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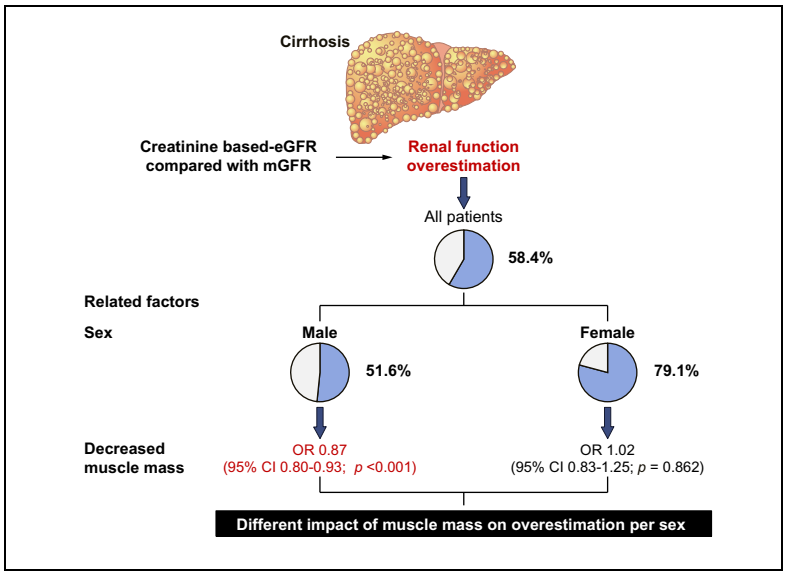
Estimation of renal function in patients with liver cirrhosis: Impact of muscle mass and sex

Graphical abstract



Highlights

- Renal function overestimation occurs frequently in patients with liver cirrhosis when using serum creatinine.
- Decreased muscle mass impacts on overestimation of kidney function especially in male patients with cirrhosis.
- Compared to creatinine, cystatin C correlated better with mGFR and had a higher predictive ability for clinical outcomes.
- Cystatin C might be a promising marker to accurately assess renal function in cirrhotic patients.

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Lay summary

Overestimation of renal function frequently occurs in patients with liver cirrhosis when using serum creatinine. Decreased muscle mass has a great impact on overestimation of kidney function especially in male patients with cirrhosis. Compared with creatinine, cystatin C was more closely correlated with measured glomerular filtration rate and had a higher predictive ability for renal complications and survival than creatinine.

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Estimation of renal function in patients with liver cirrhosis: Impact of muscle mass and sex

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Background & Aims: Accurate evaluation of renal function in patients with liver cirrhosis is critical for clinical management. However, there are still discrepancies between the measured glomerular filtration rate (mGFR) and creatinine-based estimated GFR (eGFR). In this study, we compared the performance of 2 common eGFR measurements with mGFR and evaluated the impact of low muscle mass on overestimation of renal function in patients with cirrhosis.

Methods: This study included 779 consecutive cirrhotic patients who underwent ^{51}Cr-ethylenediamine tetra acetic acid (EDTA) (as a mGFR) and abdominal computed tomography (CT). The eGFR was calculated using creatinine or cystatin C. Muscle mass was assessed in terms of the total skeletal muscle at L3 level using CT.

Results: Modification of diet in renal disease (MDRD)-eGFR was overestimated in 47% of patients. A multivariate analysis showed that female sex (adjusted odds ratio [aOR] 4.91), Child B and C *vs.* A (aOR 1.69 and 1.84) and skeletal muscle mass (aOR 0.89) were independent risk factors associated with overestimation. Interestingly, the effect of skeletal muscle mass on overestimation varied based on sex. Decreased muscle mass significantly enhanced the risk of overestimation of MDRD-eGFR in male patients, but not in female patients. Cystatin C-based eGFR showed a better correlation with mGFR than MDRD-eGFR; it was also better at predicting overall survival and the incidence of acute kidney injury than MDRD-eGFR.

Conclusions: The risk factors associated with overestimation included female sex, impaired liver function, and decreased muscle mass in males. In particular, eGFR in male patients with sarcopenia should be carefully interpreted. Creatinine-based eGFR was overestimated more often than cystatin C-based eGFR, with overestimation of eGFR closely related to poor prognostic performance.

Lay summary: Overestimation of renal function frequently occurs in patients with liver cirrhosis when using serum creatinine. Decreased muscle mass has a great impact on overestimation of kidney function especially in male patients with cirrhosis. Compared with creatinine, cystatin C was more closely correlated with measured glomerular filtration rate and had a higher predictive ability for renal complications and survival than creatinine.

Introduction

Accurate evaluation of renal function is a prerequisite for the management of patients with liver cirrhosis.[1] It facilitates diagnostic and therapeutic assessment, prognostic evaluation and indication for liver transplantation.[2] It is well known that cirrhosis is often accompanied by decreased renal function, resulting in poor outcomes even in stage I acute kidney injury (AKI).[3,4]

Creatinine (Cr), the most frequently used parameter for the evaluation of renal function, is a very powerful prognostic biomarker in cirrhotic patients, and an important element of the model for end-stage liver disease (MELD) scoring system.[5] However, renal function estimated by the Cr-based formula is relatively inaccurate considering endogenous synthesis and metabolism.[2] The actual renal function is likely to be overestimated rather than undervalued, especially in patients with liver cirrhosis because of poor nutritional status and reduced muscle mass.[6] Since Cr is produced in liver and stored in muscle following phosphorylation, its serum concentration is inevitably associated with liver function and muscle mass. It is also known to be affected by age, gender, and race, which are reflected in Cr-based formulas.[7,8] In fact, it has been reported that Cr-based equations (*e.g.* MDRD-4 equation) overestimate the true renal function by less than 30% to as much as 50%, especially, in patients with poor liver function or low glomerular filtration rate (GFR).[9–11]

However, few studies correlated the true GFR with potential markers in large series of cirrhotic patients. In this study, we investigated the extent of overestimation of 2 common estimated GFR (eGFR) calculations using Cr and cystatin C,

Keywords: Glomerular Filtration Rate; Overestimation; Muscle mass; Sex.
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compared with measured GFR (mGFR) using 51Cr-EDTA, and identified the impact of low muscle mass on over/underestimation of renal function.

Materials and methods

Patients and study protocol

Between January 2007 and December 2016, we collected data from consecutive cirrhotic patients obtained during routine clinical care in a tertiary hospital, in South Korea. Patients who fulfilled the following inclusion criteria were eligible for the study: i) clinically, pathologically, or radiologically diagnosed with liver cirrhosis; ii) those tested for serum Cr, serum cystatin C, ^{51}Cr-EDTA on the same day; iii) those who underwent abdominal computed tomography (CT) scans within 3 months before and after blood test. Patients with AKI were included in the study after complete improvement of AKI to avoid contrast induced nephropathy. Patients were excluded if: i) they were undergoing regular hemodialysis due to end-stage renal disease; ii) they were already diagnosed with chronic kidney disease (CKD) or who were suspected of having CKD in lab test or clinical history; iii) they had malignancy including liver cancer; or iv) if the patient had overt hypothyroidism or overt hyperthyroidism that can affect the cystatin C value. Finally, we retrospectively reviewed 779 patients who met the inclusion criteria. In these patients, we compared the 3 different methods of renal function measurement: (a) Modification of diet in renal disease (MDRD)-eGFR (using serum Cr); (b) cystatin C-eGFR (using serum cystatin C); and (c) ^{51}Cr-EDTA-mGFR. Clinical and laboratory records of all patients were retrospectively reviewed.

The study protocol conformed to the ethical guidelines of the World Medical Association Declaration of Helsinki and was approved by the Institutional Review Board of Soonchunhyang University Bucheon Hospital (IRB No 2017-11-013).

eGFR

Six variable-MDRD (MDRD-6)-eGFR was calculated with equations based on serum Cr as described below:[7]

$186 \times (\text{serum Cr [mg/dl]})^{-1.154} \times (\text{age})^{-0.203} \times (0.742$ if patient is female) $\times$ (1.21 in black patients);

Cystatin C-eGFR was calculated with chronic kidney disease-epidemiology collaboration cystatin C equations based on serum cystatin C as described below:[12]

i) if serum cystatin C is equal or below 0.8 mg/L,
$133 \times (\text{serum cystatin}/0.8)^{-0.499} \times 0.996^{\text{Age}}$ ($\times$0.932 if female)

ii) if serum cystatin C is over 0.8 mg/L,
$133 \times (\text{serum cystatin}/0.8)^{-1.328} \times 0.996^{\text{Age}}$ ($\times$0.932 if female)

mGFR

Before the test, we recorded the height and weight of each patient, and diluted 80 μCi of ^{51}Cr-EDTA with 8 ml of normal saline. The sum of the syringe weight + ^{51}Cr-EDTA solution + IV amount was defined as W_1. We transferred 1 ml of W_1 to a 199 ml beaker with a syringe and used it as a standard solution. The butterfly needle was connected to the syringe containing 10 ml of normal saline to determine the IV passage and fix it. The ^{51}Cr-EDTA syringe was connected and injected vertically to inject the full amount of ^{51}Cr-EDTA in the syringe. The catheter was flushed with 10 ml normal saline. The blood samples were drawn sharply at 3 h and 5 h after injection. The plasma disappearance curve was constructed using the results of these 2 time points. Plasma clearance rate and mGFR by ^{51}Cr-EDTA were calculated as described below:

$$E1 = \frac{\theta}{\int Pdt} = \frac{Q \times \lambda}{C}$$

$$E1 = \frac{Wi \times S \times \text{dilutation volume standard}}{Ws} \times \frac{\ln(C1/C2)}{\delta t} \times \frac{C2\,(t1/dt)}{C1\,(t2/dt)}$$

Body surface area (BSA) = (body weight $kg^{0.425}$ $\times$ body height $cm^{0.725}$ $\times$ 71.84)/10,000

mGFR = (0.990778 [E1 $\times$ 1.73/BSA] − 0.001218 [E1 $\times$ 1.73/BSA]^2) $\times$ (BSA/1.73)

Assessment of muscle mass

Muscularity was assessed using a method reported previously.[13] A transverse CT image at the level of L3 was assessed from each patient. Images were analyzed with the National Institutes of Health (NIH) Image J program, which enables specific tissue demarcation using previously reported Hounsfield unit (HU) thresholds. Skeletal muscle was identified and quantified using HU thresholds of −29 to +150. Muscles in the L3 region encompass psoas, erector spinae, quadratus lumborum, transversus abdominis, external and internal obliques, and rectus abdominis. The following HU thresholds were used for adipose tissues: −190 to −30 for subcutaneous and intermuscular adipose tissue, and −150 to −50 for visceral adipose tissue. Using these specific HU thresholds, measurements of the skeletal muscle index were not influenced by the presence of ascites, overweight, or obesity in patients with cirrhosis. Cross-sectional areas (cm^2) were automatically computed by summing the tissue's pixels and multiplying by pixel surface area. All CT images were analyzed by a single trained radiologist. The cross-sectional area of muscle and adipose tissue was normalized for stature (cm^2/m^2) as reported before,[14,15] and this value was referred to as the L3 skeletal muscle index (L3 SMI).

Definitions

Overestimation was defined as more than 20% increment of mGFR estimated by a Cr-based formula with reference to existing literature.[16]

The definition of AKI was followed by the International Club of Ascites (ICA) criteria.[17] AKI was defined in patients with cirrhosis by: i) an increase in serum Cr greater than 0.3 mg/dl within 48 h, or ii) a greater than 50% increase in serum Cr from baseline, which is known, or presumed, to have occurred within the past 7 days.

Competing risk analysis

The major competing outcome for the enrolled patients was liver transplantation. If liver transplantation occurs, hazards for each type of event (overall survival [OS], AKI, hepatorenal syndrome [HRS]) cannot be calculated correctly. To overcome this limitation, we conducted competing risk analysis regarding liver transplantation for the prediction of prognosis. We defined 2 mutually exclusive events, that is, competing risks: liver transplantation and others (OS or AKI or HRS).

Statistical analysis

Frequencies and percentages were used for descriptive statistics. Statistical differences between the groups were investi-

gated using the χ^2 test or Fisher's exact test for the categorical variables and Student's *t* test or Mann-Whitney *U* test for the continuous variables. To evaluate the predictive accuracy of eGFRs, the time-dependent receiver operating characteristic (ROC) curves for censored data and the area under the ROC curve (AUC) were constructed according to Heagerty *et al.*[18] A larger AUC at a given time point corresponds to a better predictability of time to event. The primary endpoint of this study was the risk factors contributing to overestimation of eGFR in cirrhotic patients. Therefore, logistic regression analysis was the primary tool used. We included the muscle mass value in the multivariable model, regardless of the *p* value of the univariate, in order to evaluate the effect of muscle mass on GFR. The final result was obtained after backward elimination based on the Akaike information criteria. All statistical analyses were performed using R (version 3.3.3, The R Foundation for Statistical Computing, Vienna, Austria) and statistical significance was defined as a $p < 0.05$.

Results

Baseline characteristics

Baseline demographic and clinical characteristics of the patients are listed in Table 1. A total of 779 cirrhotic patients were analyzed. The median observation period was 44.6 months (interquartile range [IQR], 10.7–81.0 months). About three-quarters of all patients were male (75.4%), and one-quarter were female (24.6%). The most common cause of cirrhosis was alcoholism (48.4%), followed by viral hepatitis (41.6%), and other factors (10%). The mean cross-sectional muscle mass at the level of the third lumbar vertebrae (L3), defined as L3 muscle index (L3 MI), was 10.78×10^3 mm^2. Of all patients, 24.5% were graded as Child-Pugh class A, 58.7% as Child-Pugh class B, and 16.8% as Child-Pugh class C. A total of 55.1% of the patients presented with ascites.

Correlation and comparison of MDRD-eGFR and cystatin c-eGFR with ^{51}Cr-EDTA-mGFR

The mean value of ^{51}Cr-EDTA-mGFR was 79.24 ml/min/1.73 m^2 (range, 9.94–155.77) (Table S1). Compared with MDRD-eGFR and cystatin C-eGFR, it was distributed in a relatively narrow range (Fig. S1). Correlation between ^{51}Cr-EDTA-mGFR and cystatin C-eGFR was moderately better than between ^{51}Cr-EDTA-mGFR and MDRD-eGFR ($r = 0.56$ *vs.* 0.46) (Table S2). The correlation between mGFR and cystatin C-eGFR was still higher than that of mGFR and MDRD-eGFR when patients were separated into 3 groups according to the degree of mGFR (mGFR ≤50, 50< mGFR ≤100, mGFR >100). The same results were obtained in a Bland-Altman plot when ^{51}Cr-EDTA-mGFR was used as the gold standard (Fig. S2).

Table 1. Baseline characteristics according to the presence of renal function overestimation.

Variable	Total (N = 779)	Overestimation (+) (n = 455)	Overestimation (−) (n = 324)	*p* value
Age (yr)	53.78 ± 10.95	54.98 ± 11.10	52.09 ± 10.52	<0.001
Sex				<0.001
Male	587 (75.35%)	303 (66.59%)	284 (87.65%)	
Female	192 (24.65%)	152 (33.41%)	40 (12.35%)	
Etiology				0.007
HBV	284 (36.46%)	166 (36.48%)	118 (36.42%)	
HCV	41 (5.26%)	31 (6.81%)	10 (3.09%)	
Alcohol	377 (48.40%)	202 (44.40%)	175 (54.01%)	
NAFLD	2 (0.26%)	2 (0.44%)	0 (0.00%)	
Autoimmune	14 (1.80%)	11 (2.42%)	3 (0.93%)	
Others	61 (7.83%)	43 (9.45%)	18 (5.56%)	
Muscle area (10^3 mm^2)	10.78 ± 2.72	10.66 ± 2.86	10.96 ± 2.51	0.116
MELD score	13.92 ± 5.57	13.86 ± 5.90	14.03 ± 5.00	0.737
Child-Pugh class				0.004
A	191 (24.52%)	131 (28.79%)	60 (18.52%)	
B	457 (58.66%)	253 (55.60%)	204 (62.96%)	
C	131 (16.82%)	71 (15.60%)	60 (18.52%)	
Ascites				
No	350 (44.93%)	212 (46.59%)	138 (42.59%)	
Mild-to-moderate	219 (28.11%)	125 (27.47%)	94 (29.01%)	
Severe	210 (26.96%)	118 (25.93%)	92 (28.40%)	
Laboratory factor				
Hemoglobin (mg/dl)	11.22 ± 2.18	11.32 ± 2.17	11.07 ± 2.19	0.163
Platelet (10^3 mm^3)	119.50 ± 79.89	118.57 ± 74.67	120.98 ± 87.63	0.717
AST (U/L)	112.98 ± 197.06	111.23 ± 211.59	115.83 ± 171.29	0.764
ALT (U/L)	67.23 ± 126.22	65.09 ± 105.93	70.72 ± 153.70	0.616
Total bilirubin (mg/dl)	3.40 ± 4.98	3.13 ± 4.87	3.83 ± 5.15	0.087
Albumin (mg/dl)	3.16 ± 0.66	3.17 ± 0.66	3.13 ± 0.66	0.437
PT-INR	1.35 ± 0.34	1.35 ± 0.36	1.35 ± 0.31	0.941
Creatinine (mg/dl)	1.05 ± 0.78	1.13 ± 0.97	0.92 ± 0.25	<0.001

Data were presented as mean ± standard deviation for continuous variables and n (%) for categorical variables. *p* value was calculated by Student's *t* test or Mann-Whitney *U* test for continuous variables and chi-square test or Fisher's exact test for categorical variable as appropriate.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; HBV, hepatitis B virus; HCV, hepatitis C virus; MELD, model for end-stage liver disease; NAFLD, non-alcoholic fatty liver disease; PT-INR, prothrombin time with international normalized ratio.

Overestimation of renal function by MDRD-eGFR and its risk factors

Next, we reviewed patients whose renal function was overestimated compared with mGFR, and the factors influencing the overestimation. As described earlier, overestimation was defined by values of MDRD-eGFR, which were 20% higher than those of ^{51}Cr-EDTA-mGFR. Using this definition, the renal function of 455 out of 779 patients (58.4%) was classified as an overestimation (cross mark in Fig. 1). The overestimated group comprised a larger proportion of females, decreased muscle mass, and a higher baseline Cr value (Table 1). Multivariate analysis showed that female sex (adjusted odds ratio [aOR] 4.91; 95% CI 3.09–7.79; $p < 0.001$), decreased L3 MI (aOR 0.89; 95% CI 0.83–0.90; $p = 0.001$), and liver function deterioration (Child-Pugh class B *vs.* A: aOR 1.69; 95% CI 1.17–2.46; $p = 0.006$. Child-Pugh class C *vs.* A: aOR 1.84; 95% CI 1.13–2.98; $p = 0.014$) were independent predictors of overestimation after adjustment for age (Table 2).

Differential effects of muscle mass on overestimation of renal function depending upon sex

The muscle mass, in terms of L3 MI in this study, showed no statistically significant difference between the overestimated and non-overestimated groups. However, it was a significant risk factor after adjustment for other variables. Although muscle mass was an independent risk factor for overestimation, our results showed that females had significantly lower L3 MI and that their renal function was more frequently overestimated than in males, suggesting that sex was an important effect modifier (Table S3). Muscle mass distribution in different populations according to overestimation is shown in Fig. 2. Considering this interaction, we performed multivariate analysis separately by sex (Table 3). In males, decreased muscle mass strongly affected the overestimation (aOR 0.87; 95% CI 0.80–0.93; $p < 0.001$); however, it did not affect females (aOR 1.02; 95% CI 0.83–1.25; $p = 0.862$). Next, we analyze the risk of eGFR overestimation according to the amount of muscle mass (Fig. 3). In the case of males, the risk of overestimation was markedly increased with lower muscle mass and decreased with higher muscle mass. However, this correlation was not observed in females.

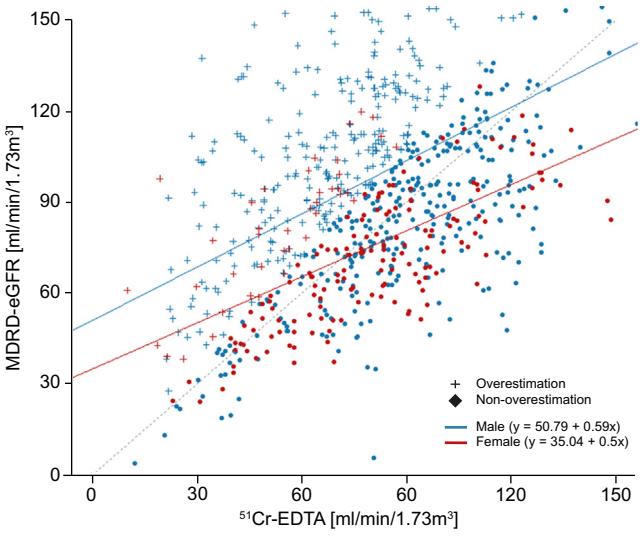

Fig. 1. Analysis of MDRD-eGFR compared with ^{51}Cr-EDTA as gold standard. A scatter plot of MDRD-eGFR and cystatin C-eGFR based on ^{51}Cr-EDTA as the gold standard. Cross mark denotes overestimation of renal function, which was defined by 20% higher MDRD-eGFR value compared with that of ^{51}Cr-EDTA-measured glomerular filtration rate (mGFR). Simple linear regression analysis yield a regression line for the male patients (y (MDRD-eGFR) = 50.79 + 0.59x(^{51}Cr- EDTA); in blue) and a regression line for the female patients (y (MDRD-eGFR) = 35.04 + 0.5x(^{51}Cr-EDTA); in red).

Comparison of MDRD-eGFR and cystatin C-eGFR for predicting prognosis

Since Cr is used in the MELD scoring system, we compared the prognostic ability of Cr- and cystatin C-based eGFR. During the observation period (median 44.6 months; IQR, 10.7–81.0 months), 407 patients (52.2%) died, and 22 patients (2.8%) underwent liver transplantation. We identified the cause of death in 202 patients based on their medical records. Liver failure (104, 51.5%) was the most common cause of death, followed by hepatocellular carcinoma (31, 15.3%), bleeding (23, 11.4%), and infection (22, 10.9%). Cystatin C or mGFR was superior to Cr in predicting the OS during all the periods of observation (Fig. 4), and the result was similar in competing risk analysis (Fig. S3). Cystatin C showed a higher AUC than Cr at 5 years (0.62 *vs.* 0.56, $p < 0.001$) as well as 1 year (0.62 *vs.* 0.56, $p < 0.001$).

During the follow-up, AKI developed in 319 patients (40.9%) according to ICA-AKI criteria, and HRS developed in 182 patients. Baseline cystatin C had a high predictive power for both AKI and HRS as well as survival rate. The higher AUC value of the cystatin C-based equation compared to the Cr-based equation both at 1 year (0.71 *vs.* 0.65, $p < 0.001$) and 5 years (0.68 *vs.* 0.64, $p = 0.004$) predicted the cumulative incidence of AKI (Fig. S4A). However, in HRS, the predictive power of cystatin C was superior only at 1 year (0.69 *vs.* 0.65, $p = 0.040$), but not at 5 years (0.66 *vs.* 0.62, $p = 0.099$) (Fig. S4B). Overall, cystatin C-based eGFR showed a superior performance to Cr-based eGFR for the prediction of survival and renal complications.

Discussion

Cr is the most commonly used renal biomarker representing GFR. However, as shown in this study, measurement of renal function using Cr and Cr-based eGFR yielded an apparently higher value than the actual GFR levels in a significant number of cirrhotic patients. Furthermore, Cr is an incomplete parameter for the measurement of renal function in these patients for the following reasons: (a) reduced hepatic production; (b) edematous state such as ascites and peripheral edema; and (c) associated muscle wasting.[19] Therefore, even in AKI, the normal range of Cr is often observed in clinical practice. In addition, the most commonly used Cr-based eGFR measurements using C-G formula and MDRD equations were originally conducted in healthy men and CKD populations, respectively, suggesting that the accuracy of GFR in a specific patient group such as cirrhosis is compromised.[7,8] Previous studies investigating the validity of eGFR reported frequent and significant discrepancies in mGFR of cirrhotic patients, consistent with our study.[16] Furthermore, Cr-based eGFR was poorly predictive of in-hospital mortality in cirrhosis, which was also consistent with our findings.[20]

The main factors affecting overestimation of GFR in our study were skeletal muscle mass, gender, and liver function. Sarcopenia has recently attracted much attention as a prognostic factor in cirrhotic patients.[21] Our results confirmed that renal function may appear good when muscle mass is decreased. In fact, lean body mass has been directly related to GFR in previous studies, and sarcopenia increased the risk of renal deterioration, represented by aspartate aminotransferase/height^2.[22] Although the mechanism is unclear, high muscle mass has a renal protective

Table 2. Logistic regression analysis of overestimated renal function.

Variable	Univariable		Multivariable	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Age (yr)	0.98 (0.96–0.99)	<0.001	0.98 (0.96–0.99)	0.001
Sex				
Male	1		1	
Female	3.56 (2.43–5.23)	<0.001	4.91 (3.09–7.79)	<0.001
Etiology				
HBV	1			
HCV	0.45 (0.21–0.96)	0.039		
Alcohol	1.22 (0.89–1.66)	0.212		
NAFLD	0 (0–Inf)	0.972		
Autoimmune	0.38 (0.1–1.41)	0.148		
Others	0.59 (0.32–1.07)	0.083		
Muscle area (10^3 mm^2)	1.04 (0.99–1.1)	0.124	0.89 (0.83–0.90)	0.001
Ascites				
No	1			
Mild-to-moderate	1.16 (0.82–1.63)	0.409		
Severe	1.2 (0.85–1.69)	0.308		
Encephalopathy				
No	1			
Mild-to-moderate	1.15 (0.67–1.97)	0.614		
Severe	0.71 (0.18–2.85)	0.626		
MELD score	1.0055 (0.9723–1.0399)	0.747		
Child-Pugh class				
A	1		1	
B	1.76 (1.23–2.52)	0.002	1.69 (1.17–2.46)	0.006
C	1.85 (1.16–2.92)	0.009	1.84 (1.13–2.98)	0.014
Laboratory factor				
Hemoglobin (mg/dl)	0.95 (0.88–1.02)	0.163		
Platelet (10^3 mm^3)	1.0004 (0.9984–1.0023)	0.707		
AST (U/L)	1.0001 (0.9993–1.0009)	0.775		
ALT (U/L)	1.0003 (0.9991–1.0016)	0.586		
Total bilirubin (mg/dl)	1.03 (1–1.06)	0.091		
Albumin (mg/dl)	0.91 (0.71–1.16)	0.436		
PT-INR	1.02 (0.63–1.63)	0.942		

NOTE. Multivariable logistic regression model was determined by the backward elimination based on the Akaike information criteria.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; HBV, hepatitis B virus; HCV, hepatitis C virus; MELD, model for end-stage liver disease; NAFLD, non-alcoholic fatty liver disease; OR, odds ratio; PT-INR, prothrombin time with international normalized ratio.

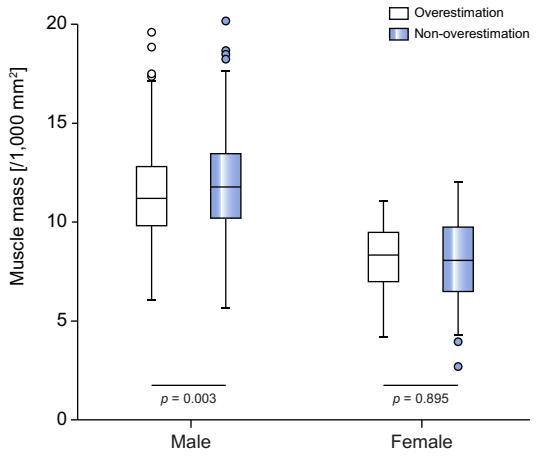

Fig. 2. Renal function overestimation by sex and muscle mass. In males, the overestimated group has lower muscle mass than the non-overestimated group, but in females, there is no difference in muscle mass according to overestimation. *p* value was calculated by Mann-Whitney *U* test for each group (overestimated and non-overestimated).

role in patients with CKD.[23] It is plausible that sarcopenia may exacerbate renal dysfunction directly and thus have adverse effects on survival in cirrhotic patients. Interestingly, in our study, decreased muscle mass was not associated with overestimation of GFR in females, rather it greatly influenced renal function in males. These results suggest that serum Cr concentrations in women may be controlled by different mechanisms compared to those in men. We think that different patterns of loss of gonadal function may explain this finding. Testosterone is the most well-known sex hormone that can affect sarcopenia.[24] In men, testosterone is relatively reduced in older people, but women have less testosterone reduction with aging than men. Women have decreased estrogen after menopause, but unlike testosterone, estrogens are not thought to have anabolic effects on skeletal muscle.[25] In some reports, anti-estrogen therapy administered in premenopausal women with breast cancer or uterine cancer was associated with progression of sarcopenia, but this effect was offset in women aged 65 years and older.[26–28] In addition, inflammation plays an important role in the development of sarcopenia, and adipose tissue is an important source of pro-inflammatory cytokines.[29] The proportion of fat is higher in women than men, suggesting that regional adiposity and gender difference could influence the risk of sarcopenia. Taken together, our findings suggest that the effect of muscle mass should be applied to the eGFR equation for the accurate evaluation of renal function, especially in male cirrhotic patients.

Table 3. Logistic regression analysis of overestimated renal function based on sex.

Variable	Male (n = 587)				Female (n = 192)			
	Univariable		Multivariable		Univariable		Multivariable	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Age (yr)	0.98 (0.96–0.99)	0.006	0.97 (0.95–0.98)	<0.001	0.99 (0.97–1.03)	0.984	1.00 (0.97–1.03)	0.894
Ascites	1.18 (0.85–1.63)	0.333			1.02 (0.51–2.05)	0.953		
Etiology-viral	0.95 (0.68–1.32)	0.752			1.02 (0.51–2.05)	0.953		
Encephalopathy	1.07 (0.59–1.96)	0.819			1.61 (0.58–4.46)	0.358		
Muscle area (10^3 mm^2)	0.90 (0.84–0.97)	0.003	0.87 (0.80–0.93)	<0.001	1.01 (0.83–1.24)	0.894	1.02 (0.83–1.25)	0.862
Laboratory factor								
Hemoglobin (mg/dl)	0.93 (0.86–1.01)	0.085			0.89 (0.74–1.08)	0.249		
Platelet (10^3 mm^3)	1.00 (0.99–1.00)	0.723			1.00 (0.99–1.01)	0.487		
AST (U/L)	1.00 (0.99–1.00)	0.206			1.00 (0.99–1.00)	0.41		
ALT (U/L)	1.00 (0.99–1.00)	0.378			1.00 (0.99–1.00)	0.16		
Total bilirubin (mg/dl)	1.03 (1.00–1.07)	0.091			0.99 (0.90–1.09)	0.882		
Albumin (mg/dl)	0.85 (0.64–1.12)	0.246			0.91 (0.51–1.60)	0.736		
PT-INR	1.23 (0.70–2.15)	0.475			0.90 (0.32–2.55)	0.842		
MELD score	1.01 (0.97–1.05)	0.619			0.99 (0.91–1.07)	0.886		
Child-Pugh class								
A	1 (Ref.)		1 (Ref.)		1 (Ref.)		1 (Ref.)	
B	1.65 (1.11–2.45)	0.014	1.54 (1.03–2.32)	0.037	2.48 (0.95–6.48)	0.064	2.50 (0.96–6.54)	0.062
C	2.16 (1.27–3.68)	0.005	1.91 (1.11–3.31)	0.020	1.62 (0.50–5.29)	0.426	1.63 (0.50–5.35)	0.419

NOTE. Multivariable logistic regression model was determined by the backward elimination based on the Akaike information criteria.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; MELD, model for end-stage liver disease; OR, odds ratio; PT-INR, prothrombin time with international normalized ratio; Ref., reference group.

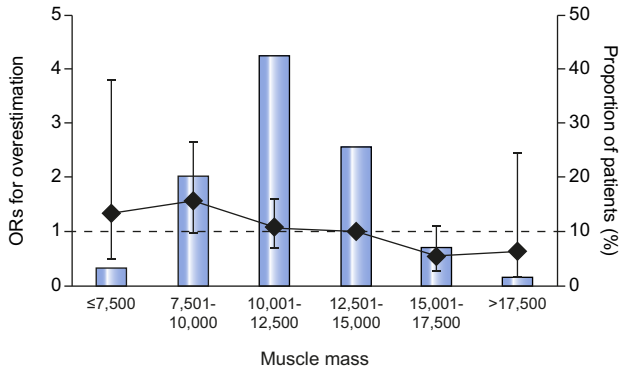

Fig. 3. Distribution of patients according to muscle mass and its effect on overestimation. The x-axis represents the distribution of muscle mass. The left y-axis and bar graph represent the proportion of patients (%). The right y-axis and the line graph with black dot represent the odds ratio on the overestimation with error bars representing 95% CI.

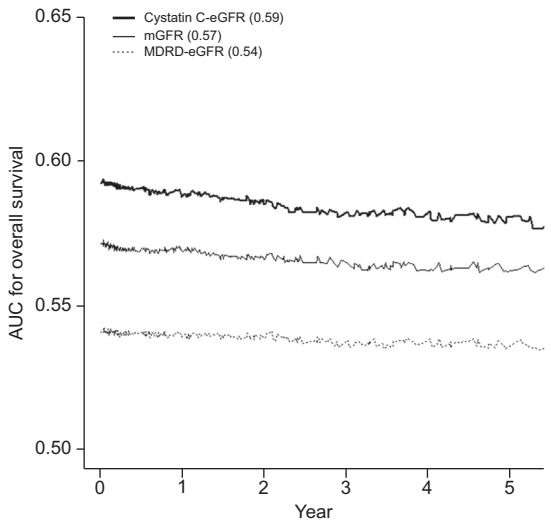

Fig. 4. Time-dependent AUC curve analysis for MDRD-eGFR, cystatin C-eGFR, and mGFR. Time-dependent AUC curve analysis for the prediction of overall survival in MDRD-eGFR and cystatin C-eGFR. The average AUC over time is given in parentheses. The predictive power of cystatin C or mGFR is superior to that of creatinine. AUC, area under the curve; eGFR, estimated glomerular filtration rate; MDRD, modified diet in renal disease; mGFR, measured glomerular filtration rate; ROC, receiver operating curve.

Next, female gender also affected overestimation. Women have a relatively low level of serum Cr even when mGFR is considerably depressed, and are therefore likely to underscore in the MELD scoring system.[30] After switching to the MELD scoring system, the proportion of male transplant recipients increased, and women had a significantly higher mortality rate than men while waiting for a liver transplant.[31,32] Women reported higher scores when Cr was replaced with mGFR in the MELD scoring system.[33] We also found that female patients were more likely to manifest overestimated renal function than male patients.

Due to the limitations of Cr for clinical application as described above, we studied cystatin C as an alternative to Cr several years ago, and we found that cystatin C was a useful marker for the estimation of GFR in cirrhotic patients. Cystatin C was more closely associated with mGFR than Cr, and superior in predicting prognosis.[34] Cystatin C, unlike Cr, is not affected by other factors except renal function and predicted renal dysfunction earlier in previous studies.[35,36] In this study, Cr-based eGFR was shown to exaggerate actual GFR in over 40% of patients compared with cystatin C-based eGFR. In addition, cystatin C was superior to Cr in predicting OS, probably via earlier detection of renal dysfunction than Cr. Cystatin C is also associated with liver fibrosis, but this has yet to be clearly established.[37,38]

Our study limitations are as follows. First, instead of inulin, ^{51}Cr-EDTA was used as a gold standard. However, ^{51}Cr-EDTA showed high accuracy compared with inulin and is relatively inexpensive and simple compared with other methods of mGFR estimation.[39] Second, even though we consecutively enrolled the patients, selection bias is inevitable in a retrospective

analysis, and therefore, our results cannot be applied to all cirrhotic patients. Ascertainment or measurement bias may have occurred even though the radiologist who measured muscle mass was blinded to the medical information of each patient. Finally, we did not monitor the dynamic variation of Cr or cystatin C, which would be a more important factor for estimation of the risk of AKI development or survival.

In summary, renal function overestimation occurs frequently in patients with liver cirrhosis, and greater attention is required, especially if patients are female, have reduced skeletal muscle mass, or advanced liver disease. Cystatin C was more closely correlated with mGFR, with a higher predictive ability compared to Cr for renal complications and survival. Therefore, cystatin C rather than Cr represents a potentially new prognostic marker in patients with cirrhosis. Of note, our results based on accurate measurement of GFR and muscle mass provide supporting evidence that sarcopenia has a great impact on overestimation of kidney function in male patients with cirrhosis. Exclusion of muscle mass in patients with cirrhosis may lead to discrepancies in renal function measurements and clinical outcomes. Nevertheless, our results need to be confirmed in a larger prospective cohort of patients with cirrhosis.

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Conflicts of interest

The authors disclose no conflicts.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Conceptualization, Writing – Original Draft: Yoo JJ and Kim SG, Methodology: Kim YS, Yoo JJ, and Kim SG, Validation of data: Jeong SW and Jang JY, Formal analysis: Lee B, Investigation: Lee SH and Kim HS, Visualization: Lee MH, Resources: Kim YD, Cheon GJ, and Kim BS, Supervision: Kim SG. Approval of final manuscript: all authors.

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Supplementary data

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References

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[1] Korean Association for the Study of the Liver (KASL). KASL clinical practice guidelines for liver cirrhosis: Ascites and related complications. Clin Mol Hepatol 2018;24:230–277.
[2] Piano S, Romano A, Di Pascoli M, Angeli P. Why and how to measure renal function in patients with liver disease. Liver Int 2017;37(Suppl 1):116–122.
[3] **Fagundes C**, **Barreto R**, Guevara M, Garcia E, Solà E, Rodríguez E, et al. A modified acute kidney injury classification for diagnosis and risk stratification of impairment of kidney function in cirrhosis. J Hepatol 2013;59:474–481.
[4] Wong F. Acute kidney injury in liver cirrhosis: new definition and application. Clin Mol Hepatol 2016;22:415–422.
[5] Romano TG, Schmidtbauer I, Silva FM, Pompilio CE, D'Albuquerque LA, Macedo E. Role of MELD score and serum creatinine as prognostic tools for the development of acute kidney injury after liver transplantation. PLoS One 2013;8:e64089.
[6] Perrone RD, Madias NE, Levey AS. Serum creatinine as an index of renal function: new insights into old concepts. Clin Chem 1992;38:1933–1953.
[7] Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16:31–41.
[8] Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med 1999;130:461–470.
[9] Proulx NL, Akbari A, Garg AX, Rostom A, Jaffey J, Clark HD. Measured creatinine clearance from timed urine collections substantially overestimates glomerular filtration rate in patients with liver cirrhosis: a systematic review and individual patient meta-analysis. Nephrol Dial Transplant 2005;20:1617–1622.
[10] Francoz C, Glotz D, Moreau R, Durand F. The evaluation of renal function and disease in patients with cirrhosis. J Hepatol 2010;52:605–613.
[11] Orlando R, Floreani M, Padrini R, Palatini P. Evaluation of measured and calculated creatinine clearances as glomerular filtration markers in different stages of liver cirrhosis. Clin Nephrol 1999;51:341–347.
[12] Inker LA, Schmid CH, Tighiouart H, Eckfeldt JH, Feldman HI, Greene T, et al. Estimating glomerular filtration rate from serum creatinine and cystatin C. N Engl J Med 2012;367:20–29.
[13] Montano-Loza AJ, Duarte-Rojo A, Meza-Junco J, Baracos VE, Sawyer MB, Pang JX, et al. Inclusion of sarcopenia within MELD (MELD-Sarcopenia) and the prediction of mortality in patients with cirrhosis. Clin Transl Gastroenterol 2015;6:e102.
[14] Mitsiopoulos N, Baumgartner RN, Heymsfield SB, Lyons W, Gallagher D, Ross R. Cadaver validation of skeletal muscle measurement by magnetic resonance imaging and computerized tomography. J Appl Physiol 1985;1998(85):115–122.
[15] Sottier D, Petit JM, Guiu S, Hamza S, Benhamiche H, Hillon P, et al. Quantification of the visceral and subcutaneous fat by computed tomography: interobserver correlation of a single slice technique. Diagn Interv Imaging 2013;94:879–884.
[16] Rosi S, Piano S, Frigo AC, Morando F, Fasolato S, Cavallin M, et al. New ICA criteria for the diagnosis of acute kidney injury in cirrhotic patients: can we use an imputed value of serum creatinine? Liver Int 2015;35:2108–2114.
[17] Angeli P, Ginès P, Wong F, Bernardi M, Boyer TD, Gerbes A, et al. Diagnosis and management of acute kidney injury in patients with cirrhosis: revised consensus recommendations of the International Club of Ascites. J Hepatol 2015;62:968–974.
[18] Heagerty PJ, Lumley T, Pepe MS. Time-dependent ROC curves for censored survival data and a diagnostic marker. Biometrics 2000;56:337–344.
[19] Cholongitas E, Shusang V, Marelli L, Nair D, Thomas M, Patch D, et al. Review article: renal function assessment in cirrhosis – difficulties and alternative measurements. Aliment Pharmacol Ther 2007;26:969–978.
[20] Piano S, Rosi S, Maresio G, Fasolato S, Cavallin M, Romano A, et al. Evaluation of the Acute Kidney Injury Network criteria in hospitalized patients with cirrhosis and ascites. J Hepatol 2013;59:482–489.
[21] Kim HY, Jang JW. Sarcopenia in the prognosis of cirrhosis: going beyond the MELD score. World J Gastroenterol 2015;21:7637–7647.
[22] Zhou Y, Hellberg M, Svensson P, Höglund P, Clyne N. Sarcopenia and relationships between muscle mass, measured glomerular filtration rate and physical function in patients with chronic kidney disease stages 3–5. Nephrol Dial Transplant 2017. https://doi.org/10.1093/ndt/gfw466.
[23] Mafra D, Guebre-Egziabher F, Fouque D. Body mass index, muscle and fat in chronic kidney disease: questions about survival. Nephrol Dial Transplant 2008;23:2461–2466.
[24] Sakuma K, Yamaguchi A. Sarcopenia and age-related endocrine function. Int J Endocrinol 2012;2012:127362.
[25] Maggio M, Lauretani F, Ceda GP. Sex hormones and sarcopenia in older persons. Curr Opin Clin Nutr Metab Care 2013;16:3–13.
[26] van Geel TA, Geusens PP, Winkens B, Sels JP, Dinant GJ. Measures of bioavailable serum testosterone and estradiol and their relationships

with muscle mass, muscle strength and bone mineral density in postmenopausal women: a cross-sectional study. Eur J Endocrinol 2009;160:681–687.
[27] Kenny AM, Dawson L, Kleppinger A, Iannuzzi-Sucich M, Judge JO. Prevalence of sarcopenia and predictors of skeletal muscle mass in nonobese women who are long-term users of estrogen-replacement therapy. J Gerontol A Biol Sci Med Sci 2003;58:M436–M440.
[28] Baumgartner RN, Waters DL, Gallagher D, Morley JE, Garry PJ. Predictors of skeletal muscle mass in elderly men and women. Mech Ageing Dev 1999;107:123–136.
[29] Tay L, Ding YY, Leung BP, Ismail NH, Yeo A, Yew S, et al. Sex-specific differences in risk factors for sarcopenia amongst community-dwelling older adults. Age (Dordr) 2015;37:121.
[30] Swedko PJ, Clark HD, Paramsothy K, Akbari A. Serum creatinine is an inadequate screening test for renal failure in elderly patients. Arch Intern Med 2003;163:356–360.
[31] Gonwa TA, McBride MA, Anderson K, Mai ML, Wadei H, Ahsan N. Continued influence of preoperative renal function on outcome of orthotopic liver transplant (OLTX) in the US: where will MELD lead us? Am J Transplant 2006;6:2651–2659.
[32] Kanwal F, Dulai GS, Spiegel BM, Yee HF, Gralnek IM. A comparison of liver transplantation outcomes in the pre- vs. post-MELD eras. Aliment Pharmacol Ther 2005;21:169–177.
[33] Cholongitas E, Marelli L, Kerry A, Goodier DW, Nair D, Thomas M, et al. Female liver transplant recipients with the same GFR as male recipients have lower MELD scores–a systematic bias. Am J Transplant 2007;7:685–692.
[34] Ahn HS, Kim YS, Kim SG, Kim HK, Min SK, Jeong SW, et al. Cystatin C is a good predictor of hepatorenal syndrome and survival in patients with cirrhosis who have normal serum creatinine levels. Hepatogastroenterology 2012;59:1168–1173.
[35] Levey AS, Coresh J, Greene T, Stevens LA, Zhang YL, Hendriksen S, et al. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. Ann Intern Med 2006;145:247–254.
[36] Gerbes AL, Gülberg V, Bilzer M, Vogeser M. Evaluation of serum cystatin C concentration as a marker of renal function in patients with cirrhosis of the liver. Gut 2002;50:106–110.
[37] Chu SC, Wang CP, Chang YH, Hsieh YS, Yang SF, Su JM, et al. Increased cystatin C serum concentrations in patients with hepatic diseases of various severities. Clin Chim Acta 2004;341:133–138.
[38] Takeuchi M, Fukuda Y, Nakano I, Katano Y, Hayakawa T. Elevation of serum cystatin C concentrations in patients with chronic liver disease. Eur J Gastroenterol Hepatol 2001;13:951–955.
[39] Medeiros FS, Sapienza MT, Prado ES, Agena F, Shimizu MH, Lemos FB, et al. Validation of plasma clearance of 51Cr-EDTA in adult renal transplant recipients: comparison with inulin renal clearance. Transpl Int 2009;22:323–331.