GFR Estimating Equations and Liver Disease

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It is important to accurately assess the glomerular filtration rate (GFR) of patients with liver disease 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 glomerular filtration rate (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, and the degree of overestimation is highest at lower measured GFR 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 kidney function in liver disease.

Key Words: 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 kidney 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 kidney 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) (Fig 1). When kidney dysfunction develops in liver disease, it is associated 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 × ln(bilirubin [mg/dL]) + 11.2 × ln(INR) + 9.6 × ln(creatinine [mg/dL]) + 6.4), where INR is the international normalized ratio.[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 kidney vasoconstriction mediated by activation of the sympathetic nervous system and the renin-angiotensin-aldosterone system. This results in a functional decrease 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 use 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. Although simplified protocols have been developed, the technical requirements and cost of these tests still make them impractical for routine clinical use.[3] Thus, we are often left using estimation methods that are clinically practical but have 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 through 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, are highly correlated with lean body mass.[5] Its stable production, coupled with its excretion mainly through 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

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based on age, race, gender, weight, and other factors. Thus, equations, which use 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 glomerular filtration rate (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 and Arieff[6] classified cirrhotic patients into 3 groups based on inulin clearance: Group I with more than 170 mL/min, Group II with more than 70 mL/min, and Group III with less than 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. 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 and others,[7] in which these 2 estimation methods were found to overestimate inulin clearance by about 50% in a similar population.

All methods of estimating GFR that use creatinine have 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 μmol/L (5.8 mg/dL), although other assays have been shown to be free of this bias up to 700 μmol/L (41 mg/dL).[9,11] Greenberg and colleagues[10] found variable degrees of bias (mostly negative, but some positive) in both Jaffe and enzymatic assays with serum bilirubin concentrations of 9 to 38 mg/dL. Additionally, using different assays leads to different MELD scores, at bilirubin more than 400 μmol/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.

CLINICAL SUMMARY

- Accurate estimation of glomerular filtration rate (GFR) in liver disease is important for detection of kidney disease, safe drug dosing, determination of prognosis, and allocation of organs.
- All methods that use 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.

Despite the limitations of this biomarker, eGFR equations using 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 4-variable MDRD equation (MDRD4) uses serum creatinine, age, gender, and race to estimate GFR (a 6-variable version [MDRD6] adds serum urea and albumin).[13] Overall, studies have shown slightly better bias and accuracy for MDRD4 compared with CG; however, MDRD4 (corrected for body surface area) still tends to overestimate mGFR by 15 to 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 used 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 1 study showed that the creatinine-based CKD-EPI equation was no better than MDRD in terms of bias, accuracy, and precision compared with 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]