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Comparative study of various glomerular filtration rate estimating equations in Egyptian patients with hepatitis C virus-related liver cirrhosis: a single-center observational study

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Abstract

Background: Accurate assessment of GFR is critical in patients with chronic liver disease for early detection of renal disease. Cystatin C is a marker of GFR that seems to be more accurate than creatinine. The aim of the study is to assess of the performance of creatinine and cystatin C-based GFR equations in Egyptian patients with hepatitis C virus (HCV)-related liver cirrhosis as compared to measured creatinine clearance. GFR was estimated using five equations; three that were based on serum creatinine, another that was based on serum cystatin C, and a third that was based on both in 120 patients with HCV-related liver cirrhosis as well as 60 age- and sex-matched healthy controls. The bias, precision, and accuracy of each equation were determined as compared to measured creatinine clearance using the traditional equation U*V/P.

Results: The mean measured creatinine clearance was 51.39 ± 16.05 ml/min per 1.73 m^2. The CKD-EPI creatinine-cystatin C equation had the greatest precision (7.5 ml/min per 1.73 m^2), and highest accuracy (68 and 93% within 10% and 30% of measured GFR, respectively), but not the lowest bias (5.4 ml/min per 1.73 m^2). The CKD-EPI creatinine-cystatin C equation remained accurate even in both males (69 and 90% within 10% and 30% of measured GFR, respectively) and females (68 and 97% within 10% and 30% of measured GFR, respectively). The CKD-EPI creatinine-cystatin C equation remained accurate even when the measured GFR was ≥ 60 ml/min per 1.73 m^2 (60 and 90% within 10% and 30% of measured GFR, respectively with precision 10.5 ml/min per 1.73 m^2).

Conclusion: CKD-EPI creatinine-cystatin C equation is more accurate at predicting GFR in HCV-related liver cirrhosis than creatinine- and cystatin-C alone based equations.

Keywords: Cystatin C, Liver cirrhosis, Estimated glomerular filtration rate, Renal dysfunction

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Background

Renal dysfunction is one of the common complications in patients with chronic liver disease with dismal impact on the patients' survival [1]. The incidence of renal dysfunction increases with the advancement of liver cirrhosis and the worsening in portal hypertension [2]. Serum creatinine is included in the Model for End Stage Liver Disease (MELD) Score, which is currently used for assessment of severity of liver disease and prioritization for liver transplantation which reflects the pivotal prognostic role of renal function in cirrhosis [3]. There is an urgent need for early and precise detection of impaired glomerular filtration rate (GFR) in cirrhotic patients, especially in those suffering from acute on chronic liver failure (ACLF) and being evaluated for liver transplantation, and in patients with refractory hepatic encephalopathy.

GFR is largely accepted as the best overall index of renal function. The GFR cannot be measured directly but can be assessed from the measured clearance of exogenous and endogenous filtration markers of which creatinine and cystatin C are the most commonly used. The 2012 Kidney Disease Improving Global Outcomes (KDIGO) guidelines recommend eGFR for routine evaluation of GFR and support the use of serum cystatin C in estimating GFR in situations where serum creatinine is unreliable. Measured GFR (mGFR) is recommended as a confirmatory test when more accuracy is needed [4].

Serum creatinine concentration is affected by several factors other than GFR, and different laboratories use different methods for measurement of serum creatinine which make results difficult to compare. Creatinine is a by-product of muscle metabolism in which creatine in the muscle is converted nonenzymatically to creatinine. Synthesis of creatinine from creatine is not constant since it is affected by the daily intake of protein and by muscle turnover. Using creatinine (Cr)-based methods to estimate GFR in advanced liver disease (ALD) patients has limitations for multiple reasons. Creatine production is decreased with the decline in hepatic functional capacity resulting in lower serum Cr levels. Patients with ALD are known to have less skeletal muscle mass, resulting in diminished creatine storage and less conversion of creatine to Cr. All of these factors lead to a decreased serum Cr level in ALD patients, making Cr an unreliable factor in estimating GFR [5]. Also, the increase in serum creatinine is often delayed 48–72 h behind the onset of injury [6]. Analytical methods used to determine the serum Cr concentration can also result in variability in Cr levels. The kinetic Jaffe method is commonly used to measure serum Cr levels and can be interfered with by elevated serum bilirubin levels, resulting in false low Cr levels [7].

Inulin clearance, the standard method for measuring the GFR, is inappropriate for practical use because of cost and complicated 24-h urinary catheterization [8]. Radio-isotopic renal scans cost is high, and they cannot be used for repeated measurements. Creatinine clearance tends to overestimate the GFR and requires accurate urine volume measurement [9]. Creatinine-based equations for estimation of GFR, Cockcroft-Gault formula and modification of diet in renal disease (MDRD), and CKD-EPI equations are of limited value in cirrhotic patients as they overestimate the GFR as well [10].

Serum cystatin C (CysC) is a low molecular weight protein (12.8 kDa) that functions as an extracellular cysteine protease inhibitor that has a constant rate of production and is freely filtered across renal glomeruli. However, it is completely reabsorbed and metabolized by the proximal tubular cells without secretion [11]. Several studies suggested that serum cystatin C is a better alternative to serum creatinine, with constant rate of production and fewer non-GFR determinants independent of GFR, despite they are frequently present in patients with cirrhosis such as elevated CRP or low serum albumin levels. Recent findings suggest that GFR may be more effectively estimated using cystatin C as a supplement or replacement for serum creatinine [12]. In the general population, serum cystatin C shows stronger associations than serum creatinine with cardiovascular disease (CVD) and all-cause mortality [13].

We compare the bias, precision, and accuracy of different equations that estimate glomerular filtration rate based on serum creatinine, cystatin C and both as compared to measured creatinine clearance for the detection of kidney disease in liver cirrhosis related to HCV Egyptian patients.

Methods

Study participants

The study was reviewed and approved by the Minia University Faculty of Medicine Research ethics committee (Approval NO. 186: 6/2016) and was conducted in accordance with the Helsinki Declaration. Informed consent was obtained from all participants. This study was an observational hospital-based, cohort study to compare the accuracy of different glomerular filtration rate equations based on creatinine, cystatin C, and both as valuable tools in the detection of kidney disease in liver cirrhosis related to HCV in Egyptian patients; with the participants being recruited from the Internal Medicine Department of Minia University hospital. The study enrolled 120 patients with hepatitis C virus (HCV)-related liver cirrhosis, as well as 60 age- and sex-matched healthy controls. The diagnosis of cirrhosis was based on a combination of physical examination, laboratory tests, and abdominal ultrasonography. The *inclusion criterion*

was HCV-related liver cirrhosis in adult patients > 18 years old of both genders. The exclusion criteria for patients and healthy controls were acute viral or bacterial infection, primary renal disease or hepatorenal syndrome (HRS), chronic obstructive pulmonary disease (COPD), diabetes mellitus, thyroid dysfunction, active GIT bleeding or gastrointestinal bleeding during the month before enrollment, hepatocellular carcinoma, congestive heart failure (CHF), amputation of whole or part-limb, medications use including corticosteroids, antiviral drugs, angiotensin-II receptor blockers, angiotensin-converting enzyme inhibitors, aminoglycosides, nonsteroidal anti-inflammatory drugs (NSAIDs), and L-ornithine-L-aspartate.

Primary outcome measures

Percentage of estimated glomerular filtration rate values within 30% of 'true' measured glomerular filtration rate were compared. The accuracy of glomerular filtration rate (GFR) estimating equations was commonly expressed as the P30 value, the percentage of estimated GFR values within 30% of 'true' GFR. The study estimated and compared the accuracy and precision of GFR-estimating equations based on Cockcroft-Gault formula, the modification of diet in renal disease (MDRD) equation, and three Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations using either creatinine or cystatin C or a combination of both in patients with liver cirrhosis related to HCV expressed as the P30 value. Cockcroft-Gault Formula was calculated with the following formula: $(140 - age) \times weight/72 \times Scr \times 0.85$ [if female]. MDRD creatinine equation was calculated with the following formula: $175 \times plasma\ creatinine^{-1.154} \times age^{-0.203}$ ($\times 0.742$ if female; $\times 1.21$ if black). CKD-EPI creatinine equation was calculated using the following formula: $141 \times min(Scr/\kappa, 1)^{\alpha} \times max(Scr/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female] $\times 1.159$ [if black], where Scr is serum creatinine, κ is 0.7 for females and 0.9 for males, $^{\alpha}$ is -0.329 for females and -0.411 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1. CKD-EPI cystatin C equation was calculated using the following formula: $133 \times min(Scys/0.8, 1)^{-0.499} \times max(Scys/0.8, 1)^{-1.328} \times 0.996^{Age} \times 0.932$ [if female], where Scys is serum cystatin C, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1. Creatinine-Cystatin C equation was calculated using the following formula: $135 \times min(Scr/\kappa, 1)^{\alpha} \times max(Scr/\kappa, 1)^{-0.601} \times min(Scys/0.8, 1)^{-0.375} \times max(Scys/0.8, 1)^{-0.711} \times 0.995^{Age} \times 0.969$ [if female] $\times 1.08$ [if black] where Scr is serum creatinine, Scys is serum cystatin C, κ is 0.7 for females and 0.9 for males, α is -0.248 for females and -0.207 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1.

Every participant was educated on proper techniques for 24-h urine collection and provided with a detailed patient education pamphlet. One day prior to visit 2, each subject completed a 24-h urine collection for timed urine creatinine clearance using the formula urine creatinine/serum creatinine multiplied by 24-h urine volume (UCr/PCr) × V. This was divided by 1440 to get the value in ml/min.

Measurement of serum cystatin C (CysC) using a two-site second-generation enzyme-linked immunosorbent assay (ELISA) kit (*Wkea Med Supplies Corp, China*) was done. The microtiter plate was coated with monoclonal purified human anti-cystatin C antibody. Fifty microliters of standards or samples are added to the appropriate microtiter plate wells and incubate for 30 min at 37 °C. Remove the liquid of each well; add 50 μl of a biotin-conjugated polyclonal goat anti-CysC antibody (Detection Reagent A) to each well and incubate for 30 min at 37 °C. Aspirate each well and wash with wash buffer, repeating the process three times for a total of three washes, followed by the addition of 100 μl of Avidin conjugated to horseradish peroxidase (HRP) (Detection Reagent B) to each microplate well and incubated for 1 h at 37 °C. Color development was achieved using a 90 μl TMB substrate solution is added to each well and incubated for 15 min at 37 °C. Only those wells that contain biotin-conjugated antibody and enzyme-conjugated Avidin will exhibit a change in color. The enzyme-substrate reaction is terminated by the addition of 50 μl sulfuric acid solution and the color change is measured spectrophotometrically at a wavelength of 450 ± 2 nm. Serial dilutions of human CysC were used to establish a standard curve. Laboratory measurements were performed at Clinical Pathology Laboratory at the Minia University Hospital. Assay range is 30 μg/L up to 800 μg/L with the intra-assay CV (%) and inter-assay CV (%) are less than 15%.

Other measurements

Demographic data, weight, height, BMI, detailed history, and thorough physical examination were obtained at enrollment. Urinalysis with microscopy was performed before the timed urine collection for GFR measurement. Complete blood count, liver function tests, renal function tests, thyroid function tests, fasting and postprandial plasma glucose, and serum alpha fetoprotein were obtained at enrollment. Complete blood count, liver function tests, urea, creatinine, and uric acid were measured using stored ethylenediaminetetraacetic acid (EDTA) plasma samples using standard techniques. CBC was obtained using *Mindray BC-3200 auto hematology counter* (Shenzhen Mindray Bio-Medical Electronics Co., Ltd. China). Serum albumin was measured using *spectrophotometry*. Liver function tests, urea, creatinine, and uric

Table 1 Baseline and demographic data

	HCV group (*n* = 120)	Control group (*n* = 60)	*p* value
Age (years)			
Range	(45–68)	(42–72)	0.274
Mean ± SD	58.05 ± 5.91	56.43.1 ± 7.75	
Sex (frequency)			
Male	58 (48.3%)	30 (50%)	0.881
Female	62 (51.7%)	30 (50%)	
Weight (kg)			
Range	(67–98)	(65–95)	0.239
Mean ± SD	81.5 ± 7.31	79.53 ± 7.65	
Height (cm)			
Range	(154–180)	(155–175)	0.756
Mean ± SD	164.65 ± 6.51	164.2 ± 6.38	
Body surface area (m^2)			
Range	1.92 ± 0.09	1.9 ± 0.1	0.141
Mean ± SD	(1.69–2.09)	(1.73–2.1)	
BMI (kg/m^2)			
Range	(22.84–38.05)	(24.45–35.3)	0.435
Mean ± SD	30.19 ± 3.49	29.59 ± 3.35	
Serum creatinine (mg/dl)			
Range	(0.78–2.3)	(0.45–0.8)	< 0.001*
Mean ± SD	1.31 ± 0.35	0.64 ± 0.1	
Blood Urea (mg/dl)			
Range	(1.38–137.23)	(18–40)	< 0.001*
Mean ± SD	44.83 ± 22.06	27.03 ± 5.32	
Serum cystatin C (μg/L)			
Range	(0.9–4.2)	(0.55–1.1)	< 0.001*
Mean ± SD	1.79 ± 0.61	0.72 ± 0.11	
Serum sodium (mEq/L)			
Range	(128–153)	(134–145)	0.155
Mean ± SD	138.9 ± 4.34	137.67 ± 2.55	
Serum potassium (mEq/L)			
Range	(3–6)	(3.40–4.50)	0.005*
Mean ± SD	4.06 ± 0.47	3.85 ± 0.21	
Fasting plasma glucose (mg/dl)			
Range	(65–110)	(75–100)	0.155
Mean ± SD	83.22 ± 11.55	86 ± 6.78	
2 h postprandial plasma glucose (mg/dl)			
Range	(3.80–140)	(96–120)	0.002*
Mean ± SD	115.91 ± 23.3	105.57 ± 6.16	
RBCs (× 10^6/mm^3)			
Range	(2.25–5.5)	(3.9–6.2)	< 0.001*
Mean ± SD	3.61 ± 0.6	5.17 ± 0.59	
HB (g/dl)			
Range	(5.8–15.1)	(8.6–15)	< 0.001*
Mean ± SD	9.89 ± 1.79	12.6 ± 1.43	
[a]Platelets (× 10^3/mm^3)			

Table 1 Baseline and demographic data *(Continued)*

	HCV group (*n* = 120)	Control group (*n* = 60)	*p* value
Median	113.5	330.5	< 0.001*
IQR	(92–180.5)	(289–361)	
WBCs ($\times 10^3/mm^3$)			
Range	(2.90–11.2)	(3.4–8.4)	0.554
Mean ± SD	6.24 ± 2.03	6 ± 1.4	
[a]Total bilirubin (mg/dl)			
Median	1.5	0.4	< 0.001*
IQR	(1.1–2.4)	(0.3–0.4)	
[a]Direct bilirubin (mg/dl)			
Median	0.8	0.2	< 0.001*
IQR	(0.4–1)	(0.2–0.3)	
[a]AST (IU/L)			
Median	54.5	22	< 0.001*
IQR	(39.4–84)	(18–24)	
[a]ALT (IU/L)			
Median	44.5	23.5	< 0.001*
IQR	(32.5–67.2)	(22–27)	
Albumin (g/dl)			
Range	(1.5–4.85)	(4.18–4.9)	< 0.001*
Mean ± SD	2.63 ± 0.64	4.56 ± 0.24	
INR			
Range	(1.03–2.85)	(0.98–1.02)	< 0.001*
Mean ± SD	1.63 ± 0.53	1 ± 0.01	
Creatinine clearance (ml/min per 1.73 m^2)			
Range	(20–87.8)	(85–138)	< 0.001*
Mean ± SD	51.39 ± 16.05	113.9 ± 12.74	
Cockcroft-Gault formula (ml/min per 1.73 m^2)			
Range	(33–108)	(69–202)	< 0.001*
Mean ± SD	70.33 ± 20.4	121.17 ± 38.29	
MDRD (ml/min per 1.73 m^2)			
Range	(25–98)	(88–225)	< 0.001*
Mean ± SD	52.78 ± 15.84	126.83 ± 29.14	
CKD-EPI (ml/min per 1.73 m^2)			
Range	(26–95)	(103–155)	< 0.001*
Mean ± SD	56.1 ± 17.24	121.4 ± 12.04	
CKD-EPI creatinine-cystatin C (ml/min per 1.73 m^2)			
Range	(16–79)	(97–161)	< 0.001*
Mean ± SD	45.95 ± 14.82	123.77 ± 14.52	
CKD-EPI cystatin C (ml/min per 1.73 m^2)			
Range	(11–87)	(78–164)	< 0.001*
Mean ± SD	40.55 ± 16.68	119.57 ± 16.86	

Independent sample *t* test for parametric quantitative data between the two groups
*Significant difference at *p* value < 0.05
[a]Mann–Whitney test for non-parametric quantitative data between the two groups. Chi square test for qualitative data between the two groups

acid were measured using *Dimension ES chemical auto-analyzer* (Dade Behring, Marburg, Germany).

Serological tests for hepatitis virus B and C were done. Anti-HCV antibodies by enzyme-linked immunosorbent assay (ELISA) and detectable serum HCV–RNA by polymerase chain reaction for 6 months or more were needed to confirm the diagnosis of HCV infection. Abdominal ultrasound was done for all patients.

Statistical analysis
All statistical analyses were performed with Statistical Package for the Social Science (SPSS for windows version 25.0) (SPSS Inc., Tokyo, Japan). The continuous variables were expressed as mean ± SD which compared using chi square test. Pearson's correlation coefficient was used to estimate the correlation between each two variables. Statistical significance was defined as a probability level of $p < 0.05$. Bias was defined as the mean difference between measured and estimated GFR; precision was defined as the SD of the difference between measured and estimated GFR. Both precision and bias were expressed as ml/min per 1.73 m^2; accuracy was defined as the proportion of values that were within 10 or 30% of the measured GFR.

Results
A total of 120 patients with hepatitis C virus (HCV)-related liver cirrhosis who met the inclusion criteria and 60 healthy volunteers as a control group were included in this observational hospital-based, cohort study. The baseline characteristics of the cohort are presented in Table 1. Both groups are age- and sex-matched (58.05 ± 5.91 years vs. 56.43.1 ± 7.75 years; $p = 0.274$). There were 62 females and 58 male patients in the HCV group compared to 30 females and 30 males in the control group. The mean measured GFR in HCV patients using measured creatinine clearance was 51.39 ± 16.05 ml/min per 1.73 m^2 with a range of 20–87.8 ml/min per 1.73 m^2.

Correlation of eGFR formulas with mGFR
There was significant positive correlation between the measured creatinine clearance and estimated GFR formulas in HCV group Table 2.

Simple linear regression analysis
As regarding simple regression analysis, each GFR formula had a significant regression model for predicting the GFR (measured creatinine clearance is the reference model). The most predictive one is CKD-EPI creatinine-cystatin C equation ($R^2 = 0.785$), then CKD-EPI Cystatin C equation ($R^2 = 0.657$) (Table 3).

Table 2 Correlation between measured creatinine clearance and estimated GFR equations in HCV group

HCV group ($n = 120$)	Creatinine clearance	
	r	*p* value
Cockcroft-Gault	0.629	< 0.001*
MDRD	0.661	< 0.001*
CKD-EPI	0.685	< 0.001*
CKD-EPI creatinine-cystatin C	0.886	< 0.001*
CKD-EPI cystatin C	0.811	< 0.001*

Pearson's correlation coefficient
*Significant correlation at *p* value < 0.05

Multiple stepwise regression analysis
To improve the accuracy of prediction of GFR from different equations, multiple stepwise regression analysis was used. The most predictive model is CKD-EPI creatinine-cystatin C ($R^2 = 0.785$) (Table 4).

Bias, precision, and accuracy of estimated GFR
The performance of the various estimates of GFR is shown in Table 5 and Fig. 1. The MDRD equation had the least bias (– 1.4 ml/min per 1.73 m^2). Meanwhile, CKD-EPI creatinine-cystatin C equation had the best precision (7.5 ml/min per 1.73 m^2) the highest percentage of values that fell within 30% of the measured GFR (93%). In addition, 68% of GFR estimates fell within 10% of the measured GFR.

Performance of the derived mathematical equations according to sex
The performance of the various estimates of GFR in male patients of the HCV study group ($n = 29$) is shown in Table 6. The MDRD equation had the least bias (– 4 ml/min per 1.73 m^2). Meanwhile, CKD-EPI creatinine-cystatin C equation had the best precision (8.5 ml/min per 1.73 m^2), the highest percentage of values that fell within 30% of the measured GFR (90%). In addition, 69% of GFR estimates fell within 10% of the measured GFR.

The performance of the various estimates of GFR in female patients of the HCV study group ($n = 31$) is shown in Table 7. The MDRD equation had the least bias (1 ml/min per 1.73 m^2). Meanwhile, CKD-EPI creatinine-cystatin C equation had the best precision (6.5 ml/min per 1.73 m^2), the highest percentage of values that fell within 30% of the measured GFR (97%). In addition, 68% of GFR estimates fell within 10% of the measured GFR.

Performance of the derived mathematical equations in patients with GFR above and below 60 ml/min/1.73 m^2
The performance of the various estimates of GFR in patients of the HCV study group GFR ≥ 60 ml/min per

Table 3 Simple linear regression analysis for determine prediction of creatinine clearance by different GFR formulas

Model	Unstandardized coefficients		*p* value	*R*	R^2
	B	Std. error			
Constant	16.57	5.88	0.007*	0.629	0.396
Cockcroft-Gault	0.5	0.08	< 0.001*		
Constant	16.07	5.5	0.005*	0.661	0.436
MDRD	0.67	0.1	< 0.001*		
Constant	15.63	5.23	0.004	0.685	0.469
CKD-EPI	0.64	0.09	< 0.001*		
Constant	7.29	3.18	0.026*	0.886	0.785
CKD-EPI creatinine-cystatin C	0.96	0.07	< 0.001*		
Constant	19.76	3.24	< 0.001*	0.811	0.657
CKD-EPI cystatin C	0.78	0.07	< 0.001*		

1.73 m^2 (n = 20) is shown in Table 8. The CKD-EPI equation had the least bias (− 1.1 ml/min per 1.73 m^2). Meanwhile, CKD-EPI creatinine cystatin-C equation had the best precision (10.5 ml/min per 1.73 m^2), the highest percentage of values that fell within 30% of the measured GFR (90%). In addition, 60% of GFR estimates fell within 10% of the measured GFR.

The performance of the various estimates of GFR in patients of the HCV study group GFR < 60 ml/min per 1.73 m^2 (n = 40) is shown in Table 9. Both MDRD and CKD-EPI creatinine-cystatin C equation had the least bias (− 4.1 ml/min per 1.73 m^2 and 4.1 ml/min per 1.73 m^2 respectively). Meanwhile, CKD-EPI creatinine-cystatin C equation had the best precision (5 ml/min per 1.73 m^2), the highest percentage of values that fell within 30% of the measured GFR (95%). In addition, 73% of GFR estimates fell within 10% of the measured GFR.

Discussion
Our cross-sectional observational study has demonstrated that eGFR using CKD-EPI creatinine-cystatin C equation (eGFRcr-cys) provide results comparable to those measured by creatinine clearance with the best performance; meanwhile, creatinine and cystatin C-based equations were inaccurate for the assessment of renal function in cirrhotic patients. All methods of estimation of GFR have limitations in patients with liver cirrhosis with Cr-based equations tend to overestimate

mGFR, and CysC-based equations tend to underestimate mGFR. This is in accordance with a previous study that highlight the potential risk of unnecessary simultaneous liver and kidney transplantation in patients with end-stage liver disease with the use of CysC-based equations with consequent underestimation of GFR [14]. In a single-center cross-sectional study to assess the accuracy of creatinine or cystatin C-based equations to estimate kidney function in orthotopic liver transplant (OLT) recipients, neither serum creatinine nor cystatin C were good predictors of GFR in cirrhotic patients, even after stratification for Child-Pugh-Turcot (CPT) score, gender, and BMI [15].

Population diversity may play a role in the performance of the eGFR equations. This is suggested by a cross-sectional analysis from the eGFR of 654 indigenous Australians known to be at high risk of end-stage kidney disease (ESKD) that showed that CysC-based eGFR equations may not perform well in populations with high levels of chronic inflammation. CKD-EPI eGFR based on serum creatinine remains the preferred equation in indigenous Australians [16].

Table 4 Multiple stepwise linear regression analysis for determine the GFR formulas predicting the creatinine clearance revealed this model

Model	Unstandardized coefficients		P value	R	R^2
	B	Std. error			
Constant	7.29	3.18	0.026*	0.886	0.785
CKD-EPI creatinine-cystatin C	0.96	0.07	< 0.001*		

Table 5 Bias, precision, and accuracy of creatinine and cystatin C estimates in HCV study group (n = 120)

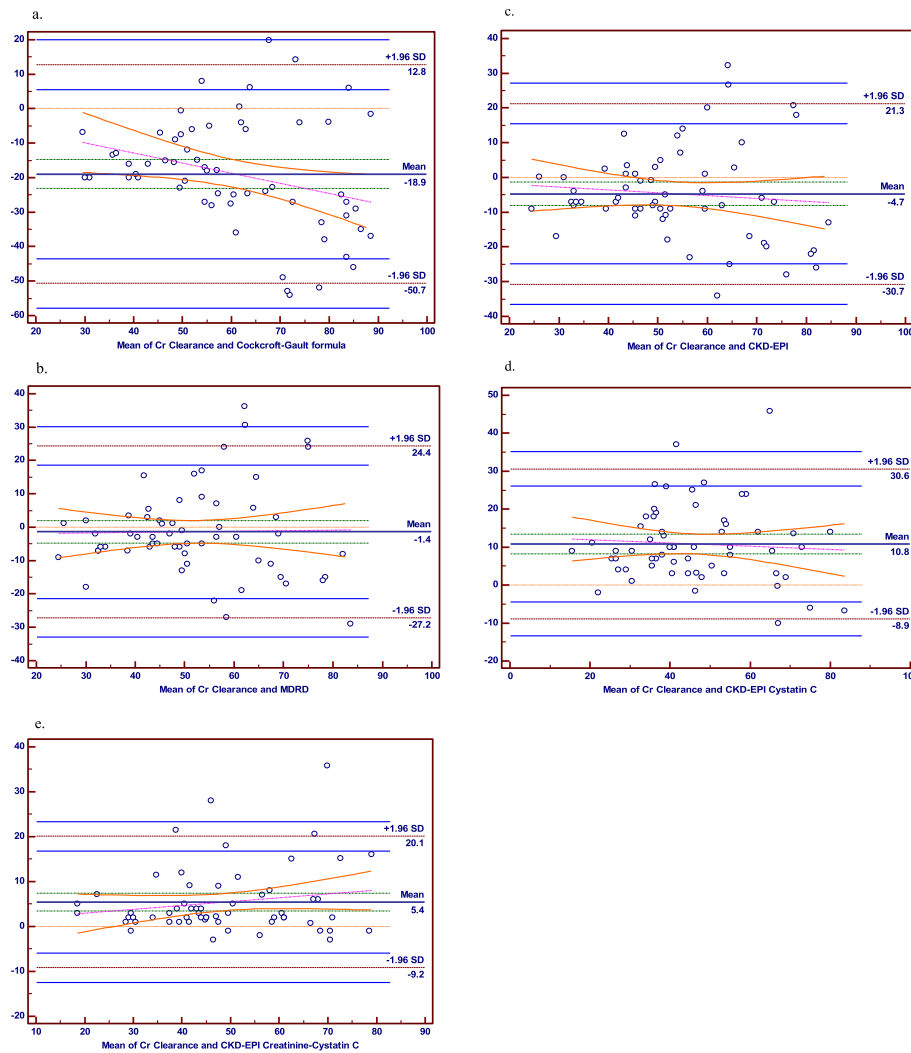|	Bias	Precision	Accuracy % within	
			10%	30%
Estimates using serum creatinine				
• Cockcroft-Gault	− 18.9	16.2	17	32
• MDRD	− 1.4	13.1	33	82
• CKD-EPI	− 4.7	13.3	27	78
Estimates using both serum creatinine and cystatin C				
• CKD-EPI creatinine-cystatin C	5.4	7.5	68	93
Estimates using serum cystatin C				
• CKD-EPI cystatin C	10.8	10.1	23	72

Fig. 1 Bland Altman plots to assess the agreement between measured creatinine clearance and different eGFR formulas. **a** Cockcroft-Gault formula. **b** MDRD formula figure. **c** CKD-EPI formula. **d** CKD-EPI cystatin C formula. **e** CKD-EPI creatinine-cystatin C formula

Table 6 Bias, precision, and accuracy of creatinine and cystatin C estimates in male patients

	Bias	Precision	Accuracy % within	
			10%	30%
Estimates using serum creatinine				
• Cockcroft-Gault	− 20.2	14.7	17	24
• MDRD	− 4	10.7	24	90
• CKD-EPI	− 6.8	10.7	24	86
Estimates using both serum creatinine and cystatin C				
• CKD-EPI creatinine-cystatin C equation	6	8.5	69	90
Estimates using serum cystatin C				
• CKD-EPI cystatin C equation	14.2	10.6	10	66

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Table 7 Bias, precision, and accuracy of creatinine and cystatin C estimates in female patients

	Bias	Precision	Accuracy % within	
			10%	30%
Estimates using serum creatinine				
• Cockcroft-Gault	− 17.8	17.6	16	39
• MDRD	1	14.8	42	74
• CKD-EPI	− 2.8	15.2	29	71
Estimates using both serum creatinine and cystatin C				
• CKD-EPI creatinine cystatin C	4.9	6.5	68	97
Estimates using serum cystatin C				
• CKD-EPI cystatin C	7.7	8.6	35	77

In our study, we have found that all eGFR formulae were positively correlated with mGFR with the most predictive formula being eGFRcr-cys using both simple and multiple stepwise regression analyses. We tested the performance of the different equations in our cohort of Egyptian patients, and we found that MDRD had the least bias but eGFRcr-cys had the best precision and accuracy within both 10% and 30%. Then we tested the influence of sex on the performance of different equations. We found the same previous results in both male and female patients excluding any influence of sex. Then we tested the performance of the equations in patients with measured GFR ≥ 60 or < 60 ml/min/m2, and we found CKD-EPI equation had the least bias with eGFRcr-cys had the best precision and accuracy in patients with GFR ≥ 60 ml/min/m^2, but with GFR < 60 ml/min/m^2 eGFRcr-cys had the least bias together with MDRD but with better precision and accuracy.

Our results agree with a study published by Adachi et al. 2015 in Japanese population who assessed the performance of GFR equations compared with inulin clearance as a gold standard in 14 patients with cirrhosis.

Table 8 Bias, precision, and accuracy of creatinine and cystatin C estimates for patients with estimated ≥ 60 ml/min per 1.73 m^2 (*n* = 20)

	Bias	Precision	Accuracy % within	
			10%	30%
Estimates using serum creatinine				
• Cockcroft-Gault	− 15.8	20.5	40	50
• MDRD	4.1	18.8	15	80
• CKD-EPI	− 1.1	19.2	20	65
Estimates using both serum creatinine and cystatin C				
• CKD-EPI creatinine cystatin C	8.2	10.5	60	90
Estimates using serum cystatin C				
• CKD-EPI cystatin C	12.9	14.2	25	75

Table 9 Bias, precision, and accuracy of creatinine and cystatin C estimates for patients with estimated < 60 ml/min per 1.73 m^2 (*n* = 20)

	Bias	Precision	Accuracy % within	
			10%	30%
Estimates using serum creatinine				
• Cockcroft-Gault	− 20.5	13.6	5	23
• MDRD	− 4.1	8.1	43	83
• CKD-EPI	− 6.5	8.7	30	85
Estimates using both serum creatinine and cystatin C				
• CKD-EPI creatinine cystatin C	4.1	5	73	95
Estimates using serum cystatin C				
• CKD-EPI cystatin C	9.8	7.3	23	70

They found that eGFRcys was more accurate than Cr-based eGFR in estimating renal function in cirrhotic patients. Moreover, they found that CysC-based eGFR and not creatinine-based eGFR equations, along with albumin, Child-Pugh grade, and the presence of hepatocellular carcinoma, was independently associated with overall survival in 49 cirrhotic patients [17]. Another study evaluated serum CysC in 70 Egyptian patients who were potential candidates for living donor liver transplantation with serum creatinine < 1.5 mg/dl, as a marker of early renal impairment (GFR of 60–89 ml/min/1.73 m^2). They found that CysC and CysC-based equations had the highest significant correlation to GFR as measured by ^{99m}Tc-DTPA renal scan [18].

Another study from Germany conducted on ninety-seven in hospital patients with cirrhosis and 24-h creatinine clearance of at least 40 ml/min to assess the value of serum CysC concentration in the detection of moderately impaired renal function. They found that serum CysC is a valuable marker for early diagnosis of moderately impaired renal function in patients with cirrhosis especially in female patients or with child-Pugh class C with high diagnostic sensitivity (77.8% and 86.7% respectively), greater than sCr (38.9% and 60%) [19].

A cross-sectional analysis conducted in diverse populations with 1119 participants from 5 different studies in which GFR was measured with CysC and Cr assays were traceable to primary reference materials. The combined Cr–CysC equation had been shown to perform better than equations based on either of these markers alone at different GFR and may be useful as a confirmatory test for chronic kidney disease [20].

Our cross-sectional study has some limitations. First, the sample size is relatively small and might affect the statistical power. Second, the survival correlation of the different equations is needed to be studied on a longer follow-up.

Conclusion

In conclusion, we report that GFRcr-cys formula has the best precision and accuracy in estimating GFR in Egyptian patients with liver cirrhosis irrespective of sex or degree of mGFR. This is of utmost importance in patients with refractory hepatic encephalopathy or being evaluated for liver transplantation. Our study in addition to similar studies should spark investigations on the influence of population diversity on different eGFR equations.

Abbreviations
GFR: Glomerular filtration rate; HCV: Hepatitis C virus; CKD-EPI: Chronic kidney disease–epidemiology collaboration; MDRD: Modification of diet in renal disease; MELD: Model for end-stage liver disease; ACLF: Acute on chronic liver failure; KDIGO: Kidney Disease Improving Global Outcomes; mGFR: Measured glomerular filtration rate; Cr: Creatinine; ALD: Advanced liver disease; CysC: Cystatin C; CRP: C-reactive protein; CVD: Cardiovascular disease; BMI: Body mass index

Authors' contributions
MAAM and HKHK equally contributed to the conception and design of the research; MMM contributed to the design of the research and laboratory work; LAA contributed to the acquisition and analysis of the data; MAAM and MMM contributed to the interpretation of data; and HKHK drafted the manuscript. All authors critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

Availability of data and materials
Available.

Declarations

Ethics approval and consent to participate
The research was conducted in accordance with the ethical standards of the Minia University committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. Informed written consent was obtained from all patients for being included in the study.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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