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Performance of race-neutral eGFR equations in patients with decompensated cirrhosis

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Abstract

The 2021 Chronic Kidney Disease Epidemiology Collaboration equation [CKD-EPI 2021] is a race-neutral equation recently developed and rapidly implemented as a reference standard to estimate glomerular filtration rate (GFR). However, its role in cirrhosis has not been examined especially in low GFR. We analyzed the performance of CKD-EPI 2021 compared to other equations with protocol measured GFR (mGFR) in cirrhosis.

We analyzed 2090 unique adult patients with cirrhosis undergoing protocol GFR measurements using iothalamate clearance from 1985-2015 when listed for liver transplantation at Baylor University in Dallas and Fort Worth, Texas. Using mGFR as a reference standard, the CKD-EPI 2021 was compared to CKD-EPI 2012, MDRD-4, MDRD-6, RFH and GRAIL overall and in certain subgroups (ascites, mGFR ≥ 30 mL/min/1.73 m², diagnosis, MELD and gender). We examined bias (difference between eGFR and mGFR), accuracy (p30: eGFR within $\pm 30\%$ of mGFR) and agreement between eGFR and mGFR categories.

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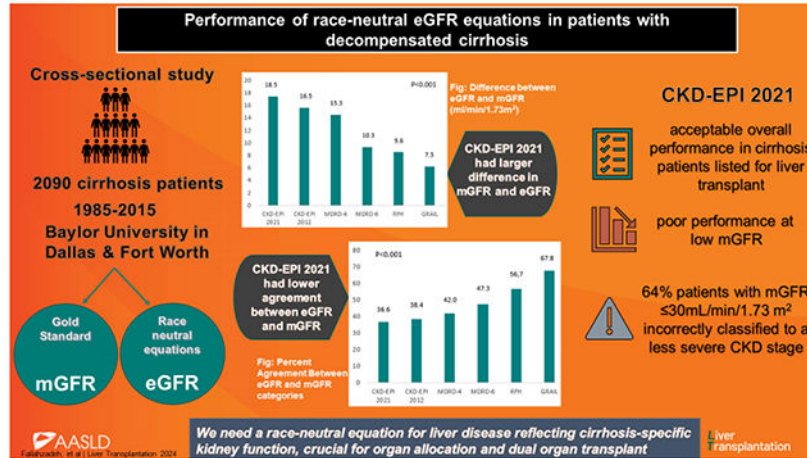
Presentation

Presentation of preliminary data was performed at a Plenary session at The Liver Meeting 2022 in Washington DC, United States.

CKD-EPI 2021 had the 2nd lowest bias across the entire range of GFR after GRAIL (6.6 vs. 4.6 mL/min/1.73 m², respectively, $p < 0.001$). Accuracy of CKD-EPI 2021 was similar to CKD-EPI 2012 ($p_{30} = 67.8\%$ vs. 67.9%, respectively) that was higher than the other equations ($p < 0.001$). It had a similar performance in patients with ascites, by diagnoses, MELD subgroups, by sex and in non-Black patients. However, it had a relatively higher overestimation in mGFR 30 mL/min/1.73 m² than most equations (18.5 mL/min/1.73 m², $p < 0.001$). Specifically, 64% of patients with mGFR 30 mL/min/1.73 m² were incorrectly classified to a less severe CKD stage by CKD-EPI 2021. In Blacks, CKD-EPI 2021 underestimated eGFR by 17.9 mL/min/1.73 m² that was higher than the alternate equations except RFH ($p < 0.001$).

The novel race-neutral eGFR equation, CKD-EPI 2021, improves the GFR estimation overall but may not accurately capture true kidney function in cirrhosis specifically at low GFR. There is an urgent need for a race-neutral equation in liver disease reflecting the complexity of kidney function physiology unique to cirrhosis given implications for organ allocation and dual organ transplant.

Graphical Abstract



Keywords

Glomerular filtration rate; kidney function; liver disease; chronic kidney disease; transplantation

Introduction

Kidney dysfunction is associated with increased mortality in patients with cirrhosis. (1, 2) Development of kidney dysfunction before liver transplantation (LT) is an important predictor of immediate and long-term outcomes after LT. (3) Additionally, presence of kidney dysfunction is a key component of eligibility criteria for simultaneous liver kidney transplantation (SLKT) and assessed using estimated glomerular filtration rate (eGFR). (4) The pathophysiology of kidney dysfunction in cirrhosis is multifactorial, related to structural and functional changes and may not be adequately captured by equations developed in the population without liver disease. (5–7) Kidney function assessment is more challenging

in patients with cirrhosis and ascites because of the increased volume of distribution of creatinine, decreased production and potentially the high incidence of sarcopenia. (8) Therefore, accurate assessment of kidney function with a validated tool is important in patients with cirrhosis. (1, 2, 9)

The 2021 Chronic Kidney Disease Epidemiology Collaboration equation [CKD-EPI 2021] is a recent race-neutral equation proposed as a new, reliable way of estimating GFR using age, gender, serum creatinine (SCr) \pm cystatin C. (10) Within a short duration after its development and validation, it was universally adopted as the reference standard and is currently recommended by the National Kidney Foundation and American Society of Nephrology to assess kidney dysfunction in patients with CKD. (11, 12) It was also widely adopted across LT centers for decisions regarding organ allocation. (6) However, its performance in patients with decompensated cirrhosis is not known.

Several limitations exist to current eGFR equations in the population with cirrhosis. First, similar to older SCr-based equations, CKD-EPI 2021 was not validated in patients with liver disease. (13–15) Second, SCr-based eGFR equations tend to overestimate GFR in cirrhosis, especially at low GFR. (8, 16) Finally, although SCr- and Cystatin C-based equations offer better risk prediction, cystatin C is slightly more costly and may not be readily available with timely turnaround in patients with cirrhosis. (17, 18) In addition, cystatin C based equations may have similar issues with performance characteristics in patients with cirrhosis. (19)

Using measured GFR (mGFR) (20) as a reference standard, we examined the performance of CKD-EPI 2021 equation in patients with cirrhosis listed for LT as compared to older SCr-based equations (CKD-EPI 2012, Modification of Diet in Renal Disease [MDRD-4, MDRD-6]) and two equations developed in patients with cirrhosis, Royal Free Hospital (RFH) cirrhosis GFR and GFR Assessment in Liver disease (GRAIL).

Methods

Patients

In this cross-sectional study, we analyzed all consecutive adult patients (age \geq 18 years) with cirrhosis listed for LT that underwent protocol measurements of GFR using iothalamate clearance between 1985 and 2015 at Baylor University Medical Center and Baylor All Saints in Dallas and Fort Worth, Texas. This study was performed in an outpatient basis. Written informed consent was obtained from each patient for sample collection. Patients listed for SLKT were not included and patients with missing mGFR data were not considered. The study design was conformed to the ethical guidelines of the 1975 Declaration of Helsinki and approved by institutional review committee at Baylor University Medical Center Hospital in Dallas, Texas.

Measured GFR

Urinary clearance of ^{125}I -iothalamate was used to measure the GFR during the study period and has been previously described. (20–22) We performed GFR measurements in stable outpatients without an acute change in renal function. Measured GFR while listed

before LT was used as the reference. GFR measurement was performed by subcutaneous administration of ^{125}I -iothalamate, and collection of blood and urine samples at timed intervals. GFR was measured in milliliters per minute (urine in counts per minute/milliliter \times urinary flow rate [milliliters/min/plasma counts per minute/milliliter]). All mGFRs and eGFRs were expressed per 1.73 m^2 of body surface area.

Estimated GFR and Analysis

Using mGFR as the reference, the performance characteristics of CKD-EPI 2021 equation was compared to CKD-EPI 2012, MDRD-4, MDRD-6, RFH and GRAIL. Pre-specified subgroup analyses were performed in patients with cirrhosis by presence of ascites, mGFR $30 \text{ mL/min/1.73 m}^2$, etiology of liver disease, MELD score, gender and race. Cutoff of $30 \text{ mL/min/1.73 m}^2$ was chosen as it is the threshold to consider SLKT rather than LT alone for a listed patient with cirrhosis and CKD. (4, 23) We had one mGFR value and one eGFR value per equation for each unique patient. Cystatin C was not included in our equations as it was not clinically available throughout the entirety of the study.

We examined bias, accuracy, and precision for all the equations. Bias was defined as the median difference between eGFR and mGFR (mGFR minus eGFR), with positive numbers suggesting underestimation and negative values implying overestimation. For example, a bias of $+10 \text{ mL/min/1.73 m}^2$ for an equation implies that for mGFR of $40 \text{ mL/min/1.73 m}^2$, the calculated eGFR will be $30 \text{ mL/min/1.73 m}^2$. Accuracy was defined as the percentage of patients whose eGFR values were within $\pm 30\%$ of the mGFR (p30) and was tested using the likelihood ratio chi-square test. (24) Precision was assessed by the width of the confidence interval of bias values. In addition, we identified the agreement between eGFR and mGFR categories by identifying pairs of eGFR and mGFR that were misclassified into separate groups using CKD stages as the reference, i.e., patients whose eGFR and mGFR values did not fall into the same CKD category as defined by KDIGO criteria.

Kruskal-Wallis rank sum test was used to compare the bias of different equations in the overall population while chi square test or Fisher's exact test were used to compare differences in accuracy and in the CKD stage agreement of the different equations. Pairwise comparisons were made using Wilcoxon rank-sum tests or Fisher's exact tests as appropriate with Bonferroni correction for multiple testing. All statistical analyses were performed using R version 4.1.3 (R Foundation for Statistical Computing, Vienna, Austria). Statistical significance was set at $p < 0.05$.

Results

Between 1985 and 2015, there were 2,090 unique patients with cirrhosis with measured GFR. The median age of patients was 49 years (interquartile range (IQR): 42-57), 40.4% of patients were female and 6.6% were Black. (Table 1). The most common etiologies of liver disease included hepatitis C (30.3%), Alcohol-associated liver disease (20.8%) and metabolic dysfunction-associated steatohepatitis (MASH)/cryptogenic cirrhosis (13.3%). The median serum Cr was 0.9 (IQR: 0.8-1.2).

Measured GFR

The median mGFR was 95.0 mL/min/1.73 m² (IQR: 66.2-120.0). The number of mGFR by CKD categories was 1,160 (55.5%) for stage I, 519 (24.8%) for stage II, 308 (14.7%) for stage III, 67 (3.2%) for stage IV, and 36 (1.7%) for stage V.

Overall

Using urinary clearance of ¹²⁵I-iothalamate as the reference standard, CKD-EPI 2021 had the 2nd lowest bias across the entire range of GFR after GRAIL (6.6 vs. 4.6 mL/min/1.73 m², respectively, p<0.001) (Table 2). This was followed by CKD-EPI 2012 (8.9 mL/min/1.73 m²), MDRD-4 (11.7 mL/min/1.73 m²), MDRD-6 (16.2 mL/min/1.73 m²) and RFH (33.2 mL/min/1.73 m²) (Figure 1). Accuracy of CKD-EPI 2021 was similar to CKD-EPI 2012 (p30=67.8% vs. 67.9%, respectively) that was higher than the other equations (p<0.001). CKD-EPI 2021 also had the highest agreement between eGFR and mGFR categories (59.5%) followed by GRAIL (58.9%) and CKD-EPI 2012 (58.8%) that was higher than MDRD-4 and MDRD-6 and RFH (p<0.001) (Table 2). Data by etiology of liver disease is presented in Supplemental Table 1, Supplemental Digital Content 1, <http://links.lww.com/LVT/A605>.

Ascites

Performance of CKD-EPI 2021 in patients with ascites was similar to the entire population. In patients with ascites, CKD-EPI 2021 had the 2nd lowest bias (3.8 mL/min/1.73 m²) after GRAIL (2.8 mL/min/1.73 m²) that was followed by CKD-EPI 2012 (6.5 mL/min/1.73 m²), MDRD-4 (9.6 mL/min/1.73 m²), MDRD-6 (15.3 mL/min/1.73 m²) and RFH (33.9 mL/min/1.73 m²) (p<0.001) (Table 2 and Supplemental Figure 1, Supplemental Digital Content 1, <http://links.lww.com/LVT/A605>). Accuracy was similar for CKD-EPI 2021 and CKD-EPI 2012 (p30: 64.1% vs. 64.7%, respectively) that was higher than the other equations (p<0.001). Furthermore, CKD-EPI 2021 had the highest agreement between eGFR and mGFR categories (56.4%) followed by CKD-EPI 2012 (55.55%) and GRAIL (51.6%) that was higher than MDRD-4 and MDRD-6 and RFH (p<0.001).

Low GFR

For mGFR \leq 30 mL/min/1.73 m², CKD-EPI 2021 **overestimated** GFR by 18.5 mL/min/1.73 m² with low precision that was higher than CKD-EPI 2012 (16.5 mL/min/1.73 m²), MDRD-4 (15.3 mL/min/1.73 m²), MDRD-6 (10.3 mL/min/1.73 m²), RFH (9.6 mL/min/1.73 m²) and GRAIL (7.3 mL/min/1.73 m²) (p<0.001) (Table 2 and Figure 2). Similarly, CKD-EPI 2021 had the lowest accuracy while GRAIL had the highest accuracy (p30: 13.4% vs. 38.0, respectively, p<0.001) (Figure 2). Also, CKD-EPI 2021 had the lowest agreement between eGFR and mGFR categories while GRAIL had the highest one (36.6% vs. 67.8%, respectively, p<0.001) (Table 2). Specifically, 64% of patients with mGFR \leq 30 mL/min/1.73 m² were incorrectly classified to a less severe CKD stage by CKD-EPI 2021.

MELD score categories

In patients with MELD \geq 29, CKD-EPI 2021 had a comparable accuracy to CKD-EPI 2012 that was higher than MDRD-4, MDRD-6, RFH and GRAIL (p<0.001). For patients with

MELD>29, CKD-EPI 2021 had a comparable accuracy (p30: 44.3%) to CKD-EPI 2012 (p30: 45.9%), MDRD-4 (p30: 43.5%), MDRD-6 (p30: 48.8%) and GRAIL (p30: 44.6%) that was higher than RFH (p30: 12.9%) ($p<0.001$) (Table 3). Similar pattern exists for agreement between eGFR and mGFR categories with comparable performance of CKD-EPI 2021 to CKD-EPI 2012 and GRAIL in MELD ≥ 29 and similar performance of CKD-EPI 2012 to all the other equations except RFH for MELD>29. Further information about bias and precision of eGFR equations in different MELD score categories are listed in Table 3.

Gender

CKD-EPI 2021 had comparable accuracy to CKD-EPI 2012 in males (p30: 67.0% vs. 67.3%, respectively) and in females (69.0% vs. 68.7%, respectively) that was higher than MDRD-4, MDRD-6, RFH and GRAIL ($p<0.001$ for both males and females) (Table 4). Moreover, CKD-EPI 2021 had the highest agreement between eGFR and mGFR categories followed by CKD-EPI 2012 for both males (60.1% vs. 59.7%, respectively) and females (58.7% vs. 57.4%, respectively) that was higher than the other equations ($p<0.001$ for both males and females) (Table 4). Further information about bias and precision of eGFR equations in different gender categories are listed in Table 4 and Supplemental Figure 1, Supplemental Digital Content 1, <http://links.lww.com/LVT/A605>.

Race

In Blacks, CKD-EPI 2021 underestimated eGFR by 17.9 mL/min/1.73 m² that was higher than the alternate equations except RFH ($p<0.001$) (Table 4). This bias was almost three times as high as non-Blacks (5.8 mL/min/1.73 m²) and twice as high when compared to CKD-EPI 2012 (7.6 mL/min/1.73 m²). However, CKD-EPI 2021 had the 2nd lowest bias (5.8 mL/min/1.73 m²) after GRAIL (4.7 mL/min/1.73 m²) in non-Black patients (Supplemental Figure 1, Supplemental Digital Content 1, <http://links.lww.com/LVT/A605>). CKD-EPI 2021 had a comparable accuracy to CKD-EPI 2012 in both Black (p30: 66.1% vs 68.5%, respectively) and non-Black (p30:59.8% vs. 58.5%, respectively) patients that was significantly higher than all the other equations only in non-Black patients ($p<0.001$). CKD-EPI 2021 had the highest agreement between eGFR and mGFR categories in non-Black patients (68%, $p<0.001$) while having the 4th highest value for Black patients (56.9%) following CKD-EPI 2012 (66.9%), GRAIL (66.9%) and MDRD-4 (66.9%) (Table 4). In fact, 12.6% of Black patients with mGFR>60 mL/min/1.73 m² were misclassified as having worse kidney function by CKD-EPI 2021.

Discussion

Our results indicate that the new race-neutral equation, CKD-EPI 2021, has acceptable overall performance in patients with cirrhosis listed for LT and the subgroup with ascites compared to the older eGFR equations. It also performed well across the different diagnostic subgroups, MELD score subgroups, different genders and non-Black patients. However, the CKD-EPI 2021 formula had a poor performance in patients with low mGFR and most of the patients with mGFR ≤ 30 mL/min/1.73 m² were incorrectly classified to a less severe CKD stage by CKD-EPI 2021.

Although mGFR is considered the reference standard for patients with cirrhosis, it is not practical to perform mGFR measurement for all the patients due to technical requirements, cost and lack of widespread availability. Therefore, eGFR equations are used instead that are more practical clinically but come with limitations. (8) SCr has been widely used as the biomarker for kidney function in eGFR equations as it is cheap and readily available. However, it is not an accurate marker for kidney dysfunction in patients with liver disease and most of the equations estimating GFR using SCr under-represented patients with liver disease. (22) Historically, demographic variables including age, sex and race have been among the variables included in most of the eGFR equations. Inclusion of race (Black vs. non-Black) was due to earlier reports suggesting higher average SCr levels in Black participants compared to non-Black ones. (14, 25, 26) However, inclusion of race in equations brings about certain issues as explained below. (10, 27, 28) Thus, recent race-neutral eGFR equations, namely CKD-EPI 2021, were developed to address these issues. (10) However, these studies also did not include a considerable number of patients with liver disease.

Race is a social and not a biologic construct. (10, 29) It is patient-reported and not verified by genetic ancestry and inclusion of race in eGFR equations ignores diversity within the different racial groups. (10, 27, 28, 30) Use of race in eGFR calculation has been associated with healthcare disparities both in kidney disease diagnosis and eligibility for kidney transplantation listing. (27, 29) Furthermore, inclusion of race as a social construct can normalize nonscientific and detrimental beliefs about race and biology in the training of future health care providers. (29, 31) Therefore, it is imperative to understand the limitations of current race-neutral equations and develop new race-neutral equations for patients with liver disease to minimize these limitations.

In a nationally representative data of National Health and Nutrition Examination Survey, it was shown that CKD-EPI 2021 could mark 434,000 Black adults with a new CKD diagnosis and categorize 584,000 to more advanced stages of CKD. However, among non-Black adults, it might remove CKD diagnoses from 5.51 million and categorize 4.59 million to less advanced stages of CKD. (32) Although CKD-EPI 2021 had an acceptable overall performance in our patients with cirrhosis, it did not perform well in low GFR and Black race. Other than management of patients with cirrhosis, this is extremely important considering the decisions about dual organ transplantation. Current United Network of Organ Sharing criteria to consider a patient for SLKT include CKD with most recent measured or calculated GFR ≥ 30 mL/min or sustained acute kidney injury with GFR ≥ 25 mL/min for at least 6 consecutive weeks. (4, 23) Considering these cutoffs, even small changes in reported eGFR in patients with cirrhosis and low GFR can alter their eligibility for SLKT. In fact, a retrospective study by Panchal et al. showed that about 3-3.6% of Black patients listed for LT would have been reclassified as qualifying for CKD-related SLKT (33) Currently, there is no specific eGFR equation validated to use for SLKT eligibility and clinicians are recommended to select a formula not including a race-based variable. (34, 35) Therefore, there is need for a standardized equation that performs well in all the spectrum of liver disease including low GFR and Black race. Work on a developing a race-neutral equation developed in patients with cirrhosis is currently underway (GRAIL 2.0) (36).

As most of the eGFR equations excluded patients with cirrhosis, eGFR equations in patients with cirrhosis such as RFH or GRAIL were developed. (22, 37) RFH equation is another equation developed in patients with cirrhosis that has a good accuracy to predict GFR. Although it is a race-neutral equation, it was developed in a relatively smaller set of patients, includes seven different variables and depends on physical examination finding of presence of significant ascites. (37) Also, a recent study showed that RFH has inferior accuracy compared to conventional equation in renal function prediction in cirrhosis that was in concordant with our findings. (38) GRAIL is a model for GFR assessment specifically developed in patients with liver disease with the potential to predict CKD development after LT. It was shown to be particularly useful at low GFR where traditional SCr-based equations exhibit a higher bias. (22) We also illustrated that GRAIL had a satisfactory performance compared to CKD-EPI 2021 especially in low GFR and Black race. However, this equation also includes the race as one of its core variables. Thus, there is an urgent need for a simpler, race-neutral equation with comparable accuracy in patients with liver disease. An updated, race-neutral version of GRAIL is currently under development and validation.

The main strength of our study was evaluation of CKD-EPI 2021 equation in a large cohort of patients with cirrhosis. Protocol measurements using iothalamate were used to calculate the mGFR that increased the accuracy of our measurements. We also examined the performance of this equation in certain subgroups of interest in comparison with alternate equations.

Nevertheless, our study was limited in several ways. We had limited number of patients with mGFR $30 \text{ mL/min/1.73m}^2$ and Black race. Although addition of cystatin C to Cr improves the accuracy of CKD-EPI 2021 equation, it was not included as it was not clinically available throughout the entirety of the study. (10) We did not have the data about the severity of ascites or use of diuretics in our patients. We had the nutritional status data available only for a small number of patients that significantly limited the analyses; therefore, they were not included. Also, patients present with different clinical presentations and clinicians could select the eGFR equation they believe would best represent their patients. However, having one equation for each subset of patients may be untenable. Prospective assessment of the ability of CKD-EPI 2021 to accurately identify future development of kidney dysfunction after transplant was not examined as the goal was to assess its performance in waitlisted patient. However, investigation of CKD-EPI 2021 as compared to other race-neutral equations is planned. As our data were mostly collected before the widespread availability of HCV direct-acting antiviral medications, our patient population had a higher representation of HCV cirrhosis that might limit the current generalizability of our findings. Finally, CKD is a disease of aged population and our patient population was relatively younger than CKD-EPI 2021 validation data set that could limit its performance in our patients.

In summary, the novel race-neutral eGFR, CKD-EPI 2021, overall improves GFR estimation compared to the other estimating equations. However, it may not accurately capture true kidney function in cirrhosis. In low GFR, it may not pick up kidney dysfunction. There is an urgent need for a race-neutral equation in liver disease that reflects the complexity of kidney

function physiology unique to cirrhosis and given implications for organ allocation and dual organ transplant.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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All authors have nothing to disclose that is directly related to the manuscript.

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Abbreviations:

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|----------------|---|
| ALT | alanine aminotransferase |
| AST | aspartate aminotransferase |
| BUN | blood urea nitrogen |
| CKD | chronic kidney disease |
| CKD-EPI | Chronic Kidney Disease Epidemiology Collaboration |
| eGFR | estimated GFR |
| GFR | glomerular filtration rate |
| GRAIL | GFR Assessment in Liver disease |
| IQR | interquartile range |
| LT | liver transplantation |
| MDRD | Modification of Diet in Renal Disease |
| mGFR | measured GFR |
| MASH | metabolic dysfunction-associated steatohepatitis |
| MELD | model for end-stage liver disease |
| RFH | Royal Free Hospital |
| SCr | serum creatinine |

SLKT simultaneous liver kidney transplantation

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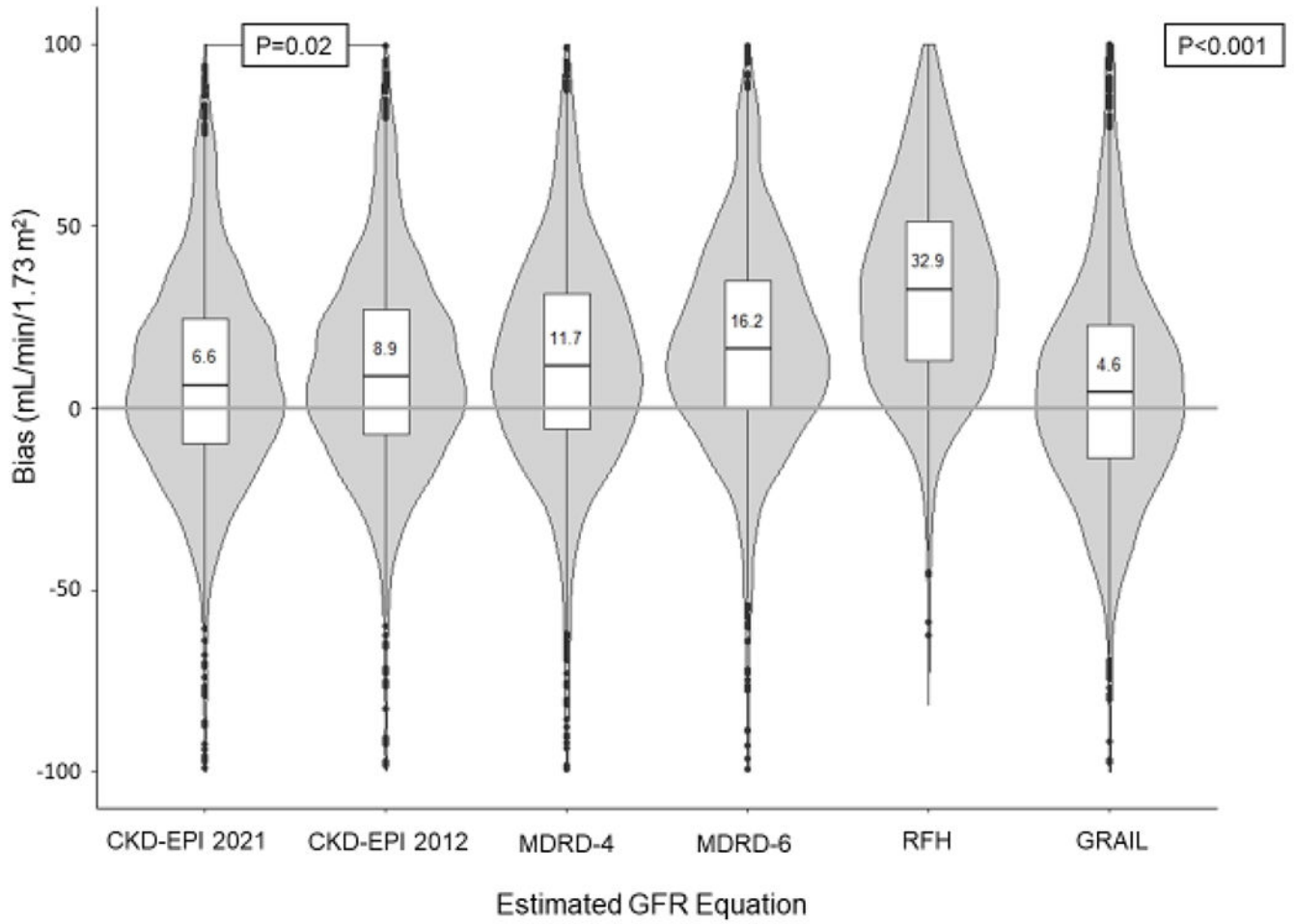


Figure 1: Bias distribution (difference between estimated and measured GFR) of CKD-EPI 2021, CKD-EPI 2012, MDRD-4, MDRD-6, RFH and GRAIL as compared with protocol measured GFR using iothalamate in all the patients with cirrhosis.

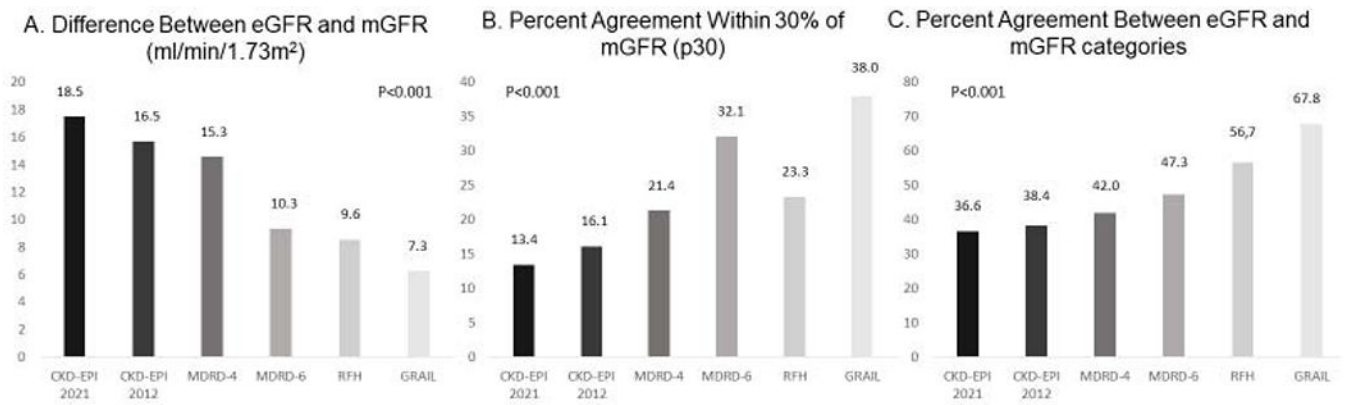


Figure 2: Performance of CKD-EPI 2021 as compared to CKD-EPI 2012, MDRD-4, MDRD-6, RFH and GRAIL in patients with low measured GFR (less than 30ml/min/1.73m²). CKD-EPI 2021 had larger difference in measured GFR and estimated GFR (**Panel A**), lower percent agreement (**Panel B**) and lower agreement between estimated GFR and measured GFR categories (**Panel C**).

Table 1.

Baseline characteristics of the patients with cirrhosis and measured glomerular filtration rate by iothalamate clearance

| | |
|----------------------------------|--------------------|
| | N=2,090 |
| Age, years | 49.0 (42.0-57.0) |
| Gender, female | 844 (40.4) |
| Race, Non-Black | 1953 (93.4) |
| Etiology of liver disease | |
| Hepatitis C virus | 633 (30.3) |
| Alcoholic | 434 (20.8) |
| MASH/Cryptogenic | 278 (13.3) |
| Primary sclerosing cholangitis | 176 (8.4) |
| Primary biliary cholangitis | 173 (8.3) |
| Hepatitis B virus | 105 (5.0) |
| Autoimmune hepatitis | 70 (3.3) |
| Alpha-1 antitrypsin deficiency | 32 (1.5) |
| Other | 189 (9.0) |
| GFR Categories | |
| 90 mL/min/1.73 m ² | 1160 (55.5) |
| 60-89 mL/min/1.73 m ² | 519 (24.8) |
| 45-59 mL/min/1.73 m ² | 180 (8.6) |
| 30-44 mL/min/1.73 m ² | 128 (6.1) |
| 15-29 mL/min/1.73 m ² | 67 (3.2) |
| <15 mL/min/1.73 m ² | 36 (1.7) |
| Ascites, present | 1397 (66.8) |
| AST (IU/L) | 53.0 (35.0, 83.0) |
| ALT (IU/L) | 79.0 (51.8, 125.0) |
| Alkaline phosphatase (IU/L) | 85.0 (64.0, 116.0) |
| Total bilirubin (mg/dL) | 3.0 (1.7, 5.8) |
| Platelets (10 ⁹ /L) | 76.0 (51.0-110.0) |
| BUN (mg/dL) | 14.0 (10.0-20.0) |
| Creatinine (mg/dL) | 0.9 (0.8-1.2) |
| Albumin (g/dL) | 3.0 (2.7-3.5) |
| MELD score | 18.3 ± 4.6 |

Data are presented as n (%), mean \pm standard deviation or median (interquartile range).

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; GFR, glomerular filtration rate; MASH, metabolic dysfunction-associated steatohepatitis; MELD, model for end-stage liver disease

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Table 2.

Bias, precision and accuracy in eGFR using CKD-EPI 2021, CKD-EPI 2012, MDRD-4 and MDRD-6, RFH and GRAIL as compared with mGFR protocol using iohalamate in all patients and selected subgroups.

| Group | eGFR Equations | | | | | | p-value |
|-----------------------------------|--|--|---------------------------------------|---------------------------------------|--------------------------------------|---------------------------------------|---------|
| | CKD-EPI 2021 | CKD-EPI 2021 | MDRD-4 | MDRD-6 | RFH | GRAIL | |
| All (N=2090) | | | | | | | |
| Median Bias 95% CI IQR | 6.6 (4.8, 7.9) (-9.6, 24.4) | 8.9* (7.6, 10.4) (-7.0, 27.6) | 11.7* (10.6, 13.3) (-5.9, 31.8) | 16.2** (14.9, 17.8) (-0.08, 35.9) | 33.2** (30.3, 35.8) (13.0, 56.0) | 4.6** (2.8, 6.0) (-13.8, 22.2) | <0.001 |
| P30% 95% CI | 67.8 (66.0, 70.0) | 67.9 (66.0, 70.0) | 62.9* (61.0, 65.0) | 61.4* (59.0, 63.0) | 34.7** (33.0, 37.0) | 63.1* (60.0, 66.0) | <0.001 |
| % Agreement (CKD Stages) 95% CI | 59.5 (57.0, 62.0) | 58.8 (57.0, 61.0) | 53.8* (52.0, 56.0) | 50.3** (0.48, 0.52) | 11.4** (9.0, 14.0) | 58.9 (57.0, 61.0) | <0.001 |
| Ascites (N=1397) | | | | | | | |
| Median Bias 95% CI IQR | 3.8 (2.4, 5.8) (-12.6, 23.9) | 6.5 (5.3, 8.4) (-10.3, 26.5) | 9.6** (7.9, 11.4) (-7.5, 30.8) | 15.3** (13.6, 16.7) (-1.3, 35.7) | 33.9** (31.0, 36.8) (13.1, 57.3) | 2.8 (0.6, 5.3) (-15.7, 23.9) | <0.001 |
| P30% 95% CI | 64.1 (62.0, 66.0) | 64.7 (58.0, 62.0) | 60.3 (58.0, 62.0) | 58.4* (56.0, 61.0) | 28.8** (26.0, 32.0) | 57.2* (55.0, 59.0) | <0.001 |
| % Agreement (CKD Stages) 95% CI | 56.4 (54.0, 59.0) | 55.5 (53.0, 58.0) | 52.8 (51.0, 55.0) | 47.7** (46.0, 50.0) | 13.7** (11.0, 16.0) | 51.6 (49.0, 54.0) | <0.001 |
| mGFR 30 (N=112) | | | | | | | |
| Median Bias (95% CI) IQR | -18.5 (-26.0, -14.9) (-39.5, -8.58) | -16.5 (-23.5, -13.1) (-36.5, -7.52) | -15.3 (-21.1, -12.1) (-31.7, -6.3) | -10.3* (-14.9, -7.5) (-29.5, -2.5) | -9.6* (-17.1, -2.8) (-23.0, -1.8) | -7.3** (-10.1, -4.2) (-17.1, -3.0) | <0.001 |
| P30% (95% CI) | 13.4 (12.0, 15.0) | 16.1 (15.0, 18.0) | 21.4 (20.0, 23.0) | 32.1* (30.0, 34.0) | 23.3** (20.0, 26.0) | 38.0* (36.0, 40.0) | <0.001 |
| % Agreement (CKD Stages) (95% CI) | 36.6 (35.0, 39.0) | 38.4 (36.0, 40.0) | 42.0 (40.0, 44.0) | 47.3 (45.0, 49.0) | 56.7 (53.0, 60.0) | 67.8** (66.0, 70.0) | <0.001 |

* p 0.05,

**

p 0.001; these values refer to direct comparison of different equations with CKD-EPI 2021.

Note: Bias, median difference between eGFR and mGFR with positive values implying underestimation and negative values implying overestimation; precision, width of IQR; accuracy, percent of estimated values within 30% of measured GFR (p30)

* GFR categories are defined according to CKD stages 1 (GFR>90 mL/min/1.73 m²), 2 (GFR=60-89 mL/min/1.73 m²), 3 (GFR=30-59 mL/min/1.73 m²), 4 (GFR=15-29 mL/min/1.73 m²) and 5 (GFR<30 mL/min/1.73 m²). Stages 4 and 5 were combined for these analyses due to small number of cases in these groups.

Abbreviations: eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate; mGFR, measured glomerular filtration rate.

Table 3.

Bias, precision and accuracy in eGFR using CKD-EPI 2021, CKD-EPI 2012, MDRD-4 and MDRD-6, RFH and GRAIL as compared with mGFR protocol using iothalamate in selected subgroups of MELD

| MELD Subgroup | eGFR Equations | | | | | | p-value |
|-----------------------------------|---------------------------------|---------------------------------|---------------------------------|----------------------------------|----------------------------------|--------------------------------|---------|
| | CKD-EPI 2021 | CKD-EPI 2021 | MDRD-4 | MDRD-6 | RFH | GRAIL | |
| MELD<15 (N=863) | | | | | | | |
| Median Bias 95% CI IQR | 9.0 (6.3, 11.2) (-7.4, 25.3) | 11.5 (8.7, 14.4) (-4.8, 27.1) | 12.9* (10.4, 15.7) (-3.4, 32.0) | 16.5** (14.5, 18.8) (1.4, 34.0) | 32.4** (26.9, 35.1) (10.7, 48.4) | 4.5* (2.2, 6.5) (-12.7, 20.7) | <0.001 |
| P30% 95% CI | 73.7 (72.0, 76.0) | 74.9 (73.0, 77.0) | 68.3 (66.0, 70.0) | 68.0 (66.0, 70.0) | 43.3** (40.0, 47.0) | 71.6 (70.0, 74.0) | <0.001 |
| % Agreement (CKD Stages) 95% CI | 64.1 (62.0, 66.0) | 63.1 (61.0, 65.0) | 56.8* (55.0, 59.0) | 55.3* (53.0, 57.0) | 8.8** (7.0, 11.0) | 63.0 (61.0, 65.0) | <0.001 |
| 15 MELD 19 (N=472) | | | | | | | |
| Median Bias 95% CI IQR | 4.2 (2.2, 6.7) (-9.5, 22.8) | 6.3 (4.6, 9.0) (-6.5, 26.5) | 10.9* (8.8, 12.8) (-5.0, 29.4) | 15.0** (13.1, 17.6) (0.5, 33.9) | 27.1** (21.9, 32.3) (11.2, 51.1) | 3.4 (0.2, 6.3) (-14.5, 21.5) | <0.001 |
| P30% 95% CI | 71.6 (70.0, 74.0) | 71.4 (69.0, 73.0) | 67.2 (65.0, 69.0) | 64.0 (62.0, 66.0) | 40.9** (37.0, 44.0) | 65.5 (63.0, 68.0) | <0.001 |
| % Agreement (CKD Stages) 95% CI | 60.4 (58.0, 62.0) | 60.6 (59.0, 63.0) | 56.3 (54.0, 58.0) | 50.4* (48.0, 53.0) | 13.4** (11.0, 16.0) | 57.4 (55.0, 60.0) | <0.001 |
| 20 MELD 29 (N=418) | | | | | | | |
| Median Bias (95% CI) IQR | 6.8 (4.0, 10.3) (-11.3, 25.0) | 9.3 (6.9, 11.8) (-9.8, 27.6) | 13.6 (9.8, 16.5) (-7.1, 31.4) | 18.25** (14.3, 21.2) (0.6, 39.6) | 36.1** (29.4, 43.2) (16.7, 59.0) | 6.8 (3.0, 11.1) (-13.2, 28.1) | <0.001 |
| P30% (95% CI) | 63.6 (62.0, 66.0) | 61.8 (60.0, 64.0) | 56.8 (55.0, 59.0) | 50.1* (48.0, 52.0) | 22.9** (20.0, 26.0) | 53.4 (51.0, 56.0) | <0.001 |
| % Agreement (CKD Stages) (95% CI) | 55.5 (53.0, 58.0) | 54.3 (52.0, 56.0) | 47.4 (45.0, 50.0) | 40.4** (38.0, 43.0) | 16.1** (14.0, 19.0) | 54.5 (52.0, 57.0) | <0.001 |
| MELD >29 (N=210) | | | | | | | |
| Median Bias (95% CI) IQR | -0.7 (-5.7, 10.5) (-15.6, 32.3) | 51.2 (-3.3, 12.8) (-13.6, 34.1) | 5.3 (-0.1, 13.5) (-10.7, 37.1) | 12.9* (7.8, 20.9) (-3.4, 43.8) | 56.3** (40.6, 70.4) (19.0, 83.1) | 1.2 (-3.3, 12.6) (-16.0, 31.4) | <0.001 |
| P30% (95% CI) | 44.3 (42.0, 46.0) | 45.9 (44.0, 48.0) | 43.5 (41.0, 46.0) | 48.8 (47.0, 51.0) | 12.9** (11.0, 15.0) | 44.6 (42.0, 47.0) | <0.001 |
| % Agreement (CKD Stages) (95% CI) | 45.7 (44.0, 48.0) | 45.2 (43.0, 47.0) | 46.7 (45.0, 49.0) | 47.6 (45.0, 50.0) | 12.9** (11.0, 15.0) | 46.2 (44.0, 48.0) | <0.001 |

* p 0.05,

** p 0.001; these values refer to direct comparison of different equations; with CKD-EPI 2021.

Note: Bias, median difference between eGFR and mGFR with positive values implying underestimation and negative values implying overestimation; precision, width of IQR; accuracy percent of estimated values within 30% of measured GFR (p30)

* GFR categories are defined according to CKD stages 1 (GFR>90 mL/min/1.73 m²), 2 (GFR=60-89 mL/min/1.73 m²), 3 (GFR=30-59 mL/min/1.73 m²), 4 (GFR=15-29 mL/min/1.73 m²) and 5 (GFR<15 mL/min/1.73 m²). Stages 4 and 5 were combined for these analyses due to small number of cases in these groups.

Abbreviations: eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate; MELD, model for end-stage liver disease; mGFR, measured glomerular filtration rate.

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Table 4.

Bias, precision and accuracy in eGFR using CKD-EPI 2021, CKD-EPI 2012, MDRD-4 and MDRD-6, RFH and GRAIL as compared with mGFR protocol using iothalamate in selected subgroups of gender and Race.

| Gender/Race | eGFR Equations | | | | | | p-value |
|---------------------------------|-------------------------------|------------------------------|----------------------------------|----------------------------------|----------------------------------|--------------------------------|---------|
| | CKD-EPI 2021 | CKD-EPI 2021 | MDRD-4 | MDRD-6 | RFH | GRAIL | |
| Female (N=843) | | | | | | | |
| Median Bias 95% CI IQR | 7.6 (5.6, 10.2) (-7.9, 23.8) | 9.7 (7.8, 11.9) (-5.8, 25.9) | 14.3** (11.8, 16.3) (-2.7, 31.1) | 16.9** (15.1, 18.8) (2.0, 33.6) | 32.7** (27.0, 35.3) (12.9, 49.9) | 4.7 (1.8, 6.5) (-12.2, 22.1) | <0.001 |
| P30% 95% CI | 69.0 (67.0, 71.0) | 68.7 (67.0, 71.0) | 61.9* (60.0, 64.0) | 61.3* (59.0, 63.0) | 37.1** (34.0, 40.0) | 65.5 (63.0, 68.0) | <0.001 |
| % Agreement (CKD Stages) 95% CI | 58.7 (57.0, 61.0) | 57.4 (55.0, 60.0) | 50.9* (49.0, 53.0) | 47.7* (46.0, 50.0) | 11.2** (9.0, 13.0) | 57.2 (55.0, 59.0) | <0.001 |
| Male (N=1247) | | | | | | | |
| Median Bias 95% CI IQR | 5.6 (3.7, 7.7) (-10.8, 26.1) | 8.3 (6.5, 10.4) (-8.0, 28.6) | 10.4* (8.1, 11.8) (-7.7, 32.1) | 15.7** (13.7, 17.8) (-1.3, 37.9) | 33.7** (30.3, 37.4) (13.9, 58.3) | 4.6 (2.4, 7.0) (-15.0, 25.3) | |
| P30% 95% CI | 67.0 (65.0, 69.0) | 67.3 (65.0, 69.0) | 63.6 (62.0, 66.0) | 61.6* (60.0, 64.0) | 33.5** (30.0, 37.0) | 61.5* (59.0, 64.0) | <0.001 |
| % Agreement (CKD Stages) 95% CI | 60.1 (58.0, 62.0) | 59.7 (58.0, 62.0) | 55.8 (54.0, 58.0) | 52.1* (50.0, 54.0) | 11.5** (9.0, 14.0) | 57.8 (56.0, 60.0) | <0.001 |
| Black (N=130) | | | | | | | |
| Median Bias 95% CI IQR | 17.9 (13.8, 23.2) (2.2, 36.6) | 7.6 (3.4, 13.0) (-7.3, 25.4) | 10.5 (5.0, 15.9) (-8.2, 30.8) | 14.5 (9.8, 21.1) (0.3, 36.4) | 45.0** (37.8, 56.7) (27.7, 74.0) | 3.8 (-2.8, 11.7) (-13.4, 25.2) | <0.001 |
| P30% 95% CI | 66.1 (64.0, 68.0) | 68.5 (67.0, 70.0) | 66.9 (65.0, 69.0) | 63.1 (61.0, 65.0) | 23.3** (20.0, 26.0) | 64.8 (63.0, 67.0) | <0.001 |
| % Agreement (CKD Stages) 95% CI | 56.9 (55.0, 59.0) | 66.9 (65.0, 69.0) | 66.9 (65.0, 69.0) | 53.8 (52.0, 56.0) | 25.0** (22.0, 28.0) | 66.9 (65.0, 69.0) | <0.001 |
| Non-Black (N=1953) | | | | | | | |
| Median Bias 95% CI IQR | 5.8 (4.3, 7.4) (-10.2, 24.3) | 9.1 (7.6, 10.7) (-7.1, 27.6) | 11.8** (10.6, 13.5) (-5.8, 31.9) | 16.3** (15.0, 18.0) (0.1, 35.8) | 32.6** (28.8, 34.6) (11.7, 54.5) | 4.7 (3.1, 6.2) (-13.7, 23.2) | <0.001 |
| P30% 95% CI | 59.8 (58.0, 62.0) | 58.5 (56.0, 61.0) | 53.1* (51.0, 55.0) | 50.3** (48.0, 52.0) | 12.0** (10.0, 14.0) | 57.0* (55.0, 59.0) | <0.001 |
| % Agreement (CKD Stages) 95% CI | 68.0 (66.0, 70.0) | 67.8 (66.0, 70.0) | 62.7* (61.0, 65.0) | 61.4** (59.0, 63.0) | 35.6** (32.0, 39.0) | 63.0 (61.0, 65.0) | <0.001 |

* p 0.05,

** p 0.001; these values refer to direct comparison of different equations with CKD-EPI 2021.

Note: Bias, median difference between eGFR and mGFR with positive values implying underestimation and negative values implying overestimation; precision, width of IQR; accuracy percent of estimated values within 30% of measured GFR (p30)

* GFR categories are defined according to CKD stages 1 (GFR>90 mL/min/1.73 m²), 2 (GFR=60-89 mL/min/1.73 m²), 3 (GFR=30-59 mL/min/1.73 m²), 4 (GFR=15-29 mL/min/1.73 m²) and 5 (GFR<15 mL/min/1.73 m²). Stages 4 and 5 were combined for these analyses due to small number of cases in these groups.

Abbreviations: eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate; mGFR, measured glomerular filtration rate.

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