Challenges in measuring renal function in liver cirrhosis : are there implications in clinical practice?

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Abstract

Renal dysfunction is frequent in liver cirrhosis, and it is associated with poor prognosis. Currently, there are major limitations when assessing renal function in cirrhotic patients. Available methods are biased and have a tendency to overestimate glomerular filtration rates (GFR) consistently. A subset of new creatinine-based formulas derived specifically from these populations may provide a more accurate estimation of renal function. In this article, we will explore the estimation methods of GFR in cirrhosis available to date and discuss possible implications in clinical practice. (Acta gastroenterol. belg., **2020**, 83, **633-638**).

Keywords : kidney, liver cirrhosis, liver transplant.

Introduction

Renal dysfunction is frequent in patients with liver cirrhosis, affecting 20% of inpatients and up to 40% of outpatients (1,2). Renal dysfunction may occur unrelated to the cause of cirrhosis (e.g., ischemia, sepsis, drugs), directly related to the cause of cirrhosis (e.g., nonalcoholic fatty liver disease, alcohol, hepatitis B and C related glomerulopathy) or arise as a consequence of cirrhosis and portal hypertension (i.e., hepatorenal syndrome [HRS]) (3). These pathologies will reflect acute kidney injury (AKI), chronic kidney disease (CKD), or "acute on chronic renal failure" (4). Regardless of the type or pattern of kidney injury, they all have a significant impact on survival in patients with advanced cirrhosis (4,5).

The acknowledgment of the prognostic value of renal function has led to the inclusion of a surrogate serum marker, creatinine, in the Model of End Stage Liver Disease (MELD) used for liver transplant prioritization lists worldwide (6). However, creatinine is an inaccurate marker of renal function in cirrhosis. Creatinine, creatinine clearance, and creatinine-based equations tend to overestimate the glomerular filtration rate (GFR). Clearance of exogenous markers remains the only reliable method for assessing GFR precisely in cirrhosis. However, it is limited by costs and complexity. Serum cystatin C and liver disease-specific equations have been proposed as alternatives, although they need further validation.

This article aims to review the available methods for the assessment of renal function and the possible implications in the management of patients with cirrhosis.

Pathophysiology of renal dysfunction in cirrhosis

Renal dysfunction in cirrhosis can be classified into two major categories : renal dysfunction reflecting circulatory disturbances secondary to decompensated cirrhosis (i.e., hepatorenal syndrome) and renal dysfunction independent of hemodynamic disturbances of cirrhosis (i.e., volume depletion, drug-induced nephrotoxicity, glomerulopathies) (5).

Disturbances in circulatory function are the mainstay for renal dysfunction in liver cirrhosis (7,8). Portal hypertension leads to arterial vasodilation of the splanchnic circulation, which in turn leads to reduced systemic vascular resistance and low adequate arterial blood volume (9). In compensated cirrhosis, there is a steady increase in the cardiac output to maintain appropriate arterial blood volume. In decompensated cirrhosis, however, the increased cardiac output is insufficient, so vasoconstrictors such as renin, angiotensin, sympathetic nervous system, and antidiuretic hormone are released (8). In advanced stages of disease, the further increase of splanchnic vasodilation cannot be adequately compensated by the vasoconstrictor system. Additional water and sodium retention lead to the appearance of ascites and dilutional hyponatremia. In the most advanced stages, the maximal activation of vasoconstrictor systems causes severe intrarenal vasoconstriction and hypoperfusion, the hallmark of HRS (10). Therefore, episodic events such as hypovolemia (e.g., gastroesophageal variceal hemorrhage, diuretics) or further vasodilatation (e.g., infections) can disturb the delicate hemodynamic balance leading to a rapid decline of renal function.

Also, some etiologies of cirrhosis are associated with the development of CKD. Chronic viral hepatitis are classically described in association with glomerulopathies – chronic hepatitis C with membranoproliferative glomerulonephritis or cryoglobulinemia and chronic hepatitis B with membranous glomerulonephritis (5).

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A secondary IgA nephropathy has also been described in alcohol-related cirrhosis due to impaired hepatic clearance of IgA complexes (11).

Recently, a strong association between the presence and severity of nonalcoholic fatty liver disease and CKD has been described, mostly through a process of accelerated atherothrombosis, that is independent of obesity, hypertension, type-2 diabetes mellitus, and other common cardio-renal risk factors (12).

Defining AKI and CKD in cirrhosis

The definition of AKI in cirrhosis is provided by the latest recommendations of the International Club of Ascites (ICA), which are in line with the Kidney Disease : Improving Global Outcomes (KDIGO) working group. AKI is defined by an increase of serum creatinine (sCr) ≥ 0,3 mg/dl within 48 hours or a percentage increase of sCr ≥ 50% from baseline, which is presumed to have occurred in the last 7 days. Baseline sCr was defined as a stable sCr within the previous 3 months (13). Unlike the first definition, there is no threshold of SCr, allowing the diagnosis of AKI in lower sCr levels and acknowledging the negative prognostic impact of small rises in sCr (14). KDIGO recommendations of urinary output and definition of baseline sCr from reverse calculation of sCr formulas were discouraged due to inaccuracy in liver cirrhosis (13). AKI is further staged in 3 degrees according to the extent of the increase of sCr (Table 1) (13). Staging has important prognostic implications and guides therapeutic management.

Patients with cirrhosis are susceptible to different types of AKI, most frequently prerenal AKI (hypovolemia and HRS-AKI) and intrinsic AKI (mainly acute tubular necrosis) (15). Post-renal AKI is a rare finding in cirrhosis. HRS-AKI is the prototype of AKI in liver cirrhosis and is currently defined as a ≥ stage 2 AKI, with no improvement of sCr after ≥48h of diuretic withdrawal and volume expansion (albumin 1g/kg of body weight up to 100g/day) in the absence of shock, current or recent use of nephrotoxins, and no signs of structural kidney damage (proteinuria <500mg/day, hematuria <50 red blood cells/ high power field, normal renal ultrasonography) (13).

Initial steps in HRS-AKI management involve a careful assessment of volume status, removal of potential offenders (e.g., nephrotoxic drugs), and empiric antibiotic treatment if suspected infection. While these measures are usually effective in most of the patients with AKI stage 1, patients with stages 2 and 3 should receive from the beginning volume expansion through the administration of intravenous (i.v) albumin (1 gr/Kg of body weight), as appropriate. For those patients who do not achieve a favorable response after 2 days, an in-depth examination of clinical presentation is required to exclude cases of parenchymal or obstructive causes of AKI. If other causes of AKI are excluded, and HRS criteria are met, vasoconstrictor therapy plus albumin (20-40 gr/day) should be implemented (10,15).Terlipressin, the first-line agent, should be administered as i.v boluses (0,5-1mg every 4 to 6 hours) or as a continuous i.v infusion. The latter is as effective and better tolerated. Noradrenaline as a continuous iv infusion (0,5 mg/h up to 3 mg/h) is an alternative with similar efficacy. Midodrine plus octreotide are less effective alternatives (10). Treatment should be continued until sCr normalization or up to 14 days in non-responsive patients. Renal replacement therapy may be considered as a bridge to liver transplant (LT) in patients who fail to respond to medical therapies (5).

Table 1. — **Definitions of acute kidney injury and chronic kidney disease by the ICA and KDIGO, respectively**

Terminology	Definition
Acute kidney injury	Increase in sCr ≥ 0.3 mg/dL within 48 hours or a percentage increase sCr ≥ 50% from baseline (known, or presumed to have occurred within the prior 7 days)
Stages of Acute Kidney Injury	Stage 1: increase in sCr ≥0.3 mg/dL or an increase in sCr≥1.5-fold to 2-fold from baseline Stage 2: increase in sCr > 2- to 3-fold from baseline Stage 3: increase of sCr > 3-fold from baseline or sCr ≥4.0 mg/dL with an acute increase ≥0.3 mg/dL or initiation of renal replacement therapy
Chronic Kidney Disease	Either the presence of ≥ 1 marker of kidney injury (albuminuria, urine sediment abnormalities electrolyte and other abnormalities due to tubular disorders, abnormalities detected by histology, structural abnormalities detected by imaging, history of kidney transplantation) or decrease GFR <60 mL/min/1.73m^2
Stages of Chronic Kidney Disease	Grade 1: GFR ≥ 90 mL/min/1.73 m^2 Grade 2: GFR 60-89 mL/min/1.73 m^2 Grade 3a: GFR 45-59 mL/min/1.73 m^2 Grade 3b: GFR 30-44 mL/min/1.73 m^2 Grade 4: GFR 15-29 mL/min/1.73 m^2 Grade 5: GFR <15 mL/min/1.73 m^2

Abbreviations : GFR : glomerular filtration rate ; ICA : International Club of Ascites ; KDIGO : Kidney Disease Improving Global Outcomes ; sCr : serum creatinine.

CKD is defined as abnormalities of kidney structure (albuminuria, urine sediment alterations, histological or ultrasound abnormalities) or function (GFR < 60ml/min/1.73m^2), present for > 3 months (16). CKD is further staged from stage 1 to 5, according to the severity of GFR (Table 1). As previously stated, there are several underlying, and sometimes conflicting causes of CKD in cirrhosis. HRS type 2 (HRS2) is a specific form of slowly progressive CKD in patients with liver cirrhosis and refractory ascites (17). It is a result of progressive circulatory dysfunction and is characterized by the absence of macroscopic signs of parenchymal kidney damage. Since it is related to a progression in liver disease, it is associated with low survival and only reversible with a liver transplant (17). Whether it is related to structural renal disease or HRS2, CKD is a common finding in cirrhosis, occurring in 46.8% of patients admitted to

Table 2. — **Characteristics and limitations of current methods for renal function assessment in liver cirrhosis**

Marker	Advantages	Limitations
Clearance of exogenous markers	Most accurate method for renal function estimation; Urinary inulin clearance is the gold standard; Plasma clearance of synthetic polyfructosans, radiolabeled compounds, or non-radioactive agents are alternative methods.	Time-consuming (several collections); Potential errors in sampling and potentially invasive (if urine collection required); Overestimation of GFR if increased volumes of distribution (ascites and edema) in plasma clearance methods; Expensive; Not appropriate for routine practice.
Serum creatinine	Most widely accepted and available routine test.	Influenced by several factors (e.g., age, gender, ethnicity, body weight, muscle mass); In cirrhotic patients influenced by sarcopenia, bilirubin, diuretic therapy, and cephalosporin treatment; Not sensitive for early detection of acute renal failure.
Creatinine clearance	Widely available.	Potential errors in urine collection; Influenced by muscle mass, inflammatory diseases, and malnutrition; Overestimates GFR in liver cirrhosis.
C-G, CKD-EPI, MDRD-4, and MDRD-6	Easy to use; Variables used in equations are readily available in clinical practice.	None included cirrhotic patients when developed; Has the same limitations as sCr; All overestimate GFR in liver cirrhosis.
RFHC-GFR and GRAIL	Easy to use; Variables are readily available; Derived from patients with liver cirrhosis; Better accuracy than all the other sCr-based equations.	Still dependent on sCr as reference biomarker; GRAIL uses serum albumin (biased by recent albumin infusions), RFHC uses ascites assessment (subjective); Require further validation.
CysC and CysC-related formulas	Not significantly affected by race, age, muscle mass, or liver function; Less bias than sCr-based formulas and higher performance in lower GFR.	Not widely available; Expensive.
Beta-2 microglobulin	Freely filtered by the glomerulus, further reabsorbed and metabolized in the proximal tubule; Readily available.	Affected by several conditions such as malignancies, autoimmune diseases, and inflammatory states.

Abbreviations : Cockcroft-Gault (C-G), Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), GFR (Glomerular filtration rate), Glomerular Filtration Rate Assessment in Liver Disease (GRAIL), Modification of Diet in Renal Disease (MDRD-4, MDRD-6), Royal Free Hospital Cirrhosis Glomerular Filtration Rate (RFHC-GFR), sCr (serum creatinine

the hospital (18). The presence of CKD predisposes the admitted patients with cirrhosis to worse renal and hospital outcomes, together with reduced overall survival (18). Therefore underlying CKD risk factors should be carefully sought and treated in order to minimize CKD progression (3).

Estimation methods of GFR in cirrhosis

Glomerular filtration rate GFR is the universally accepted measure of renal function (19). There are several methods of estimation of GFR (Table 2) with different accuracies. In cirrhotic patients, however, no GFR estimation method has been considered to be optimal.

Clearance of exogenous markers is considered the most accurate method for renal function estimation in cirrhosis (20). Inulin clearance is considered the *gold standard*. Inulin is freely filtered by the glomerulus and not secreted, reabsorbed, synthesized, or metabolized by the kidney. Therefore, the amount of filtered inulin by the glomerulus is equal to the amount excreted in the urine. However, this technique requires continuous intravenous infusion and timed urine collections over a period of several hours, which is time-consuming, costly, and potentially invasive (if bladder catheterization has to be performed for urine collection). There are alternative techniques using markers such as synthetic polyfructosans, radiolabeled compounds, or non-radioactive agents. After bolus injection, measurement of GFR is based on the total area under the curve of the plasma concentration of the marker, after repeated blood samples were taken after 3-6 h (20). However, they are imprecise in liver disease and can lead to an overestimation of GFR due to increased volumes of distribution secondary to ascites and edema (20). In these patients, following the bolus injection of an exogenous marker, there is an initial faster decline of plasma isotope concentration (secondary to redistribution into the ascitic fluid) followed by a slower decay curve (as the isotope returns from the ascitic fluid back to the plasma) (20). In order to overcome this limitation, Wickham et al. have described and validated a modified plasma clearance method that can be used in liver patients with ascites (21). Plasma samples are taken at 2,4,8 and 24 hours, and a log-linear trapezoidal rule with extrapolation to zero and infinity is used to calculate the area under the plasma clearance curve (21,22). Overall, these techniques are technically demanding, costly, and therefore unviable for routine use (6,19).

Creatinine clearance is based on the assumption that creatinine is the perfect renal marker and requires 24h

urine collection (19). Despite being widely available and simple to obtain, it has several limitations, namely errors during urine collection and overestimation of results related to creatinine tubular secretion, muscle mass, diet, inflammatory diseases, and malnutrition. (6,19) In a meta-analysis, creatinine clearance has been shown to overestimate real GFR in cirrhotic patients with the highest difference seen in patients with lower GFR (23). In liver cirrhosis, this overestimation can be explained by an increased tubular secretion of creatinine. It has also not been shown to be superior to serum creatinine (19,20).

Serum creatinine is the most widely accepted and available routine test for renal function assessment. Creatinine is the breakdown product of creatine. Creatine is synthesized in the liver and is further metabolized in the muscle trough phosphorylation into creatinine. Creatinine is finally excreted by the kidneys mainly through glomerular filtration but also by proximal tubular secretion. Despite wide creatinine use in clinical practice, it has several pitfalls. Serum creatinine is influenced by several factors such as age, sex, muscle mass, dietary meat ingestion, level of hydration, creatine metabolism, renal tubular secretion, and urinary flow rate (20). Additionally, bilirubin, glucose, uric acid, ketoacids, pyruvate, and some antibiotics can interfere with creatinine assays leading to creatinine underestimation (6,20). To overcome the major role of bilirubin interference, most laboratories now use the modified Jaffe method, which shows the least interference with bilirubin levels (24). Studies comparing creatinine with clearance of exogenous markers in cirrhotic patients have shown that creatinine consistently overestimates GFR (25-28). In cirrhosis, decreased liver production of creatine, malnutrition, muscle depletion, larger distribution volumes (edema) seem to justify these findings. Diuretic therapy and cephalosporin can also contribute due to increased tubular secretion of creatinine (6,19,20). Therefore, it is not surprising that in this subset of patients, impairment of GFR may exist even with the normal range of serum creatinine.

Mathematical formulas based on serum creatinine, such as the Cockcroft-Gault (C-G), Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) and Modification of Diet in Renal Disease (MDRD-4, MDRD-6) are also inaccurate for GFR prediction in patients with liver cirrhosis. Several studies have evaluated the performance of these formulas (against different reference methods) with an overall tendency to overestimate GFR (19). Of the previous, MDRD-6 may be more the most accurate so it has been proposed as the reference equation to identify candidates for simultaneous liver and kidney transplantation according to consensus guidelines (29).

There are some obvious reasons why these formulas are inaccurate in liver cirrhosis. First of all, they were derived from healthy male populations or with chronic kidney disease and have not included patients with liver cirrhosis (20). Secondly, as previously stated, creatinine is affected by several factors (liver function, muscle mass, age, gender, race), which are reflected in these creatinine-based formulas. Some patients may be at higher risk. In a recent large cohort study by Yoo et al. sarcopenia, female gender and advanced liver disease were independent risk factors for real GFR by the MDRD-4 equation (30).

The Royal Free Hospital Cirrhosis Glomerular Filtration Rate (RFHC-GFR) equation was the first creatinine-based mathematical formula that was derived from a population of patients with liver disease (31). It includes the variables of age, gender, creatinine, urea, sodium, international normalized ratio, and the presence or absence of ascites. The authors included 469 consecutive patients with liver cirrhosis that were evaluated for liver transplant (plus 174 patients in the internal validation and 82 patients in the external validation cohort). Real GFR was assessed using Cr-51 ethylenediaminetetraacetic acid or Tc-99m diethylene triamine pentaacetic acid clearance (adjusted with the Wickham method). The RFHC-GFR formula had the highest performance when compared with existing formulas MDRD, CKD-EPI, CKD-EPI cystatin C, CKD-EPI cystatin C-creatinine) 89% versus 27-75% of estimates being within 30% of true GFR, respectively (31). The formula is available online, and it can be easily implemented in current clinical practice.

Recently, a new estimation model has been published for patients with liver disease – the Glomerular Filtration Rate Assessment in Liver Disease (GRAIL) (32). In this multicenter cohort study, over 12,000 GFR measurements from 3000 patients on the liver transplantation list and after transplantation (one month, three months, one year, and annually for 25 years) were analyzed. Real GFR was assessed using iothalamate clearance. It includes the variables of age, gender, race, creatinine, blood urea nitrogen, and albumin. Like the RFHC-GFR, the acuity of GRAIL was assessed and further compared with CKD-EPI, MDRD-4, and MDRD-6.

GRAIL had less bias and better accuracy and precision for estimating low GFR (<30 mL/minute/1.73m^2). Prior to LT, GRAIL correctly classified 75% as having real GFR<30 ml/minute/1.73m^2 vs. 36.1% with CDK-EPI, 36.1% with MDRD-4, and 52,8% with MDRD-6 (ρ<0.01) (32). At higher GFR levels, however, GRAIL performed similarly to other equations.

There are some obvious differences between the two formulas. GRAIL comprises ethnicity, a well-established determinant of GFR estimation that was not assessed in the RHFC due to a type 2 error. The incorporation of serum albumin in the GRAIL equation may be biased by recent albumin infusions and the assessment of ascites in RFHC is subjective. Also, a comparison study between the two is lacking.

Cystatin C and new biomarkers

Cystatin C (CysC) is a low molecular weight protein produced at a constant rate by all nucleated cells and eliminated almost exclusively by glomerular filtration.

After filtration, CysC is reabsorbed and catabolized by the proximal tubular cells, so urinary clearance cannot be measured (10). CysC has been proposed as a surrogate marker in patients with liver cirrhosis since serum levels are not significantly affected by race, age, muscle mass, or liver function (20). Also, CysC has shown to have a better correlation with inulin clearance than SCr in liver cirrhosis (33). CysC-based formulas have also been developed and validated in patients with liver disease. Overall, CysC-based formulas have less bias than Cr-based formulas with higher performance in patients with lower GFR (19,34). The fact that CysC is not widely available in all centers and is more expensive is still cumbersome for its application in clinical practice.

Apart from CysC, beta-2 microglobulin has been proposed as a biomarker for GFR estimation (29). Beta-2 microglobulin is a small molecule present in all nucleated cells, freely filtered by the glomerulus, further reabsorbed and metabolized in the proximal tubule. Serum levels of beta-2 microglobulin increase earlier than sCr and correlate with GFR decline. However, beta-2 microglobulin levels are affected by a number of conditions such as malignancies, autoimmune diseases, and inflammatory states (29).

Implications in Clinical Practice

The assessment of renal function is essential for the management of patients with cirrhosis. It provides information regarding prognostic stratification, dose adjustment of drugs metabolized by the kidney, diagnosis, and management of AKI, and defining transplant strategies.

Implications in AKI and CKD

Creatinine is a relatively insensitive marker for early acute changes in kidney function, especially in liver patients. Rises in sCr may occur only 24-48h after the renal injury, resulting in a significant delay in AKI diagnosis with poorer prognosis (3). Reduced urinary output is able to identify AKI before changes in Cr become apparent (35). In cirrhotic patients, however, this alternative is also flawed, since due to avid sodium and water retention, these patients are frequently oliguric with preserved renal function (10).

As we previously stated, the oldest HRS definition was dictated by defined cut-offs in the absolute value of sCr. The latest ICA recommendation eliminated sCr cut-offs and substituted for relative changes in sCr instead. However, a dependence on sCr as a marker of kidney function still persists. Relative changes in sCr are affected by its absolute values, and those values, in turn, have significant limitations in the context of cirrhosis (15). Thus, we must remain aware of the limitations of serum creatinine measurements when assessing absolute and relative changes in its value.

The prevalence and characteristics of CKD in patients with cirrhosis has been poorly elucidated, mainly due to the mentioned limitations of SCr-based equations. We already know that actual GFR will be significantly lower than what is provided by general sCr-based equations. When a more specific sCr formula, the RFHC-GFR, was compared with other general sCr-based equations, in terms of renal function stage classification, significantly more patients (55%) had advanced renal dysfunction, corresponding to stage III to V renal failure, compared with 30 to 35% of patients when GFR was estimated using the MDRD-4, MDRD-6 or CKD-EPI equations (36). This means that a significant percentage of patients may require dose adjustment of drugs and nephrology consultations with seemingly normal sCr.

Implications in Liver Transplant Allocation

Liver transplant allocation is currently based on predictive models, *i.e*., the MELD-Na score that uses objective laboratory elements such as bilirubin, INR, creatinine, and serum sodium. One significant implication when we address the limitations of creatinine in patients with liver disease is how this would affect MELD scores and, subsequently, liver transplant prioritization. We are already aware of this limitation from evidence from gender disparity (37).

The same authors that developed the GRAIL model have also recently published a study to assess whether replacement of serum creatinine with the estimated glomerular filtration rate by the GRAIL model improved the accuracy in prediction of mortality of the MELD score (38). The new model incorporating this variable, the MELD-GRAIL-Na, was built with data from over 17,000 patients on the liver transplantation list. Prediction of 90-day waitlist mortality was then compared between MELD-GRAIL-Na and MELD-Na. The MELD-GRAIL-Na model was a better predictor of waiting list mortality than MELD and MELD-Na (c=0.83, c=0.81, and c=0.82, respectively) (38). MELD-GRAIL-Na also outperformed in the subset of patients with higher disease severity scores and women. More importantly, MELD-GRAIL-Na reclassified 16,7% of patients on the waitlist list (38).

Conclusion

Besides the detrimental effect of renal failure in mortality of patients with liver cirrhosis, current methods of GFR estimation in this population still present many limitations. A subset of new creatinine-based formulas derived specifically from these populations may provide a more accurate estimate of renal function. Further studies are needed to assess whether the inclusion of a better discriminant of GRF estimation may alter liver transplant allocation.

Conflict of Interests

None to declare

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