



WJG 20th Anniversary Special Issues (11): Cirrhosis

Evaluation of renal function in patients with cirrhosis: Where are we now?

Nicolas Rognant, Sandrine Lemoine

Nicolas Rognant, Sandrine Lemoine, Nephrology Department, Hospices Civils de Lyon, France and University Claude Bernard Lyon I, F-69008 Lyon, France

Nicolas Rognant, School of Biochemistry, University of Bristol, University Walk, Medical Sciences Building, Bristol BS8 1TD, United Kingdom

Author contributions: Rognant N and Lemoine S designed the research, performed data analysis and revised the manuscript; Rognant N wrote the manuscript.

Correspondence to: Nicolas Rognant, MD, PhD, School of Biochemistry, University of Bristol, University Walk, Medical Sciences Building, Bristol BS8 1TD, United Kingdom. nicolasrog@hotmail.com

Telephone: +44-758-4357845 Fax: +44-758-4357845

Received: October 29, 2013 Revised: January 3, 2013

Accepted: January 20, 2014

Published online: March 14, 2014

Abstract

In the clinical context of the patients with liver cirrhosis, accurate evaluation of the renal function is potentially crucial. Indeed, it can lead to early diagnosis of both acute kidney injury and chronic kidney disease and to reliable characterization of the renal status of the patient before performing a liver transplantation. Despite some limitations, the assay of serum creatinine (SCr) is universally used to estimate glomerular filtration rate (GFR) because of its wide availability, its simplicity and because it is inexpensive. Nevertheless, several reports show that the value of this assay to estimate GFR is strongly challenged in cirrhotic patients, especially in patients with liver failure and/or severely impaired renal function. This has led to seek new alternatives to estimate more reliably the GFR in these patients. Although the reference methods, based on the utilization of exogenous markers, allow measuring GFR and thereby constitute the "gold standard" to evaluate renal function, they are not feasible in routine clinical practice. Several studies have shown that a cystatin C (CysC) based formula perform better than the SCr-

based estimates in cirrhotic patients and the estimation of GFR by these formulas could therefore lead to optimize the management of the patients. A new estimate based on CysC has been recently developed using a large number of patients and the first results regarding the evaluation of its performance are promising, making this new formula the best candidate for a reference estimate of the renal function in cirrhotic patients.

© 2014 Baishideng Publishing Group Co., Limited. All rights reserved.

Key words: Cirrhosis; Glomerular filtration rate; Formula; Estimation; Agreement; Plasma creatinine; Cystatin C

Core tip: Cirrhotic patient management frequently requires evaluation of renal function. However, these patients present some specific disturbances that affect the serum creatinine value, making its use to estimate glomerular filtration rate unsuitable. To get a more appropriate evaluation of the glomerular filtration rate, other methods are available such as the use of exogenous markers or assaying cystatin C in the blood, which avoid the drawbacks of the serum creatinine. Recently, a convenient new cystatin C based formula was tested and showed correct performance in cirrhotic patients, even in case of liver failure and/or severely decrease renal function.

Rognant N, Lemoine S. Evaluation of renal function in patients with cirrhosis: Where are we now? *World J Gastroenterol* 2014; 20(10): 2533-2541 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v20/i10/2533.htm> DOI: <http://dx.doi.org/10.3748/wjg.v20.i10.2533>

INTRODUCTION

Liver cirrhosis (LC) is a frequent disease with various causes and a severe prognosis. Thus, after a first episode

of decompensation, the 5-year mortality in the absence of liver transplantation (LT) is as high as 85%^[1]. Renal impairment, whether acute or chronic, is a highly prevalent comorbid condition in cirrhotic patients, which is associated with a poor prognosis^[2]. In this clinical context, acute kidney injury (AKI)^[3] is frequent and often of functional origin (around 70%). However, AKI of other origin are not rare, mainly secondary to hepato-renal syndrome (HRS), drug nephrotoxicity or severe sepsis^[4]. Chronic Kidney Disease (CKD) is not infrequent as well and can be of various origins (glomerulonephritis, diabetic nephropathy or hypertensive nephrosclerosis). Although several studies assessed the frequency of renal impairment in patients with cirrhosis, it is not always clear whether it was acute or chronic kidney disease. About the prevalence of CKD, several studies suggest a prevalence of CKD stage 3 or higher (*i.e.*, estimated Glomerular Filtration Rate (eGFR) < 60 mL/min per 1.73 m²) between 20% and 40%. In a study including more than 1400 cirrhotic patients who underwent an evaluation of renal function by a reference method in pre LT clinical assessment, 11.3% had a GFR below 40 mL/min^[5]. In our cohort of alcoholic cirrhotic patients, about 40% had a measured GFR below 60 mL/min per 1.73 m²^[6]. Finally, in the study by Ojo *et al*^[7] a prevalence of 26.8 % of stage 3-5 CKD was found in patients who subsequently received a liver transplant between 1990 and 2000 in the United States [however, in this study, analysis was based on the eGFR instead of measured GFR (mGFR)]. Nevertheless, it is likely that some of these studies provide an underestimated prevalence of CKD in cirrhotic patients because they included only candidates for LT, whereas the CKD prevalence may be higher in patients contraindicated for receiving a LT. Moreover, it is not always known whether the renal impairment might have been (at least partly) acute in these studies. About the frequency of AKI in cirrhotic patients, some authors found that it could occur in 50% to more than 90% of patients in the perioperative period of LT and in 20% of hospitalized patients with LC^[4].

The detrimental clinical impact of the existence of either CKD and/or AKI on the outcomes of cirrhotic patients has been highlighted by several studies. About the impact on mortality, a recent systematic review summarized results from 74 studies that assessed the effect of renal failure on early mortality in cirrhotic patients and found an increased risk of death with a pooled odds ratio of 7.6. Whether the renal failure was acute or chronic in some studies included in the systematic review was not clear but an increased risk of death was found in studies in which renal failure was defined as an acute renal failure and in those which renal failure was not clearly defined as chronic or acute (pooled odds ratio of 6.38 and 7.39 respectively). Although analysis in this study found significant heterogeneity (consequence of the heterogeneous definition of the renal failure used in some studies) the majority of the studies found an increased odds ratio, which strongly suggests a negative impact of impaired renal function, either acute or chronic, on the

survival of cirrhotic patients^[8]. In case of subsequent LT, the presence of prior CKD or the occurrence of AKI has also a negative impact on both survival and “renal” prognosis of the patients. Indeed, it is known that the occurrence of perioperative AKI or the existence of preLT CKD decreases the survival of liver transplant recipient^[4]. Furthermore, pre-transplant CKD promotes the development of post-transplant CKD and/or is associated with increased risk of End-Stage Renal Disease (ESRD) requiring renal replacement therapy (RRT) during follow-up^[4,7]. In summary, the cirrhotic patients may face clinical situations with increased risk of acute and/or chronic renal disease and the occurrence of renal disease is known to have strong prognostic implication. Therefore, it appears that accurate evaluation of renal function is important firstly to optimize the management of these patients and secondly to properly determine patients prognosis in order to prioritize access to LT. Taken together, the previously cited data suggest that the level of renal function is a parameter of crucial importance that should be determined (sometimes iteratively) in the clinical evaluation of cirrhotic patients in order to optimize their management.

DIAGNOSIS OF AKI

According to the recent Kidney Disease Improving Global Outcomes (KDIGO) guidelines about AKI, the diagnosis of AKI should be based on Serum Creatinine (SCr) increase and urine output, whereas RIFLE criteria, which were former reference in the field and are still largely used, were additionally based on GFR decrease. Although SCr is the historical marker, cheap and widely available, it is just a marker of renal function and thus increases tardily after the beginning of injury^[4]. New marker such as Neutrophil Gelatinase Associated Lipocalin (NGAL) is able to detect renal parenchymal damage before SCr increase and thus allows, theoretically, to initiate early treatment that might mitigate the severity of AKI. It is a crucial point to optimize management of cirrhotic patients with AKI because some authors found that the mortality is related to the severity of renal failure^[8,9]. So far, some studies suggested an interest of using NGAL assay in cirrhotic patients in the diagnosis of renal dysfunction, In the study by Verna *et al*^[10] the authors found the ability of elevated NGAL level to predict independently short-term mortality in cirrhotic patients. Moreover, Fagundes *et al*^[11] showed that NGAL increase was useful to differentiate AKI due to acute tubular necrosis from CKD and HRS as well as to differentiate HRS from CKD. However, to our knowledge, no studies clearly showed a positive clinical impact of the NGAL use in the management of the cirrhotic patients and more studies are needed to ascertain the clinical interest of this new marker in this context.

DIAGNOSIS OF CKD

According to the KDIGO clinical practice guidelines for

the evaluation and management of CKD, CKD is defined as the existence since at least 3 mo of abnormalities of kidney function and/or structure with implications for health. The persistence of GFR below 60 mL/min/1.73 m² is one of these abnormalities and in case of the existence of other criteria, calculation of GFR is requested to determine the stage of the CKD^[12]. Therefore, calculation of GFR is a key element in detection and/or staging of CKD. So, we will focus on the methods that might allow evaluating reliably the renal function and on the studies that assessed the performance of these methods.

METHODS OF EVALUATION OF THE RENAL FUNCTION

The GFR is the universally used index to quantify kidney function (with value given in mL/min). It can be measured by using a reference method of GFR measurement, or estimated, by using an endogenous marker (typically SCr) and different formulas (also called equations). In case of GFR measurement, the principle is to determine the body clearance of a substance with supposed exclusive renal elimination. The substance used is also supposed to be freely filtered and neither secreted nor reabsorbed along the renal tubule. In all probability, no extrarenal excretion of the substance occurs and it cannot be stored or be bound to plasma proteins: then it can be assumed that the plasmatic clearance is only due to renal clearance. Thus, the GFR can be inferred, at least theoretically, from the plasma disappearance of the substance. Considering the renal clearance of a marker occurs only through glomerular filtration, then the following relationship is satisfied: the amount that leaves the body per unit of time is strictly equal to the quantity of the same substance that appears in the urine per unit of time: $[S]_p \times \text{GFR} = [S]_u \times V_u$ (with $[S]_p$ and $[S]_u$ respectively the plasma and urine concentration of the substance and V_u the volume of urine during a certain amount of time)^[13].

Secondarily, a normalization on arbitrarily fixed body surface area (BSA) set to 1.73 m² is commonly done on the assumption that the GFR is positively correlated with the basal metabolism rate of individuals which is proportional to their stature^[14]. Some authors have questioned this normalization^[15] and standardization on other criteria (for example, the volume of total body water) has been proposed^[16]. Nevertheless, the adjustment on the body surface remains widely used. The formula most commonly used to determine the BSA is the Dubois formula^[17].

REFERENCE METHODS: HOW TO MEASURE GFR?

These methods utilize exogenous markers, which should present several properties to be considered as “ideal markers”. These properties include free filtration in the glomerulus without secretion nor reabsorption by the tubule, unable to bind to plasma proteins and with exclusive elimination by the kidneys. Moreover, the dosage of the com-

pound must be accurate, inexpensive, and without interference with other plasma components. Finally, there should be no side effects for the patient^[13]. The commonly used exogenous markers in clinical practice are inulin, iothexol and iohalamate. Several methods can be used to measure the GFR. The method originally proposed by Homer Smith is still one of the most frequently used. It is based on the continuous infusion of exogenous marker by varying the infusion rate until a stable plasma concentration is reached^[13]. Urine collection over several time periods is then performed and the final GFR is the mean value of these measurements. Three samples are generally collected but up to five may be necessary. Although being a “gold standard” method, it has several drawbacks. It is time consuming, requires trained and experienced staff, the marker can be relatively expensive and the assay of inulin is sensitive to changes in glucose. Finally, the utilization of a bladder catheter may be required to exclude the impact of a problem of bladder voiding that can artificially reduce the GFR value^[13]. Because of these drawbacks, other investigators have proposed simpler methods without urine collection. The proposed technique is to measure the infusion rate of the marker required to obtain a constant plasma concentration of the marker. Assuming that elimination is exclusively renal then the value of the infusion rate permits determination of the GFR value. Another increasingly used technique is to measure the disappearance of the marker in the plasma after a bolus infusion. This technique requires using a model of the behavior of the marker in the body to deduce the GFR value. Obviously, the reliability of the GFR measurement strongly relies on how realistic the model used is. Some investigators have demonstrated these bolus techniques allow appropriate assessment of the GFR by retrieving just two blood samples. In some studies just one assay was sufficient during the decrease phase of the marker concentration in the plasma. However, the single sample methods require careful timing of sample retrieval that must be chosen based on the expected level of renal function. Alternatively, the sample is taken according to the presence of certain clinical conditions: at least several hours after injection are required for normal renal function, whereas a sample after a longer period of time is needed when renal impairment is expected or if ascites is present^[18]. Alternatively, radioactive (isotopic) markers can be used instead of usual marker: the most commonly used isotopic markers are the ¹²⁵I-iothalamate, ⁵¹Cr-EDTA and ⁹⁹Tc-iodohippuran^[13]. In cirrhotic patients, some authors have reported a risk of overestimation of the GFR when alternative methods to urine collection are used, due to the possible existence of extra-renal clearance of the marker^[19]. This seems to be true when the samples of plasma are taken too early after the bolus marker administration. Indeed, investigators have recently stressed the faster initial decrease and slower subsequent decrease in plasma marker concentration in patients with fluid overload^[20]. In such cases, late measures might correct the overestimation by compensating for the faster initial decrease, but this remains to be confirmed. Therefore, the most reliable reference method appears to

be the “classic” Homer Smith method with the collection of urine and prior administration of an exogenous marker until reaching the equilibrium concentrations. However, as stated above, this is time consuming and necessitates trained staff.

SERUM CREATININE

This endogenous marker of renal function is used universally as it is simple to measure, inexpensive and easily accessible. Initially, SCr was used for the assessment of renal function due to the assumption that its production remains broadly stable over time if the body weight was also stable. In addition, it was assumed that SCr production among gender-, weight- and age-matched patients was comparable. However, in patients with severe cirrhosis, daily creatinine production is decreased comparing with patients from the general population for two main reasons. Liver failure is responsible for decreased creatine production while some degree of malnutrition causes decreased conversion of creatine to creatinine. Therefore, the potential of SCr to be a reliable marker of renal function is strongly challenged in this clinical setting^[21]. Additional difficulty when interpreting the value of SCr in cirrhotic patients comes from the interference, when using the Jaffe assay, of “non-creatinine” chromogens present in the plasma (typically bilirubin)^[22]. Recently, Kuster *et al.*^[23] showed that comparing with an enzymatic assay, even a compensated Jaffe assay accounted for an average decrease of 6.14 $\mu\text{mol/L}$ of the SCr in cirrhotic patients. This resulted in a median overestimation of GFR estimated by CKD-EPI formula and a reduced MELD score in patients with SCr > 1 mg/dL. Finally, it is known that there is a significant secretion of creatinine by the tubule in patients with decreased renal function, which increases when the CKD becomes more severe^[24]. Several studies sought to determine the ability of SCr to estimate renal function and to detect CKD in cirrhotic patients, by using a reference method to measure GFR (Table 1). They showed that a large proportion of cirrhotic patients with moderate to large decrease in GFR had normal or just slightly increased SCr^[25-28]. Moreover, some studies also found a non-significant correlation between 1/SCr or log SCr with GFR or poor performance of 1/SCr for detecting a decrease in GFR^[26-27]. Apart from questioning the level of SCr that should be considered as really “normal” in cirrhotic patients, other previously cited factors contribute to jeopardizing the capacity of SCr as a reliable marker of the true GFR in cirrhotic patients. Therefore, what is the true clinical meaning of SCr in patients with severe cirrhosis? Assuming the absence of measurement error, SCr reflects a mix of clinical parameters including the degree of liver dysfunction, malnutrition and the patient GFR. Nevertheless, it was included in the MELD score, now widely used to prioritize patients in the access to LT, because of its (expected) capacity to serve as a proper marker of renal function. However, because of all the limitations previously cited, some authors have since highlighted the limitations of the use of SCr into

the MELD score to properly classify the patients with the most severe cirrhosis^[20,29-31]. It is well established that the MELD score penalizes patients that, in absence of any renal impairment, exhibit lower SCr, especially women^[30,32]. In a study from our group in patients with severe alcoholic cirrhosis, we found lower SCr in women than in men, despite lower GFR in female patients^[6]. Some studies have shown that replacing the SCr by eGFR or mGFR allowed more accurate classification of patients awaiting LT according to their risk of death^[33,34]. This raises questions about the need to refine the MELD score in order to achieve a fairer assessment amongst cirrhotic patients awaiting LT.

CREATININE CLEARANCE

It is a simple method to estimate GFR, based on the assumption that creatinine has the characteristics of a perfect renal marker. It requests the patients are able to collect accurately the urines from a 24 h period. Although very convenient, it has several limitations: mainly, the occurrence of tubular secretion of creatinine (which leads to overestimation of the GFR) and the possible inadequate urine collection by the patients, that is on a longer or shorter than 24h time period. Calculation of the eGFR requires normalization to BSA. Studies that tested the performance of this method showed a clear trend to overestimate mGFR by 4%-80%^[25,27,35-37] (Table 1). In a meta-analysis including data from seven studies with 193 cirrhotic patients, Proulx *et al.*^[38] found a mean bias of +13 mL/min per 1.73 m² between GFR estimated by the Creatinine Clearance method (CrCl) and GFR measured by the inulin clearance. The authors also found that the bias tended to be higher in patients with lower GFR with a mean overestimation of 18% in patients with GFR > 60 mL/min per 1.73 m² and of 49% in patients with GFR < 60 mL/min per 1.73 m². The relationship between GFR level and overestimation could be explained by the secretion of creatinine by the tubule in patients with CKD. However, the importance of this overestimation does not seem to be related to the severity of cirrhosis. Some investigators have suggested that pharmacological inhibition of creatinine secretion by means of cimetidine could help to get more robust estimation of GFR with the CrCl^[13,39]. However, limitations such as the effective level of tubular secretion inhibition that can be obtained with cimetidine remain. Cimetidine can have varying effects depending on several factors and the clinical safety of cimetidine administration is a matter of concern. To our knowledge there is no study that evaluated the performance of CrCl with cimetidine administration in cirrhotic patients. In conclusion, because of its limitations, the CrCl method is not largely used to estimate GFR in current clinical practice.

SERUM CREATININE BASED FORMULA TO ESTIMATE GFR

They are probably the most widely used in current clinical

Table 1 Summary of the results of the main studies which evaluated the performance of renal function markers and/or glomerular filtration rate estimates comparatively to a reference method in patients with cirrhosis

Ref.	Number of patients	Reference method	Performance of the estimate(s)
Papadakis <i>et al</i> ^[25] , 1987	23 (mGFR = 66)	Inulin	Difference between mean mGFR and ClCr and CG -24 and -52 mL/min respectively in group with decreased mGFR (+10 and +4 in patients with normal mGFR)
Caregaro <i>et al</i> ^[35] , 1994	56 (mGFR = 86.7)	Inulin	Difference between mean mGFR and ClCr and CG -14.6 and -4.9 respectively. Mean overestimation was 51% and 40% respectively in patients with GFR < 80
Roy <i>et al</i> ^[36] , 1998	30 (mGFR = 30)	Inulin	Mean relative overestimation 80% with ClCr when moderate to severe CKD
Orlando <i>et al</i> ^[37] , 1999	20	Inulin	Mean relative overestimation of 4% and 23% respectively for ClCr and CG in Child C patients. Relative difference only +3% and -6% respectively in Child A patients
Woitash <i>et al</i> ^[26] , 2000	44 (mGFR = 37)	Inulin	Sensitivity to detect GFR < 90, 85.7% and 28.5% respectively for elevated CysC and SCr
Demirtaş <i>et al</i> ^[27] , 2001	26 (HRS) (mGFR = 33.5)	⁹⁹ Tc-DTPA	Difference between mean mGFR and ClCr +7
Orlando <i>et al</i> ^[28] , 2002	36 (mGFR = 71.5)	Inulin	Mean overestimation was 75% and 30% respectively for CG and ClCr in patients with decreased GFR (14% and 9% in patients with normal GFR). Sensitivity to detect GFR < 72 were 73%, 23%, 53% and 86% respectively for elevated CysC and SCr, CG and ClCr
Gonwa <i>et al</i> ^[5] , 2004	1447 (Pretransplant) (mGFR = 90.7)	¹²⁵ I-Iothalamate	P30 were 60.8% and 66.7% for respectively CG and MDRD4. Difference between means mGFR and CG and MDRD4 +23.5 and +21.9 respectively
Pöge <i>et al</i> ^[41] , 2006	44 (mGFR = 35.3)	Inulin	Mean absolute bias and P30 was 51.7/4.5%, 48.3/6.8%, 33.3/11.4% and 33.9/13.6% for respectively CG, MDRD4, Hoek and Larsson GFR formula
MacAulay <i>et al</i> ^[42] , 2006	57 (mGFR = 83)	⁹⁹ Tc-DTPA Iohexol	Mean difference between formula and mGFR was lower for MDRD6 comparing with CG (+3.5 <i>vs</i> +15.4). However, mean absolute difference was high and similar (23.4 <i>vs</i> 23.6) and poor precision was found with both eGFR (root mean square error 31.5 <i>vs</i> 30.5 for respectively MDRD6 and CG)
Francoz <i>et al</i> ^[31] , 2010	157 (mGFR = 85)	Inulin	Mean absolute bias \pm SD was 17 \pm 32, 16 \pm 29 and 8 \pm 22 for CG, MDRD4 and CKD-EPI respectively. In patients with GFR < 70, CKD-EPI bias rose to 19 \pm 20
Rognant <i>et al</i> ^[6] , 2010	148 (Alcoholic Cirrhosis) (mGFR = 77)	Inulin	Median absolute bias \pm SD and P30 was 23 \pm 23/33.3% and 22 \pm 20/40% for CG and MDRD4 respectively
Kim <i>et al</i> ^[43] , 2011	89 (normal SCr) (mGFR = 73)	⁹⁹ Tc-DTPA	Difference between mean mGFR and ClCr, CG and MDRD6 was -14.4/+ 19.1 and -40.1 respectively. AUC of ROC to detect GFR < 60 was 0.721, 0.561, 0.463 and 0.659 for 1/CysC, ClCr, CG and MDRD6 respectively
Xirouchakis <i>et al</i> ^[47] , 2011	74 (mGFR = 81.7)	⁵¹ Cr-EDTA	Concordance correlation coefficient was 0.61, 0.38 and 0.46 for respectively MDRD4, Larsson and Hoek estimates. P30 was 64% for MDRD4 and 68% for Hoek.
Gerhardt <i>et al</i> ^[48] , 2011	44 (mGFR = 35.3)	Inulin	Median absolute bias and P30 was 40.1/6.8% and 42.5/6.8% for respectively MDRD175 and CKD-EPI
De Souza <i>et al</i> ^[49] , 2013	202 (Pretransplant) (mGFR = 83)	Inulin	Concordance correlation coefficient and P30 was 0.75/78.7, 0.56/42.6, 0.62/56.4, 0.8/83.2 and 0.82/78.2 for respectively Hoek, MDRD175, CKD-EPI, CKD-EPI CysC and mixed CKD-EPI formula

Acronyms description can be found in the text. GFR: Glomerular filtration rate; HRS: Hepato-renal syndrome; CKD: Chronic kidney disease; CG: Cockcroft and Gault formula; SCr: Serum creatinine.

cal practice to assess the GFR because estimation can be obtained quickly and easily. The parameters of the population used to work out the main SCr based formulas are given in Table 2. This information is important to take into account to understand the poor global performance of these formulas in cirrhotic patients. Indeed, it appears unlikely that some cirrhotic patients were included in the populations used to elaborate these formulas.

Historically, the Cockcroft and Gault formula (CG) was the most popular before the MDRD formula was published in the early 2000s. It was developed in the early 70s using population data from 249 men. Furthermore, it is important to note that the reference method used to develop this formula was the CrCl method, which is not really a reference method^[40]. This formula is not adjusted to the patient BSA and the adjustment has, theoretically, to be done afterwards (even if the relevance of this adjustment remains to be assessed in cirrhotic patients). Repeated testing of the CG formula in cirrhotic patients confirmed poor performance in most of

the studies^[5,6,25,28,35,37,41-43]. Similarly to the CrCl, the CG clearly tends to overestimate GFR, especially in some clinical contexts. According to major studies in the field, this overestimation may be between 5 and 51 mL/min, in some instances reaching 80% of the mGFR value. This overestimation seems to be more important for lower GFR and more severe cirrhosis as well^[5,28,37]. Another point of concern is the impact of BSA normalization of the eGFR when evaluating CG performance. Not every study utilized normalized eGFR, which may have a confounding effect on the results. Intuitively, the overestimation in patients with large retention of ascites that are artificially overweight may decrease. Apart from our group^[6], several other authors have underlined the limitations of the CG formula in the assessment of renal function in cirrhotic patients^[18,29].

The MDRD formula was developed in 1999 in a large-sized North American population, which was more heterogeneous than the one used to derive the CG formula (Table 2). In addition, the authors utilized

Table 2 Description of the characteristics of the studies used to develop the common glomerular filtration rate estimates

Name of the study	Number of patients	Country	Reference method	Marker(s)	Mean GFR	Comments
CG 1976	249	Canada	24 h CrCr	SCr	30-130	No normalization on BSA Male patients only in the population of the study
MDRD 1999	1628	United States	Renal clearance ¹²⁵ I-iothalamate	SCr	39.8 ± 21.2	Characteristics of the study population: Male 60% Black patients 12% > 55 yr 42% Diabetic patients 6% Re-expressed in 2007 to be used with IDMS traceable creatinine assay (MDRD 175)
CKD EPI (PCr) 2009	8254	United States	Various (urinary clearance of exogenous markers)	SCr	68 ± 40	Characteristics of the study population: Male 57% Black patients 32% > 65 yr 13% Diabetic patients 29%
Hoek 2003	123	The Netherlands	Renal clearance ¹²⁵ I-iothalamate	CysC	Median = 81	Characteristics of the study population: Male 48% Median age 50 yr Diabetic patients 24%
CKDEPI (Cys C and mixed PCr + CysC) 2012	5352	United States	Various (urinary or plasma clearance of exogenous markers)	CysC alone and both CysC and SCr	68 ± 39	Characteristics of the study population: Male 58% Black patients 40% Age > 65 yr 13% Diabetic patients 32% Patients with BMI > 30 31%

Acronyms description can be found in the text. GFR: Glomerular filtration rate. CKD: Chronic kidney disease; CG: Cockcroft and Gault formula; BMI: Body mass index.

a measured GFR as the reference method and provided an eGFR normalized to BSA^[44]. Initially, several MDRD formulas were developed, with the simplest or 4-variables MDRD including SCr, age, gender and ethnical origin. This formula rapidly became the most popular compared to the 6-variables MDRD formula, which additionally requires blood urea nitrogen and serum albumin concentration to estimate GFR^[45]. In 2007, the formula with 4 variables (MDRD4) has been re-expressed for SCr measured with assay traceable to the IDMS reference assay. This formula is also known as MDRD 175, which refers to the first multiplicative factor of the equation^[46]. The performance of these formulas has been tested several times in cirrhotic patients^[5,6,34,41,42,43,47-49]. The studies have shown, as for the CG, a clear tendency to overestimate mGFR with a bias between 15 and 48 mL/min per 1.73 m² depending on the average GFR of the patients included in the studies. As for the CG formula, the level of the bias is inversely proportional to the level of the mGFR. Agreement between MDRD eGFR and measured GFR assessed *via* the accuracy 30% (which is the proportion of patients with eGFR between mGFR minus 30% and mGFR plus 30% and is also called P30) is poor. Indeed P30 was between 6.8 % and 42.6 % depending on the study. Importantly, MDRD formulas did not seem to perform better than CG formula, whereas, our recent study suggested that the performance of MDRD6 is possibly better than other SCr based formulas (but remained lower comparing with CysC based formulas). In 2009, the Levey group, which developed the MDRD formula, published a new formula for estimating GFR. It was

based on the same parameters as the MDRD4 and used measurements of the GFR collected from more than 8000 patients^[50]. The mean mGFR of the population was higher than for the MDRD formula (68 mL/min per 1.73 m²). The main advantage of this new and more complicated formula named CKD-EPI, is the lower underestimation of the eGFR comparing with the MDRD for GFR higher than 60 mL/min per 1.73 m². However, an improvement is not observed in some categories of patients such as the elderly. Therefore, some authors challenged the supposed clinical improvement in the patient management brought by the CKD-EPI comparing with the MDRD^[51]. In cirrhotic patients, studies that tested the CKD-EPI formula found a slightly better performance comparing with CG and MDRD although eGFR was higher than the mGFR in every study^[34,48,49]. For example, in the study by Francoz *et al*^[34] the mean bias was +8 mL/min per 1.73 m² *vs* +17 and +16 mL/min per 1.73 m² respectively for CG and MDRD4. However, the mean bias was similar to MDRD in patients with GFR below 70 mL/min per 1.73 m² (+19 mL/min per 1.73 m²) suggesting strong overestimation of GFR in patients with CKD. Assessing the agreement by the mean of P30, our group recently found better results for CKD-EPI with the P30 being 56.4 % *vs* 42.6% for MDRD175^[49]. However, a recent study highlighted the poor performance of the CKD-EPI formula in patients with severely decreased GFR (mean mGFR of 35.3 mL/min per 1.73 m²) with low P30 at 6.8%, similar to those of MDRD^[48]. Taken together, these data suggest that CKD-EPI may give a fairly good estimation of GFR in cirrhotic patients

with normal renal function. In patients with decreased renal function it presents the same limitations as CG and MDRD, which is mainly to overestimate the GFR.

CYSTATIN C BASED FORMULA TO ESTIMATE GFR

These formulas were developed more recently. The mainly used formulas so far, are the Hoek^[52] and the Larsson formula^[53]. However, the Levey group published two new CKD-EPI formulas in 2012, one based on CysC (CKD-EPI CysC) and another based on both SCr and CysC (mixed CKD-EPI)^[54]. While the CKD-EPI formulas were developed on a large group of patients, the Hoek formula was developed from a small group of 123 patients (Table 2).

In cirrhotic patients, some investigators tested the ability of these formulas to estimate the GFR appropriately^[41,47,49]. Although one study, in a small group of patients with severely decreased renal function, found a poor performance of the Hoek formula (reflected by an important overestimation of the GFR and low accuracy with P30 of 11.4%)^[41], subsequent studies showed a better performance, at least comparing with SCr based formulas. In the study by Xirouchakis *et al*^[47] P30 was observed to be 68%. Recent work by our group showed that the P30 could be even better at 78.7% but it dropped to 66.7% in patients with refractory ascites and to 53.8% in patients with GFR below 60 mL/min per 1.73 m². Nonetheless, performance remained higher than those of the SCr based formulas^[49]. Concerning the two newly developed CKD-EPI formulas (CKD-EPI CysC and mixed CKD-EPI), we are the first to evaluate their performance in our recent study including 202 cirrhotic patient candidates for LT in whom an inulin renal clearance was performed^[49]. We found that CKD-EPI CysC had the best performance compared to the other formulas tested in the study (*i.e.*, Hoek, MDRD 175, mixed CKD-EPI and “classic” CKD-EPI). The Hoek and CKD-EPI CysC formulas exhibited the lowest difference between eGFR and mGFR (respectively +4.3 and +4.4 mL/min per 1.73 m²). However, the agreement, measured by the concordance correlation coefficient (CCC) and the P30, were improved for the CKD-EPI CysC formula (respectively 0.8 and 83.2% *vs* 0.75 and 78.7% for Hoek). Similarly to the Hoek formula, the P30 was lower in patients with refractory ascites (66.1%) and in case of GFR < 60 mL/min per 1.73 m² (73.1%). The ability to detect a GFR < 60 mL/min per 1.73 m² was the best for Hoek and CKD-EPI CysC formulas (both AUC of the ROC curve at 0.86). The ability to detect GFR < 90 mL/min per 1.73 m² was better in MDRD6 (0.77) and mixed CKD-EPI (0.78) formulas. Finally, regarding the new mixed CKD-EPI formula, its interest seems to be limited in cirrhotic patients with stage 3 to 5 CKD because of a poor agreement in cirrhotic patients with stage 3 to 5 CKD reflected by low P30 at 38.5% and overestimation of mGFR with a difference between mean eGFR and mean mGFR

of +14.6 mL/min per 1.73 m². However, the mixed CKD-EPI performed similarly to CKD-EPI CysC in patients with refractory ascites (P30 = 63.9%) and even better than all other formulas in patients with GFR > 90 mL/min per 1.73 m² (P30 = 98.7% and P10 = 54.7%). In conclusion, these recent data suggest that the CysC based formula, especially the CKD-EPI CysC formula, yielded less biased eGFR than SCr based formulas, with a clear better performance in cirrhotic patients with CKD. Therefore, this formula should be used preferentially in cirrhotic patients with GFR < 60 mL/min per 1.73 m² and in those with refractory ascites. However, in patients with normal renal function, our results suggest that the mixed CKD-EPI has the best performance.

CONCLUSION

Accurate and reliable assessment of GFR is warranted in cirrhotic patients in order to achieve optimal clinical management. Indeed, AKI and/or CKD are frequent complications in this context, impacting seriously on the prognosis of the patients. Moreover, several clinical conditions require the use of eGFR to adapt the treatment. Most of the available formulas estimating GFR exhibit limited suitability, particularly in case of a decreased renal function and/or severe cirrhosis, limiting their interest. The development of formulas based on CysC rather than SCr for estimating GFR opened the possibility to get a more robust and simple estimate of the GFR in daily clinical practice. Before developing a widespread use of CysC based eGFR in cirrhotic patients, however, further studies should be undertaken to confirm the clinical value of these formulas, especially those of the new CKD-EPI CysC.

ACKNOWLEDGMENTS

We thank Dr Andreas M. Rossbach from the school of Biochemistry, University of Bristol, for his help in the edition of the manuscript.

REFERENCES

- 1 Schuppan D, Afdhal NH. Liver cirrhosis. *Lancet* 2008; **371**: 838-851 [PMID: 18328931 DOI: 10.1016/S0140-6736(08)60383-9]
- 2 Ginès P, Schrier RW. Renal failure in cirrhosis. *N Engl J Med* 2009; **361**: 1279-1290 [PMID: 19776409 DOI: 10.1056/NEJM-ra0809139]
- 3 KDIGO Clinical Practice Guideline on Acute Kidney Injury. *Kidney Int Suppl* 2012; **2**: 6-138 [DOI: 10.1038/kisup.2012.7]
- 4 Charlton MR, Wall WJ, Ojo AO, Ginès P, Textor S, Shihab FS, Marotta P, Cantarovich M, Eason JD, Wiesner RH, Ramsay MA, Garcia-Valdecasas JC, Neuberger JM, Feng S, Davis CL, Gonwa TA. Report of the first international liver transplantation society expert panel consensus conference on renal insufficiency in liver transplantation. *Liver Transpl* 2009; **15**: S1-34 [PMID: 19877213 DOI: 10.1002/lt.21877]
- 5 Gonwa TA, Jennings L, Mai ML, Stark PC, Levey AS, Klintmalm GB. Estimation of glomerular filtration rates before and after orthotopic liver transplantation: evaluation of current equations. *Liver Transpl* 2004; **10**: 301-309 [PMID: 14762871 DOI: 10.1002/lt.20017]

- 6 **Rognant N**, Bacchetta J, Dubourg L, Ahmed SN, Radenne S, Dumortier J, Hadj-Aïssa A. What is the best alternative to inulin clearance to estimate GFR in patients with decompensated alcoholic cirrhosis? *Nephrol Dial Transplant* 2010; **25**: 3569-3575 [PMID: 20466685 DOI: 10.1093/ndt/gfq248]
- 7 **Ojo AO**, Held PJ, Port FK, Wolfe RA, Leichtman AB, Young EW, Arndorfer J, Christensen L, Merion RM. Chronic renal failure after transplantation of a nonrenal organ. *N Engl J Med* 2003; **349**: 931-940 [PMID: 12954741 DOI: 10.1056/NEJ-Moa021744]
- 8 **Fede G**, D'Amico G, Arvaniti V, Tsochatzis E, Germani G, Georgiadis D, Morabito A, Burroughs AK. Renal failure and cirrhosis: a systematic review of mortality and prognosis. *J Hepatol* 2012; **56**: 810-818 [PMID: 22173162 DOI: 10.1016/j.jhep.2011]
- 9 **Belcher JM**, Garcia-Tsao G, Sanyal AJ, Bhogal H, Lim JK, Ansari N, Coca SG, Parikh CR. Association of AKI with mortality and complications in hospitalized patients with cirrhosis. *Hepatology* 2013; **57**: 753-762 [PMID: 22454364 DOI: 10.1002/hep.25735]
- 10 **Verna EC**, Brown RS, Farrand E, Pichardo EM, Forster CS, Sola-Del Valle DA, Adkins SH, Sise ME, Oliver JA, Radhakrishnan J, Barasch JM, Nickolas TL. Urinary neutrophil gelatinase-associated lipocalin predicts mortality and identifies acute kidney injury in cirrhosis. *Dig Dis Sci* 2012; **57**: 2362-2370 [PMID: 22562534 DOI: 10.1007/s10620-012-2180-x]
- 11 **Fagundes C**, Pépin MN, Guevara M, Barreto R, Casals G, Solà E, Pereira G, Rodríguez E, Garcia E, Prado V, Poch E, Jiménez W, Fernández J, Arroyo V, Ginès P. Urinary neutrophil gelatinase-associated lipocalin as biomarker in the differential diagnosis of impairment of kidney function in cirrhosis. *J Hepatol* 2012; **57**: 267-273 [PMID: 22521351 DOI: 10.1016/j.jhep.2012.03.015]
- 12 KDIGO Clinical Practice Guideline for the evaluation and management of Chronic Kidney Disease. *Kidney Int Suppl* 2013; **3**: 1-150 [DOI: 10.1038/kisup.2012.76]
- 13 **Israni AK**, Kasiske BL. Laboratory assessment of kidney disease: Clearance, Urinalysis and Kidney Biopsy. In: Brenner BM. Brenner and Rector's The Kidney. 8th ed. Philadelphia: Saunders Elsevier, 2008: 724-750
- 14 **Mccance RA**, Widdowson EM. The correct physiological basis on which to compare infant and adult renal function. *Lancet* 1952; **2**: 860-862 [PMID: 12991615]
- 15 **Delanaye P**, Krzesinski JM. Indexing of renal function parameters by body surface area: intelligence or folly? *Nephron Clin Pract* 2011; **119**: c289-c292 [PMID: 21934328 DOI: 10.1159/000330276]
- 16 **Eriksen BO**, Melsom T, Mathisen UD, Jenssen TG, Solbu MD, Toft I. GFR normalized to total body water allows comparisons across genders and body sizes. *J Am Soc Nephrol* 2011; **22**: 1517-1525 [PMID: 21784894 DOI: 10.1681/ASN.2010121321]
- 17 **Du Bois D**, Du Bois EF. A formula to estimate the approximate surface area if height and weight be known. 1916. *Nutrition* 1989; **5**: 303-311; discussion 312-313 [PMID: 2520314]
- 18 **Brøchner-Mortensen J**. Current status on assessment and measurement of glomerular filtration rate. *Clin Physiol* 1985; **5**: 1-17 [PMID: 3882316]
- 19 **Henriksen JH**, Brøchner-Mortensen J, Malchow-Møller A, Schlichting P. Over-estimation of glomerular filtration rate by single injection [51Cr]EDTA plasma clearance determination in patients with ascites. *Scand J Clin Lab Invest* 1980; **40**: 279-284 [PMID: 6777855]
- 20 **Davenport A**, Cholongitas E, Xirouchakis E, Burroughs AK. Pitfalls in assessing renal function in patients with cirrhosis-potential inequity for access to treatment of hepatorenal failure and liver transplantation. *Nephrol Dial Transplant* 2011; **26**: 2735-2742 [PMID: 21690201 DOI: 10.1093/ndt/gfr354]
- 21 **Sherman DS**, Fish DN, Teitelbaum I. Assessing renal function in cirrhotic patients: problems and pitfalls. *Am J Kidney Dis* 2003; **41**: 269-278 [PMID: 12552488 DOI: 10.1053/ajkd.2003.50035]
- 22 **Cholongitas E**, Shusang V, Marelli L, Nair D, Thomas M, Patch D, Burns A, Sweny P, Burroughs AK. Review article: renal function assessment in cirrhosis - difficulties and alternative measurements. *Aliment Pharmacol Ther* 2007; **26**: 969-978 [PMID: 17877504 DOI: 10.1111/j.1365-2036.2007.03443.x]
- 23 **Kuster N**, Bargnoux AS, Pageaux GP, Cristol JP. Limitations of compensated Jaffe creatinine assays in cirrhotic patients. *Clin Biochem* 2012; **45**: 320-325 [PMID: 22178107 DOI: 10.1016/j.clinbiochem.2011.11.008]
- 24 **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 [PMID: 1394976]
- 25 **Papadakis MA**, Arieff AI. Unpredictability of clinical evaluation of renal function in cirrhosis. Prospective study. *Am J Med* 1987; **82**: 945-952 [PMID: 3578363]
- 26 **Woitas RP**, Stoffel-Wagner B, Flommersfeld S, Poege U, Schiedermaier P, Klehr HU, Spengler U, Bidlingmaier F, Sauerbruch T. Correlation of serum concentrations of cystatin C and creatinine to inulin clearance in liver cirrhosis. *Clin Chem* 2000; **46**: 712-715 [PMID: 10794756]
- 27 **Demirtaş S**, Bozbaş A, Akbay A, Yavuz Y, Karaca L. Diagnostic value of serum cystatin C for evaluation of hepatorenal syndrome. *Clin Chim Acta* 2001; **311**: 81-89 [PMID: 11566167]
- 28 **Orlando R**, Mussap M, Plebani M, Piccoli P, De Martin S, Floreani M, Padrini R, Palatini P. Diagnostic value of plasma cystatin C as a glomerular filtration marker in decompensated liver cirrhosis. *Clin Chem* 2002; **48**: 850-858 [PMID: 12029000]
- 29 **Cholongitas E**, Marelli L, Shusang V, Senzolo M, Rolles K, Patch D, Burroughs AK. A systematic review of the performance of the model for end-stage liver disease (MELD) in the setting of liver transplantation. *Liver Transpl* 2006; **12**: 1049-1061 [PMID: 16799946 DOI: 10.1002/lt.20824]
- 30 **Cholongitas E**, Marelli L, Kerry A, Goodier DW, Nair D, Thomas M, Patch D, Burroughs AK. 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 [PMID: 17217437 DOI: 10.1111/j.1600-6143.2007.01666.x]
- 31 **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 [PMID: 20185192 DOI: 10.1016/j.jhep.2009.11.025]
- 32 **Moylan CA**, Brady CW, Johnson JL, Smith AD, Tuttle-Ne-whall JE, Muir AJ. Disparities in liver transplantation before and after introduction of the MELD score. *JAMA* 2008; **300**: 2371-2378 [PMID: 19033587 DOI: 10.1001/jama.2008.720]
- 33 **Lim YS**, Larson TS, Benson JT, Kamath PS, Kremers WK, Therneau TM, Kim WR. Serum sodium, renal function, and survival of patients with end-stage liver disease. *J Hepatol* 2010; **52**: 523-528 [PMID: 20185195 DOI: 10.1016/j.jhep.2010.01.009]
- 34 **Francoz C**, Prié D, Abdelrazek W, Moreau R, Mandot A, Belghiti J, Valla D, Durand F. Inaccuracies of creatinine and creatinine-based equations in candidates for liver transplantation with low creatinine: impact on the model for end-stage liver disease score. *Liver Transpl* 2010; **16**: 1169-1177 [PMID: 20879015 DOI: 10.1002/lt.22128]
- 35 **Caregaro L**, Menon F, Angeli P, Amodio P, Merkel C, Bortoluzzi A, Alberino F, Gatta A. Limitations of serum creatinine level and creatinine clearance as filtration markers in cirrhosis. *Arch Intern Med* 1994; **154**: 201-205 [PMID: 8285815 DOI: 10.1001/archinte.1994.00420020117013]
- 36 **Roy L**, Legault L, Pomier-Layrargues G. Glomerular filtration rate measurement in cirrhotic patients with renal failure. *Clin Nephrol* 1998; **50**: 342-346 [PMID: 9877106]
- 37 **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 [PMID: 10404694]
- 38 **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 [PMID: 15855207 DOI: 10.1093/ndt/gfh839]
- 39 **van Acker BA**, Koomen GC, Koopman MG, de Waart DR, Arisz L. Creatinine clearance during cimetidine administration for measurement of glomerular filtration rate. *Lancet* 1992; **340**: 1326-1329 [PMID: 1360044]
- 40 **Cockcroft DW**, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron* 1976; **16**: 31-41 [PMID: 1244564]
- 41 **Pöge U**, Gerhardt T, Stoffel-Wagner B, Klehr HU, Sauerbruch T, Woitas RP. Calculation of glomerular filtration rate based on cystatin C in cirrhotic patients. *Nephrol Dial Transplant* 2006; **21**: 660-664 [PMID: 16326735 DOI: 10.1093/ndt/gfi305]
- 42 **MacAulay J**, Thompson K, Kiberd BA, Barnes DC, Peltekian KM. Serum creatinine in patients with advanced liver disease is of limited value for identification of moderate renal dysfunction: are the equations for estimating renal function better? *Can J Gastroenterol* 2006; **20**: 521-526 [PMID: 16955148]
- 43 **Kim DJ**, Kang HS, Choi HS, Cho HJ, Kim ES, Keum B, An H, Kim JH, Seo YS, Kim YS, Yim HJ, Jeon YT, Lee HS, Um SH, Kim CD, Ryu HS. Serum cystatin C level is a useful marker for the evaluation of renal function in patients with cirrhotic ascites and normal serum creatinine levels. *Korean J Hepatol* 2011; **17**: 130-138 [PMID: 21757984 DOI: 10.3350/kjhep.2011.17.2.130]
- 44 **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 [PMID: 10075613 DOI: 10.7326/0003-4819-130-6-199903160-00002]
- 45 **Stevens LA**, Coresh J, Greene T, Levey AS. Assessing kidney function—measured and estimated glomerular filtration rate. *N Engl J Med* 2006; **354**: 2473-2483 [PMID: 16760447 DOI: 10.1056/NEJMra054415]
- 46 **Levey AS**, Coresh J, Greene T, Marsh J, Stevens LA, Kusek JW, Van Lente F. Expressing the Modification of Diet in Renal Disease Study equation for estimating glomerular filtration rate with standardized serum creatinine values. *Clin Chem* 2007; **53**: 766-772 [PMID: 17332152 DOI: 10.1373/clinchem.2006.077180]
- 47 **Xirouchakis E**, Marelli L, Cholongitas E, Manousou P, Calvaruso V, Pleguezuelo M, Guerrini GP, Maimone S, Kerry A, Hajjawi M, Nair D, Thomas M, Patch D, Burroughs AK. Comparison of cystatin C and creatinine-based glomerular filtration rate formulas with ⁵¹Cr-EDTA clearance in patients with cirrhosis. *Clin J Am Soc Nephrol* 2011; **6**: 84-92 [PMID: 20829419 DOI: 10.2215/CJN.03400410]
- 48 **Gerhardt T**, Pöge U, Stoffel-Wagner B, Palmedo H, Sauerbruch T, Woitas RP. Creatinine-based glomerular filtration rate estimation in patients with liver disease: the new Chronic Kidney Disease Epidemiology Collaboration equation is not better. *Eur J Gastroenterol Hepatol* 2011; **23**: 969-973 [PMID: 21897265 DOI: 10.1097/MEG.0b013e32834991f1]
- 49 **Souza VD**, Hadj-Aissa A, Dolomanova O, Rabilloud M, Rognant N, Lemoine S, Radenne S, Dumortier J, Chapuis-Cellier C, Beyerle F, Bon C, Iwaz J, Selistre L, Dubourg L. Creatinine- versus cystatine C-based equations in assessing the renal function of candidates for liver transplantation with cirrhosis. *Hepatology* 2013; Epub ahead of print [PMID: 24123197 DOI: 10.1002/hep.26886]
- 50 **Levey AS**, Stevens LA, Schmid CH, Zhang YL, Castro AF, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, Coresh J. A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009; **150**: 604-612 [PMID: 19414839 DOI: 10.7326/0003-4819-150-9-200905050-00006]
- 51 **Delanaye P**, Pottel H, Botev R, Inker LA, Levey AS. Con: Should we abandon the use of the MDRD equation in favour of the CKD-EPI equation? *Nephrol Dial Transplant* 2013; **28**: 1396-403; discussion 403 [PMID: 23780677 DOI: 10.1093/ndt/gft006]
- 52 **Hoek FJ**, Kemperman FA, Krediet RT. A comparison between cystatin C, plasma creatinine and the Cockcroft and Gault formula for the estimation of glomerular filtration rate. *Nephrol Dial Transplant* 2003; **18**: 2024-2031 [PMID: 13679476 DOI: 10.1093/ndt/gfg349]
- 53 **Larsson A**, Malm J, Grubb A, Hansson LO. Calculation of glomerular filtration rate expressed in mL/min from plasma cystatin C values in mg/L. *Scand J Clin Lab Invest* 2004; **64**: 25-30 [PMID: 15025426]
- 54 **Inker LA**, Schmid CH, Tighiouart H, Eckfeldt JH, Feldman HI, Greene T, Kusek JW, Manzi J, Van Lente F, Zhang YL, Coresh J, Levey AS. Estimating glomerular filtration rate from serum creatinine and cystatin C. *N Engl J Med* 2012; **367**: 20-29 [PMID: 22762315 DOI: 10.1056/NEJMoa1114248]

P- Reviewers: Banales JM, Lopez-Delgado JC, Maruyama H
S- Editor: Qi Y **L- Editor:** A **E- Editor:** Zhang DN





百世登

Baishideng®

Published by **Baishideng Publishing Group Co., Limited**

Flat C, 23/F., Lucky Plaza,

315-321 Lockhart Road, Wan Chai, Hong Kong, China

Fax: +852-65557188

Telephone: +852-31779906

E-mail: bpgoffice@wjgnet.com

<http://www.wjgnet.com>



ISSN 1007-9327



9 771007 932045