies that creatinine based eGFRs are misleading and underestimate renal dysfunction in cirrhosis. In comparison, both KDIGO 2012 Cystatin C based equations performed better across all stages of liver disease in our study. Among them, CKD-EPI-Cr-CysC equation had the best precision and highest P10 and P30 accuracy when compared with CKD-EPI-CyC formula (Table 6). Bland-Altman graphs also showed least mean bias and best agreement with the measured GFR favoring the CKD-EPI-Cr-CysC equation (Figure 4). The diagnostic ability to detect CKD as a GFR below 60 ml/min/1.73 m^2 was highest with CKD-EPI-Cr-CysC equation (93.3%) compared to other test formulas as demonstrated by best ROC plots (AUC-0.985; sensitivity-87.5%; specificity-96%)(Table 6). The study from Omar et al. [14] with similar methodology, has also reported superiority of CKD-EPI-Cr-CysC with sensitivity 77.3% and specificity 61.4%.

Our study has several strengths. Carefully structured inclusion and exclusion criteria enabled us to enroll a homogenous population with advanced cirrhosis. Those with exposures that could cause acute changes in renal function (recent use of aminoglycosides and NSAIDs) or influence cystatin C values (thyroid disease, diabetes and steroid use) were excluded. Cystatin C estimation was done by Particle Enhanced Turbidimetric Immunoassay (PETIA) which has shown good agreement with Chromium-51 labeled Ethylenediamine Tetraacetic Acid (^{51}Cr-EDTA) GFR in published reports [21]. The results of our study are robust even though the sample size was relatively small because we have used the isotopic GFR as reference. ^{99}Tc-DTPA is relatively inexpensive, has low radiation dose and its clearance correlates well with ^{51}Cr-EDTA, the radionuclide of choice for GFR measurement [22]. Recent reports in 2015 from Kim et al. [23] in a post nephrectomy population have shown that ^{99}Tc-DTPA scintigraphy by revised gates equation correlated well with ^{51}Cr-EDTA GFR's and was not inferior to iothalamate or iohexol measurements especially in patients with low GFR values.

The study has certain limitations. All participants were from a single centre of uniform ethnicity and predominantly alcoholic cirrhosis. The sample size, though statistically adequate, was smaller than some other validation studies of estimating equations. The volume of distribution and kinetics of ^{99}Tc-DTPA into the third space in cirrhosis have not been studied adequately. Actually, such a flaw should result in systematic overestimation of GFR rather than its underestimation.

Based on our study, in patients with advanced cirrhosis, we suggest physicians to consider combined creatinine and cystatin C-based equation when a true estimate of GFR is required.

Conclusions

1. Sixty one percent of patients with advanced cirrhosis had significant renal dysfunction (GFR ≤ 60 ml/min/1.73 m^2) by ^{99}Tc-DTPA despite normal serum creatinine. Serum creatinine and creatinine based eGFR is fallacious and misleading in cirrhosis.

2. Cystatin C can unmask renal failure in these patients. CKD-EPI-Creatinine-CystC equation showed the best correlation and accuracy with DTPA GFR in our study.

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