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GFR Estimating Equations and Liver Disease

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Abstract

It is important to accurately assess the glomerular filtration rate (GFR) of patients with liver disease in order to deliver care and allocate organs for transplantation in a way that improves outcomes. The most commonly used methods to estimate GFR in this population are based on creatinine, which is biased by these patients' low creatinine production and potentially by elevated serum bilirubin and decreased albumin levels. None of the creatinine based estimated GFR (eGFR) equations have been specifically modified for a population with liver disease, and even measurement of a 24 hour creatinine clearance has limitations. In liver disease, all creatinine based estimates of GFR overestimate gold standard measured GFR (mGFR), and the degree of overestimation is highest at lower mGFR values and in more severe liver disease.

Cystatin C based eGFR has shown promise in general population studies by demonstrating less bias than creatinine based eGFR and improved association with clinically important outcomes, but results in the liver disease population have been mixed and further studies are necessary.

Ultimately, specific eGFR equations for liver disease or novel methods for estimating GFR may be necessary. However, for now, the limitations of currently available methods need to be appreciated to understand renal function in liver disease.

Keywords

estimated GFR; cirrhosis

Introduction

The accurate assessment of glomerular filtration rate (GFR) in patients with liver disease is a crucial aspect of their clinical care and outcomes. It determines when renal dysfunction is recognized, potentially lessening side effects of inappropriate drug dosing, while also facilitating early therapeutic interventions and decisions about simultaneous liver kidney (SLK) transplantation. Patients with liver disease are susceptible not only to altered hemodynamics and volume shifts related to cirrhosis and portal hypertension, but also to sepsis and intrinsic renal diseases related to their comorbidities.¹ As a result, they are prone to develop reversible acute kidney injury (AKI), irreversible AKI, and chronic kidney disease (CKD) (Figure 1). When renal dysfunction develops in liver disease, it is associated

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with a poor prognosis, and serum creatinine level is an integral part of determining liver allocation through the Model of End-stage Liver Disease (MELD) scoring system [MELD = $3.8 \times \ln(\text{bilirubin [mg/dL]}) + 11.2 \times \ln(\text{INR}) + 9.6 \times \ln(\text{creatinine [mg/dL]}) + 6.4$].² Although the MELD score and most clinical determinations of GFR are based on the measurement of serum creatinine, this value is affected by the comorbidities of cirrhosis in a way that leads to an overestimation of GFR.

GFR is mainly determined by renal plasma flow (RPF) and the Starling Forces that govern filtration at the level of each glomerulus. Normally, GFR, RPF, and glomerular capillary pressure are maintained through autoregulation achieved by adjustments in arteriolar tone. In advanced liver disease, this system becomes overwhelmed as splanchnic arterial vasodilation and decreased systemic vascular resistance lead to compensatory renal vasoconstriction mediated by activation of the sympathetic nervous system and the renin-angiotensin-aldosterone system. This results in a functional decline in RPF and GFR. The situation may be aggravated by further vasodilation from infections; by volume shifts related to ascites, diuresis, and paracentesis; and by the loss of functioning nephrons from multiple possible causes ranging from hepatitis C related glomerulonephritis to comorbid diabetic nephropathy (Table 1).¹

Ideally, the estimation of GFR in liver disease would employ an easily measurable endogenous marker that is freely filtered at the glomerulus without significant reabsorption or secretion and whose rate of production is unaffected by liver disease. Gold standard measured GFR (mGFR) is determined through the clearance of exogenous substances, such as inulin, iothalamate, or radioactive tracers, and should provide valid estimates of true GFR in those with liver disease. However, the most accurate of these methods require a continuous infusion of the marker, frequent blood sampling, and accurate urinary measurement. While simplified protocols have been developed, the technical requirements and cost of these tests still make them impractical for routine clinical usage.³ Thus, we are often left using estimation methods that are clinically practical but suffer from limitations.

Creatinine Based Estimates of GFR

The most widely used estimates of GFR are based on serum creatinine levels. Creatinine is a small molecule (molar mass 113.1 g/mol), which is formed via the nonenzymatic cyclization of creatine.⁴ Although creatine is synthesized in the liver, it is primarily stored in muscle tissue, and thus the production and excretion of its breakdown product, creatinine, is highly correlated with lean body mass.⁵ Its stable production, coupled with its excretion mainly via glomerular filtration, makes it a good marker for GFR in most circumstances. The simplest way to use creatinine as a proxy for GFR is to compare a patient's serum level to population norms. However, lean body mass, and thus creatinine production, varies based on age, race, gender, weight, and other factors. Thus, equations, which employ creatinine and some of these other factors, have been developed to calculate an estimated creatinine clearance (eC_{Cr}) [e.g., Cockcroft-Gault (CG) equation], or an estimated GFR (eGFR) [e.g., Modification of Diet in Renal Disease (MDRD) and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations].

Despite its usefulness as a GFR marker in the general population, the discordance between serum creatinine level and mGFR in liver disease has long been known. In 1987, Papadakis et al. classified cirrhotic patients into three groups based on inulin clearance: Group I with >170 mL/min, Group II with >70 mL/min, and Group III with <60 mL/min. Despite their starkly different mGFRs, all these groups had similar and “normal” mean serum creatinine levels: 0.8 ± 0.1 mg/dL for I, 0.9 ± 0.1 mg/dL for II, and 1.2 ± 0.1 mg/dL for III.⁶ Furthermore, despite performing well in the normal mGFR groups, both the CG eC_{Cr} and 24 hour creatinine clearance overestimated inulin clearance in cirrhotic patients with low mGFR (<60 mL/min) by 308% and 196%, respectively. Similar results, albeit lesser in degree, were obtained by Caregaro et al., in which these two estimation methods were found to overestimate inulin clearance by about 50% in a similar population.⁷

All methods of estimating GFR that employ creatinine suffer from the limitations of this marker. As a result of impaired liver function, low muscle mass, and protein malnutrition, these patients tend to produce less creatine, and consequently creatinine.⁸ Equations used to calculate eGFR or eC_{Cr} do not account for the increased volume of distribution of creatinine in cirrhotics with ascites. Additionally, their inclusion of weight or normalization for body surface area assumes a standard body composition, which does not hold true for cirrhotic patients with muscle wasting and ascites.² Furthermore, patients with the lowest GFRs tend to secrete proportionally more creatinine in their tubules. The end result is that for any given mGFR, serum creatinine is lower and eC_{Cr} or eGFR are higher in this population.

Further inaccuracies in creatinine measurement in liver disease patients stem from the limitations of creatinine assays. Although modern assays based on Jaffe or enzymatic methods are calibrated against an isotope dilution mass spectrometry reference measurement, they both involve a colorimetric step that is susceptible to interference. For example, the compensated Jaffe method is calibrated in a way to cancel out the effect an expected amount of nonspecific chromogens (mainly proteins), and may be negatively biased by the low serum albumin concentration found in cirrhosis.⁹ However, a recent study of commercially available assays using blood with a low median albumin concentration of 2.0 mg/dL found both positive and negative bias in both Jaffe and enzymatic methods that differed based on the assay manufacturer and was more pronounced at higher creatinine concentrations.¹⁰ Additionally, both Jaffe and enzymatic methods may be negatively biased by elevated bilirubin concentrations. Manufacturer specific techniques have been developed to mitigate this, but interference may occur for some assays at total bilirubin levels that exceed 100 μ mol/L (5.8 mg/dL), though other assays have been shown to be free of this bias up to 700 μ mol/L (41 mg/dL).^{9,11} Greenberg et al. found variable degrees of bias (mostly negative, but some positive) in both Jaffe and enzymatic assays with serum bilirubin concentrations of 9-38 mg/dL.¹⁰ Additionally, using different assays leads to different MELD scores: at bilirubin > 400 μ mol/L (23.4 mg/dL), bias among different assays was shown to lead to MELD scores that differed by 3 or more points in 78% of cases.¹² However, different manufacturers use different compensation techniques in their assays, making it difficult to generalize about the effect that low albumin or high bilirubin will have on creatinine measurement.

Despite the limitations of this biomarker, eGFR equations utilizing creatinine are widely used because their calculation can be easily automated and reported alongside serum creatinine. However, none of the study populations used to derive the CG, MDRD, or CKD-EPI equations contained patients with liver disease, making their applicability to this population questionable. The four variable MDRD equation (MDRD4) utilizes serum creatinine, age, gender, and race to estimate GFR (a six variable version [MDRD6] adds serum urea and albumin).¹³ Overall, studies have shown slightly better bias and accuracy for MDRD4 as compared with Cockcroft Gault, however, MDRD4 (corrected for body surface area) still tends to overestimate mGFR by 15-30 mL/min.¹⁴⁻¹⁶ One study did show that MDRD6 may perform better with less overestimation of mGFR, but no direct comparison was made to the 4 variable version.¹⁷ In 2009, the creatinine based CKD-EPI equation was developed, which utilized the same components as MDRD4.¹⁸ A few studies have shown CKD-EPI eGFR in cirrhosis to have an improved bias and correlation with mGFR than older equations.^{19,20} However, results are mixed, and one study showed that the creatinine based CKD-EPI equation was no better than MDRD in terms of bias, accuracy, and precision when compared to mGFR.²¹ Additionally, across all the creatinine based estimating equations, the common trend is that they perform better in liver disease patients with a relatively normal mGFR, but break down when the mGFR is lower.³

One might assume that calculating a creatinine clearance using a 24 hour urine collection would help to account for the low creatinine production in cirrhotic patients that biases estimating equations. However, in general, since creatinine is not only filtered at the glomerulus but also secreted by the tubules, this approach has still been shown to overestimate mGFR in most studies.^{6,7,22,23} This problem is magnified by the higher proportion of secreted to filtered creatinine that manifests at low GFR. Additionally, in clinical practice, a 25% variation in results has been reported due to over or under-collection of urine and other potential errors in the process.²⁴ Yet, results are variable in the literature, and one study showed creatinine clearance to overestimate inulin clearance by only 5%, 3%, and 4% in Child class A, B, and C cirrhotics, respectively, with superior performance to Cockcroft Gault estimates, especially in Child class C cirrhotics.²⁵ Nevertheless, other studies have found creatinine clearance to overestimate GFR by higher amounts in both Child class A²⁶ and class C²⁷ cirrhotics. Overall, a meta-analysis in 2005 showed that timed creatinine clearance overestimates inulin clearance by a mean of +13 mL/min, with an increase in the overestimate as GFR falls.²⁸ A recent study also showed that a timed creatinine clearance is no better at detecting a GFR <60 mL/min (i.e., CKD stage 3) than MDRD6 or cystatin C.²⁹ Sometimes a urea clearance, which generally underestimates GFR, is measured along with a creatinine clearance, with the expectation that taking the mean of the two results may improve accuracy. However, to our knowledge, this practice has not been studied in the liver disease population.

Cystatin C Based Estimates of GFR

Due to the limitations of creatinine, alternative endogenous filtration markers have been investigated. The most studied of these is cystatin C, which is a low molecular weight protein of 13.3 kDa that is expressed by all nucleated cells and is cleared by glomerular filtration. It does not appear in the urine in appreciable amounts because it is catabolized and

reabsorbed by tubular cells, and thus a urinary clearance cannot be calculated.³⁰ Nevertheless, its serum levels have been extensively investigated as a marker of kidney function that may be less biased by demographics and muscle mass. However, its levels may be increased by high cell turnover states, such as hyperthyroidism, corticosteroid usage, and malignancy.³¹ Additionally, it has been shown to be affected by demographic factors, diabetes status, white blood cell count, albumin and C-reactive protein levels independent of GFR.³² Yet, in the general population, cystatin C has been shown to correlate with mGFR more strongly than creatinine.^{33,34} Furthermore, eGFR calculated using cystatin C has been shown to have stronger associations with cardiovascular disease, all-cause mortality, and ESRD when compared with eGFR calculated using creatinine.³⁵

Initial investigations of cystatin C in liver disease showed it to be more sensitive than creatinine in detecting a GFR <90 mL/min (i.e., CKD stage 2),³⁶ and further studies showed it to be equally predictive of renal disease in both cirrhotics and non-cirrhotics.²³ However, not all studies have agreed, with one showing a lack of superiority of using cystatin C over creatinine in predicting a GFR <80 mL/min in cirrhotics.³⁷ More detailed comparisons, using cystatin C based Hoek³³ and Larsson³⁸ equations to estimate GFR, demonstrated that while these equations lead to less bias than creatinine based eGFR, they still overestimate inulin mGFR.¹⁶ Another study of 74 patients failed to show any improvement in using cystatin C over creatinine in cirrhotics, reporting a P30 (percentage of eGFRs within 30% above or below mGFR) of 64% using creatinine based MDRD4 and 68% using the cystatin C based Hoek equation. They further derived a new GFR estimating equation for this population using multivariate linear regression and found the P30 for the creatinine based equation to be 78%, as compared with 74% for the cystatin C based equation.³⁹ Most of these studies have been relatively small and have either used cystatin C alone or simple cystatin C estimating equations that were derived in relatively small cohorts; additionally, prior poor standardization of cystatin C assays may have led to discordant results.

More recently, a new cystatin C based GFR estimating equation, which takes into account demographic factors, has been developed as part of CKD-EPI 2012.⁴⁰ Although few data are available on its usage in cirrhosis, one study did find the CKD-EPI Cystatin C 2012 equation to be superior to most other estimating equations in its correlation with inulin mGFR.²⁰ Specifically, in 202 patients with a mGFR of 80.3 ± 31.1 mL/min, the P30 for CKD-EPI Cystatin C 2012 eGFR was 83.2%, as compared with 42.6% for MDRD4, 58.4% for MDRD6, 56.4% for CKD-EPI Creatinine 2012, and 78.7% for the cystatin C based Hoek equation. Whereas other equations lost significant accuracy in a subgroup with severe ascites and a mean mGFR of 64.4 ± 23.1 mL/min/1.73 m² (P30 of 16.7, 33.3, and 33.3% respectively for MDRD-4, MDRD-6, and CKD-EPI Creatinine 2012), the cystatin C based equations (Hoek and CKD EPI Cystatin C 2012) still performed well, both with a P30 of 66.7%. Similarly, when participants were stratified for liver disease severity (MELD 15 vs. > 15), cystatin C based equations had good performance in both groups (CKD EPI Cystatin C P30s of 83 vs. 85% for the low MELD vs. high MELD and Hoek P30s of 75.5 vs. 85.1%) while creatinine based equations showed worse performance in the higher MELD groups (MDRD4 P30s of 45.5 vs. 24.2% and CKD-EPI Creatinine 2012 P30s of 58.0 vs. 48.4%).²⁰

Although it has been shown that cystatin C measurements are not biased by bilirubin,³⁹ a potential confounding factor for cystatin C is that some studies have correlated it with the degree of liver fibrosis and inflammation,⁴¹ hypothesizing that it may be a marker of liver pathology and inflammation. However, it has not been established whether this results directly from liver pathology or simply reflects concomitant renal dysfunction.²

Other Estimates of GFR

The limitations of current methods used to estimate GFR in liver disease leave open the door for the development of novel techniques. Magnetic resonance renography is one modality that has been preliminarily studied for this purpose in cirrhotics.⁴² Similar to inulin, gadolinium is freely filtered by the glomerulus, but neither secreted or reabsorbed. Imaging plus kinetic models analyzing the disappearance of gadolinium can be used to estimate GFR that correlates well with ^{99m}Tc-DTPA mGFR in both normal patients and cirrhotics.^{42,43} However, its requirement for gadolinium and consequent risk of nephrogenic systemic fibrosis limits its usefulness. In the future, other methods, such as real time noninvasive point of care estimates of GFR employing fluorescent tracers may warrant further study in this population.⁴⁴

The Importance of Accurate eGFR for the Care of the Hospitalized Patient with Liver Disease

It is important to recognize decreased GFR and AKI in hospitalized cirrhotics because it often accompanies other complications and is independently associated with an increased risk of mortality.⁴⁵ Simply looking at a creatinine value or using a GFR estimating equation is often inadequate in this population since a patient who presents with a creatinine of 1.0 mg/dL and an eGFR of $> 60 \text{ mL/min/1.73m}^2$ may be inappropriately classified as having normal kidney function. It has been shown that an early rise in cystatin C during AKI in liver disease is more predictive of mortality and dialysis than a rise in creatinine.⁴⁶ However, even the best GFR estimating equation may be inadequate as a hospitalized cirrhotic patient's serum creatinine or cystatin C may not be in steady state. Overestimation of GFR may lead to the inappropriately high dosing of antibiotics, such as vancomycin, or the usage of intravenous contrast agents that would otherwise be avoided if mGFR were known. Further, this may affect decisions on the usage of diuretics and the performance of a paracentesis. Additionally, it may delay the diagnosis of hepatorenal syndrome and the start of therapies, such as terlipressin, which may be more effective earlier in the course. Thus, there is no substitute for clinical judgment, in which one analyzes the trend of lab values over time, considers that eGFR is almost always an overestimate, and takes into account the patient's overall clinical state when making decisions about their care.

The Importance of Accurate eGFR for Transplant Allocation

Kidney function is currently an important component of determining liver transplant allocation. Despite the significant limitations of using serum creatinine to impute kidney function, it has been associated with mortality in liver disease. Along with serum bilirubin and the international normalized ratio (INR), it is a component of the MELD score used to

determine liver allocation.⁴⁷ Since a higher creatinine (up to 4 mg/dL) results in a higher MELD score, this puts low creatinine producers, including women, elderly, and frail patients at a disadvantage. In fact, the odds ratio of death or becoming too sick to receive a transplant rose from 1.08 (95% CI 0.91–1.26) pre-MELD to 1.30 (95% CI 1.08–1.47) post-MELD in women relative to men.⁴⁸ Interestingly, the same odds ratio improved from 1.51 (95% CI 1.15–1.98) pre-MELD to 0.96 (95% CI 0.74–1.26) post-MELD in black relative to white patients. In both cases, differing creatinine production likely plays a role. In women, it has been demonstrated that the same mGFR leads to a 2–3 point lower MELD score than in men.⁴⁹ As a further limitation, the MELD score treats all values of creatinine either 1 mg/dL or 4 mg/dL the same, and a value of 4 mg/dL is assigned to those on dialysis.²

As waiting times for a liver transplant lengthen, cirrhotic patients often develop either acute or prolonged kidney injury, and the question of whether they will benefit from SLK transplantation arises. Theoretically, those with hepatorenal syndrome should recover function at some point after transplant, but those with significant intrinsic renal disease or fibrosis will not. It has been suggested that such patients undergo renal biopsy,⁵⁰ but in many cases, this is clinically infeasible since they are coagulopathic or unstable. Outcomes data to guide this decision are limited, and both recommendations and practice patterns vary widely. In general, a longer duration of AKI, CKD, or dialysis need and signs of intrinsic renal disease, such as proteinuria, comprise most recommendations.⁵¹

While no estimate of GFR can tell the degree to which a process is reversible, accurate estimates may give us useful information that can be correlated to outcomes. An analysis of registry data comprised of 4997 liver transplant patients showed that patients who always had an MDRD eGFR <30 mL/min/1.73 m² in the 90 days before transplant had a 31% risk of ESRD over 3 years post-transplant, as compared with a <10% risk in those who always had an eGFR > 30 mL/min/1.73 m² or whose eGFR fluctuated between these two ranges.⁵² Additionally, diabetics with a time averaged mean eGFR of <30 mL/min/1.73 m² had a 25.6% risk of ESRD. Thus, the authors concluded that SLK should be considered for both of these high risk groups. Recently, the SLK Transplantation Summit cited the following indications for SLK: 1.) AKI for 4 weeks by stage 3 RIFLE criteria, and eGFR 35 mL/min/1.73m² (MDRD-6) or mGFR 25 mL/min (iothalamate) or 2.) CKD for 3 months with eGFR 40 mL/min/1.73m² (MDRD-6) or mGFR 25 mL/min (iothalamate), proteinuria 2g/day, > 30% global glomerular sclerosis or interstitial fibrosis, or metabolic disease.⁵¹ Higher cutoffs were included for eGFR compared to mGFR to account for the overestimation of eGFR relative to mGFR that occurs with creatinine based MDRD.

Conclusion

It is both important and difficult to accurately estimate GFR in patients with liver disease. Creatinine based eGFR tends to overestimate mGFR in this population, likely due to low muscle mass, decreased liver function, protein malnutrition, and proportionally increased secretion of creatinine, especially at low GFR. No specific equations or correction factors for creatinine based eGFR are available for this population. In recent years, cystatin C has been proposed as a marker of GFR that would be theoretically less biased by the changes that occur in cirrhotics. However, further studies on its application to this population are

needed as current results have been mixed. Going forward, developing improved methods for estimating GFR in liver disease is important not only to optimize care for these patients, but also to make decisions on organ allocation.

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Clinical Summary Bullet Points

- Accurate estimation of GFR in liver disease is important for detection of kidney disease, safe drug dosing, determination of prognosis, and allocation of organs.
- All methods that utilize creatinine to estimate GFR in patients with liver disease overestimate GFR, and the degree of overestimation is highest when GFR is lower and liver disease is more severe.
- The use of cystatin C to estimate GFR in liver disease is potentially promising, but has yielded mixed results and further studies are needed to evaluate its utility.

Figure 1. Current, Recoverable and Unrecoverable GFR

The column on the left represents hypothetical proportions of current GFR, potentially recoverable GFR, and unrecoverable GFR in a cirrhotic patient. Potentially recoverable GFR represents hemodynamic insults (e.g., hepato-renal syndrome or prerenal AKI) while unrecoverable GFR represents conditions that lead to glomerular and interstitial fibrosis. The bars to the right of the column represent mGFR, which will reflect current GFR and eGFR, which often overestimates GFR in this population. Note that neither of these give a good reflection of overall recoverable GFR.

GFR = glomerular filtration rate; mGFR = measured GFR; eGFR = estimated GFR; AKI = acute kidney injury

Table 1

Conditions that Affect GFR and its Measurement in Cirrhosis

Directly Affect GFR	Affect the Measurement of GFR
Intrinsic Renal Disease	Low creatinine production
Membranoproliferative GN	Low muscle mass
IgA nephropathy	Low liver production of creatine
Membranous nephropathy	Malnutrition
Diabetic Nephropathy	Interfere with creatinine assays
Fibrosis from prior insults	High bilirubin
Hemodynamic Changes	Low albumin
Paracentesis	
Diuretics	
Blood loss	
Sepsis	
Hepatorenal Syndrome	
Acute tubular necrosis	