PATHOGENESIS AND ASSESSMENT OF RENAL FUNCTION IN PATIENTS WITH LIVER CIRRHOSIS

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ABSTRACT
In liver cirrhosis patients awaiting liver transplantation, it is prognostically equally important to assess the renal function before and after transplantation. This is evidenced by the inclusion of serum creatinine in the Model for End-Stage Liver Disease (MELD) score. Most of the causes of renal failure in liver cirrhosis are functional, the acute kidney damage including prerenal azotemia, acute tubular necrosis and hepatorenal syndrome. A major index of the renal function, the glomerular filtration rate (GFR) is determined in a specific way in patients with liver cirrhosis. Clinically, serum creatinine is considered the best indicator of kidney function, although it is rather unreliable when it comes to early assessment of renal dysfunction. Most of the patients with liver cirrhosis have several concomitant conditions, which are the reason for the false low creatinine levels, even in the presence of moderate to severe kidney damage. This also holds for the creatinine clearance and creatinine-based estimation equations for assessment of the glomerular filtration rate (the Cockroft-Gault and MDRD formulas), which overestimate the real glomerular filtration. Clearance of exogenous markers is considered a gold standard, but the methods for their determination are rather costly and hard to apply. Alternative serum markers (e.g., cystatin C) have been used, but they should be better studied in cases of liver cirrhosis assessment.

Key words: liver cirrhosis, renal failure, glomerular filtration, creatinine, creatinine clearance, cystatin C

INTRODUCTION
Liver cirrhosis (LC) is associated with considerably high morbidity and mortality rates, therefore knowledge of the prognostic factors related to it is important for a successful treatment and an eventual liver transplantation. Disturbed renal function is among the main complications of liver cirrhosis, frequently accompanying its later stages. It is related to poorer prognosis, especially if it has resulted from acute complications (sepsis) or has followed liver transplantation. Hence the crucial importance that an accurate assessment of the renal function in patients with liver cirrhosis has for the prognosis and therapeutic approach. The term “acute renal failure” (ARF) in liver cirrhosis has been replaced with “acute kidney injury”. ARF is relatively common – it occurs in approximately 20% of hospitalized patients with liver cirrhosis and includes prerenal azotemia, acute tubular necrosis and hepatorenal syndrome (HRS). With the progression of liver cirrhosis and portal hypertension, the renal dysfunction usually evolves to HRS, which is associated with high mortality rate, especially type I HRS (mean survival without specific treatment is only 2 weeks). Chronic renal disorders occur in approximately 1% of all patients with liver cirrhosis. These patients are exceptionally sensitive to the reduction in the plasma volume and are at increased risk of renal function impairment due to frequent presence of infection (including spontaneous bacterial peritonitis), gastrointestinal bleeding or subjecting to abdominal paracentesis and/or inadequate diuretic therapy, etc.

MELD INDEX
The Child-Pugh score (accounting for ascites, encephalopathy, international normalized ratio (INR), serum bilirubin and albumin) has been used as a
prognostic tool in liver cirrhosis for more than 30 years. Its weak points are the subjective interpretation of ascites and encephalopathy. A meta-analysis of 118 studies shows that both parameters of liver (Child-Pugh) and renal (nitrogen species) failure are important prognostic factors in decompensated liver cirrhosis. A study on 231 patients aiming to create a predictive model for the 3-month mortality after application of transjugular portosystemic shunt, shows that increased serum creatinine levels are an independent factor related to higher mortality. It led to the creation of the MELD (Model for End-Stage Liver Disease) score in 2000 for assessment of terminal stages of liver disease. Its three components, serum bilirubin, creatinine and INR, are derived by statistical analysis and not chosen empirically:

\[
\text{MELD score} = 10 \times [0.957 \times \text{serum creatinine} + (0.378 \times \text{serum bilirubin}) + 1.120 \times \text{INR}] + 0.643 \times \text{etiology of LC} \ (0 - \text{alcohol; cholestasis; } 1 - \text{other etiology}).
\]

Serum creatinine and bilirubin are measured in mg/dl. Later the score was validated in a cohort study with candidates for liver transplantation; its introduction resulted in a greater number of patients with liver cirrhosis and RF who had liver transplantation thus reducing lethal outcomes in patients awaiting transplantation. MELD score is considered to be more precise than the Child-Pugh score due to the inclusion of serum creatinine and a better prognostic tool for the 3-month survival in liver cirrhosis. The inclusion of serum sodium might improve its predictive capacity. Generally, serum concentrations of creatinine and sodium in patients with advanced liver cirrhosis are indicators of decreased renal function.

TYPES OF KIDNEY INJURY IN LIVER CIRRHOSIS

The majority of causes of RF in liver cirrhosis are functional – resulting from alterations in hemodynamics, renal autoregulatory mechanisms and cardiac function. The number of patients with liver cirrhosis, accompanied by morphologic renal alterations, is also not insignificant. Acute kidney injury includes all causes of acute renal function impairment and is characterized by elevation of serum creatinine levels \(\geq 50\%\) of the baseline or \(\geq 0.3\ \text{mg/dl} (\geq 26.4\ \mu\text{mol/l})\) for less than 48 hours. Chronic renal disease is present if the value of the estimated glomerular filtration rate (eGFR), calculated by the MDRD 6 formula is \(< 60\ \text{ml/min for more than 3 months, although the formula is known to overestimate the glomerular filtration in liver cirrhosis. Acute-on-chronic RF is defined as an acute kidney injury occurring in addition to an underlying chronic kidney disease (Table 1).}^{10,11}

In a prospective study including 463 patients with liver cirrhosis and RF, the most frequent causes of RF were found to be infections (46%), then hypovolemia-associated renal failures (32%), HRS (13%) and parenchymatous nephropathy (9%); the remaining patients had a combination of causes or miscellaneous conditions. In patients with liver cirrhosis and spontaneous bacterial peritonitis, renal dysfunction is the most important independent predictor, followed by MELD index. ARF in liver cirrhosis is a result of prerenal (functional) RF (68%), HRS type I, acute tubular necrosis and osmotic tubulopathy. An ARF episode may be reversible, but the kidney function impairment may persist for a long period of time and the patients may develop a chronic kidney disorder. It is rarely seen in cirrhosis and is a consequence of diabetic glomerulosclerosis, ischemic nephropathy, alcohol-induced IgA-nephropathy, hepatitis C-related membrane proliferative glomerulonephritis, hepatitis B-related membranous nephropathy, nondiabetic glomerulosclerosis and HRS type II (the most frequent cause for chronic RF). The etiology of RF is independently related to the prognosis and determines the 3-month survival rate - 73% for parenchymal nephropathy, 46% for hypovolemic RF, 31% for infection-related RF and 15% for HRS.

PATHOGENESIS OF ARF IN LIVER CIRRHOSIS

Renal dysfunction in liver cirrhosis includes impaired natriuresis, decreased clearance of free water and decreased glomerular filtration, clinically presented with hyponatriemia, ascites and HRS. A key factor in the pathogenesis of ARF in liver cirrhosis is the hyperdynamic circulatory state – resulting from peripheral vasodilation and increased cardiac output, leading to relative vasoconstriction in other organs, including kidneys. The progressive vasodilation – splanchnic and systemic, in the presence of portal hypertension, leads to relative hypovolemia with sodium retention mechanisms activation (sympathetic nervous system – SNS; renin-angiotenzin-aldosterone system – RAAS and non-osmotic secretion of arginine vasopresine (antidiuretic hormone - ADH). These factors cause renal vasoconstriction and decreased renal function and, in advanced stages of liver cirrhosis, sodium and water retention with
ascites and hyponatriemia. The vasodilation is due to increased release and/or activity of endogenous vasodilators, especially nitric oxide, and to a lesser extent due to decreased hepatic clearance, reduced sensitivity to them and increased resistance to pressor hormones. It precedes renal sodium and water retention (Fig. 1).

The severity of circulatory dysfunction correlates with the severity of liver cirrhosis, HRS being considered its terminal manifestation. In 1996 International Ascites Club defined HRS as a condition of chronic liver disease with advanced liver failure and portal hypertension, characterized by impaired renal function and impaired arterial circulation, due to endogenous vasoactive system activation. It is a type of RF, unresponsive to volume replacement, resulting from hypoperfusion and reduced glomerular filtration, due to splanchnic arterial vasodilation and peripheral-vascular vasoconstriction, with cardiac dysfunction also contributing to its pathogenesis. Type I HRS is preceded by peripheral vasodilation, more often in spontaneous bacterial peritonitis (SBP), occurs acutely with severe circulatory impairment. It is a rapidly progressing functional RF, in which creatinine levels rise over 100%, compared to baseline, up to levels over 220 μmol/l in two weeks. Unlike this type, type II HRS evolves with more prolonged renal function impairment (creatinine is increased to 130-180 μmol/l), and usually occurs in cases of increased splanchnic vasodilation in refractory ascites and is prognostically better.

In the presence of hyperdynamic circulation, renal circulation is susceptible to conditions re-
lated to further reduction in the effective arterial blood flow. Acute fluids loss and the presence of bacterial infection lead to or worsen the present hypovolemia. The vasoconstrictor systems are compensatorily activated leading to enhanced renal hypoperfusion and significantly reduced glomerular filtration. Any cause of prerenal RF may lead to ischemic tubular injury.\textsuperscript{11,15}

**DIAGNOSIS OF RENAL DYSFUNCTION IN LIVER CIRRHOSIS**

Renal dysfunction in liver cirrhosis can be diagnosed by finding a reduction in the rate of glomerular filtration. Tubular and interstitial damage is also an important predictor of RF, but determining their function is not of any practical value. The ideal marker of glomerular filtration should be endogenously produced at constant rate, freely filtrated through the glomerules, and not be secreted or reabsorbed in the tubules or eliminated extrarenally. The glomerular filtration rate (GFR) is best measured by:

1. Clearance of an exogenous marker – inulin, inulin-like polyfructosans, non-radioactive contrast agents (iohexol or iotalamate) and radioisotopic methods (clearance of radiopharmacies, excreted by glomerular filtration like $^{51}$Cr- EDTA, $^{99m}$Tc-DTPA and $^{125}$I-iotalamate).
2. Clearance of an endogenous marker – creatinine clearance (determined by diuresis, collected for a certain period).
3. Estimated glomerular filtration rate (eGFR) – by serum creatinine-based formulas – Cockroft-Gault

\textbf{Figure 1.} Pathogenesis of Circulatory Abnormalities and Renal Failure in Cirrhosis (Gines P, Schrier R. N Engl J Med, 2009).
formula and MDRD (Modification of Diet in Renal Disease) formula in adults; formulas using cystatin C.

4. Serum markers - creatinine, urea, cystatin C, β2- microglobulin.

New early markers of acute renal injury – serum gelatinase-associated neutrophil lipocalin (sNGAL) and urine markers: gelatinase-associated neutrophil lipocalin (uNGAL), interleukin-18 (IL-18) and kidney injury molecule-1 (KIM-1), require complex methodology and further investigation on their efficacy. In liver cirrhosis, the interpretation of urine osmolarity and sodium, as well as that of fractional sodium excretion, is not informative due to water and sodium retention systems activation, the presence of diuretic treatment or volume replacement therapy in these patients. Proteinuria measurement is also of limited value, because of the hypoproteinemia, typical for liver cirrhosis, besides, the normal quantitative proteinuria does not exclude glomerular alterations.11

Doppler ultrasonography may also be used as an early diagnostic method for renal dysfunction.16 The increased resistive index is related to increased risk of renal function impairment and its determination is included in the diagnostic algorithm for HRS.16

It has been found to be increased in patients with liver cirrhosis in comparison to healthy controls, which may even coexist with normal creatinine levels. Despite that, the resistive index does not correlate with GFR.17 Since main causes of ARF in liver cirrhosis are prerenal failure and HRS, renal biopsy is rarely necessary, while precutaneous biopsy is related to increased risk of hemorrhages.

CLEARANCE OF EXOGENOUS MARKERS

Inulin clearance is considered gold standard in the measurement of GFR, being the sole accurate method of renal function assessment in liver cirrhosis.18 The clearance of synthetic inulin-like substances, radiopharmaceuticals (51Cr- EDTA, 99mTc-DTPA and 125I-iotalamate) or non-radioactive agents is also with good accuracy. Isotope determination of GFR is a reliable method, especially in decreased RF or variations in the muscle mass. It is more practical in comparison with inulin clearance – requires a single application and diuresis measurement is not needed. Inulin clearance and clearance of 51Cr- EDTA are the most accurate methods of GFR assessment, and 99mTc-DTPA clearance is less accurate than the inulin clearance only by 5% and correlates with it in normal and impaired renal function. Gamma scintigraphy with 99mTc-DTPA ensures semiquantitative analysis of both perfusion and filtration phases. 99mTc-DTPA is filtered through the glomerules and is not reabsorbed or excreted in the tubules, but GFR determined by it may overestimate the inulin clearance one. All disadvantages of these methods stem from the facts that they are technically hard to implement, expensive, impractical for repeating investigation of the renal function, imprecise at GFR < 20-30 ml/min and not validated in patients with liver cirrhosis.19

CREATININE

Although routinely used in clinical practice, creatinine (plasma or serum) is just an indirect indicator of glomerular filtration. Creatine is produced in the liver, stored in skeletal muscles, where is phosphorylated to creatinine. The latter is freely filtered through the kidney, but has no constant rate of production, has tubular secretion and is eliminated extrarrenally.20 Its concentrations are affected by some extrarenal factors such as weight, race, age, gender, diet (protein intake), transformation of creatine into creatinine, level of hydration, as well as the overall organism storage of creatine (overall muscle mass). It is highly specific, but less sensitive in regard to the diagnosis of chronic renal diseases and detection of mild GFR decrease. The correlation between glomerular filtration and serum creatinine is hyperbolic – its increase over the upper limit occurs only when GFR declines to 50% of the norm (60-40 ml/min/1.73 m²) – there is the so called „creatinine-blind” zone between 100 and 50 ml/min/1.73 m².

In addition to patient-related factors, some disadvantages of the analytical methods for determination of creatinine concentration are present. The most commonly used method is the kinetic method based on Jaffe’s reaction. Its use may result in false low levels due to possible interference of certain chromogens, such as bilirubin, uric acid, glucose, ketone bodies, piruvate, etc with creatinine measurement. Interlaboratory variations may influence MELD index, which varies significantly, depending on the method used for creatinine measurement, especially if hyperbilirubinemia over 400 μmol/l is present.21 Another important problem is related to the lack of reference standard for creatinine measurement which might contribute to difference reduction.20

Creatinine is an important prognostic parameter in liver cirrhosis (included in MELD index) and is sufficient for HRS diagnosis. Despite that, it is
an inaccurate renal marker and has to be carefully interpreted (similarly to urea). Its concentrations may be normal, even in the presence of moderate to severe impairment of renal function. This leads to „overestimation” of the real GFR, which is more pronounced in moderately decreased GFR and in patients with advanced liver disease, in the presence of hyperbilirubinemia and refractory ascites.\textsuperscript{19,22,23} Additionally, serum creatinine cannot be used to distinguish acute from chronic RF in liver cirrhosis. Causes of false low creatinine levels in cirrhotics are:

1. Impaired liver function, causing decreased creatinine and therefore creatinine production.
2. Protein-poor diet and reduction in muscle mass (frequent in patients with liver cirrhosis) contribute to the reduced production of creatinine. Malnutrition in these cases may be further enhanced due to the hypercatabolic state, related to disease exacerbation.\textsuperscript{19}
3. Serum creatinine increase leads to intensification of its tubular secretion.\textsuperscript{23} Patients with liver cirrhosis and decreased inulin clearance (below 80 ml/min) have significantly higher fractions of creatinine excreted via the tubules in comparison with those with normal RF.\textsuperscript{23} Serum creatinine concentrations are significantly higher in patients with chronic RF, compared to ones in liver cirrhosis with similar inulin clearance.\textsuperscript{24} It is hard to determine whether increased tubular secretion is related to impaired liver function or to RF.
4. Oedematous state, leading to significant redistribution of creatinine in the body and lower serum concentrations. Patients with liver cirrhosis and refractory ascites and/or these on diuretic therapy, have fluctuating levels of serum creatinine. In these cases the values best correlating with disease outcome are questionable.
5. Use of nephrotoxic drugs, such as cephalosporines, influencing tubular secretion of creatinine.
6. In liver cirrhosis, RF may be due to various causes, often combined, rendering serum creatinine even more inaccurate as a renal parameter. ARF is usually developed on the basis of complications like variceal bleeding, spontaneous bacterial peritonitis or sepsis – conditions related to increased tubular creatinine excretion\textsuperscript{19}.

\textbf{CREATININE CLEARANCE}

The creatinine clearance determined on the basis of the amount of diuresis for a certain period of time, is considered better than the serum creatinine. It is also dependent on muscle metabolism, diet, inflammatory diseases and malnutrition and overestimates GFR in proteinuria and renal dysfunction. Non-specific factors such as mistakes in urine collection process (because of hepatic encephalopathy) and in period length, may cause its inaccuracy.\textsuperscript{19} The creatinine clearance „overestimates” true GFR by 40% to 90% on average in patients with liver cirrhosis\textsuperscript{22}, sometimes up to 200%\textsuperscript{19}, the „overestimation” is most significant in patients with GFR at the lower limit\textsuperscript{19}. The creatinine clearance decreases with the progression of the liver disease despite the normal values of the serum creatinine.\textsuperscript{24-26} This may lead to inappropriate classification and/or therapy in 50% of the patients.\textsuperscript{19}

\textbf{SERUM CREATININE BASED FORMULAS}

The most commonly used formulas, based on serum creatinine for determination of GFR in adults, are the Cockcroft-Gault formula and MDRD, which overestimate the true GFR in liver cirrhosis.\textsuperscript{19,23} The Cockcroft-Gault formula is:

\[
eGFR (\text{ml/min}) = (140 - \text{age[ys]}) \times \left(\frac{\text{weight[kg]}}{72 \times \text{serum creatinine [mg/dl]}}\right) \times 0.85 \quad \text{(in women)} / \times 1.22 \quad \text{(in men)}.
\]

It significantly overestimates GFR in patients with liver cirrhosis and reduced RF\textsuperscript{22} – compared to the inulin clearance, its sensitivity is 51%.\textsuperscript{23} A weak point of the formula is that the body weight is hard to determine if there are edemas and/or ascites and malnutrition.

The MDRD formula may be calculated based on 4 or 6 variables, including values of serum creatinine, urea and albumin:

\[
eGFR (\text{ml/min/1.73 m²}) = 170 \times \left[\text{serum creatinine (mg/ dl)}\right]^{0.999} \times \left[\text{age (yrs)}\right]^{-0.176} \times \left[\text{serum urea (mg/ dl)}\right]^{0.170} \times \left[\text{serum albumin (g/ dl)}\right]^{0.318} - 0.762 \quad \text{(in women)} / \times 1.180 \quad \text{(in Afro-Americans)}.
\]

This formula is considered advantageous in liver cirrhosis, due to substitution of weight with albumin and urea, and correlates better with GFR determined by radiomarker clearance.\textsuperscript{29} Nevertheless, the accuracy of the MDRD formula is also limited.\textsuperscript{19} The recently proposed creatinine based formula - CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) is claimed to be more accurate than the two previously discussed formulas, but has not yet been validated in patients with liver cirrhosis.
Generally, these formulas are not precise in the assessment of RF in liver cirrhosis – they do not overcome the disadvantages of creatinine, that is adjusted for several variables, which significantly influence GFR for the overall population (for example age, weight, gender for the Cockcroft-Gault formula; age, gender and race for the simplified MDRD formula). They are imprecise, regardless of the etiology and stage of the liver disease or the renal dysfunction and creation of specific formulas in liver cirrhosis is necessary.

ALTERNATIVE SERUM MARKERS FOR RF ASSESSMENT

In order to find a better marker for the GFR assessment, several low-molecular-weight proteins – cystatin C (CysC), β2-microglobuline; β-trace protein, the serum cystatin C being the marker to which there is much interest (the last 2 parameters are not sufficiently accurate indicators of RF).  

CysC is a 13.3 kDa protein, representative of cystein-protease inhibitors. It is produced by all nucleus-containing cells with constant speed, is freely filtrated through the glomerules, is entirely reabsorbed and catabolized in the proximal tubular cells, does not have tubular secretion and reabsorption back into circulation. Its plasma concentration is a function solely of its synthesis and clearance through the kidneys. Its concentration is stable, easily measured by fast automated immunoturbidimetric (PETIA) and immunonephelometric methods (PENIA). It is not influenced by inflammatory or malignant diseases, age, gender, muscle mass, diet, bilirubine and BMI (body mass index), does not interfere with bilirubine.  

CysC better correlates with GFR compared to creatinine, is more sensitive for the diagnosis of mild decrease of GFR (60-90 ml/min/1.73 m²) and is a better early predictor of creatinine in ARF.  

Its disadvantages compared to creatinine are related to higher test price and need of standardization. Data for the dependence of its levels on advanced age (especially > 50 yrs), male gender, overweight, height, smoking and higher C-reactive protein levels, malignant diseases and some drugs (corticosteroids, ACE-inhibitors) are disputable.

A series of studies demonstrated its superiority to creatinine as an indicator of GFR in liver cirrhosis. CysC is more precise in determination of non-azotemic patients with liver cirrhosis and reduced GFR and is more sensitive to early decrease in GFR, in all patients with liver cirrhosis and ascites, irrespective of HRS risk. In a study on 89 patients with liver cirrhosis and ascites, only the serum CysC correlates well with the GFR scintigraphically determined by 99mTc-DTPA clearance, its values being the only independent predictor of significant kidney injury. It is a good predictor of ARF and the mortality in patients with liver cirrhosis with or without ascites and with normal creatinine levels. CysC is the only independent prognostic factor for HRS.

Formulas based on CysC, like those of Hoek and Larsson, are designed to overcome some of its shortcomings and are more precise for GFR determination in cirrhosis. Their advantage is in GFR determination especially in the presence of high bilirubin levels and posttransplant patients. The disadvantages are related to the fact that original studies in which they were constructed, did not include patients with LC, were validated in relatively small patient groups, used different methods as a gold standard for GFR measurement, in comparison with creatinine formulas and correlate weakly with real GFR in liver cirrhosis.

CONCLUSIONS

Renal dysfunction is common in liver cirrhosis, especially in patients with refractory ascites and influences negatively their survival. Its precise assessment and early diagnosis before and after liver transplantation are of great significance for the therapeutic strategy and prognosis. This is especially important for the liver transplantation candidates, in whom the MELD index determines their priority. Unfortunately, all present methods of RF assessment have some disadvantages and do not correlate well with GFR. The use of serum markers like cystatin C is promising – it could replace creatinine in prognostic formulas for GFR assessment in liver cirrhosis, but additional studies are needed to elucidate its advantages.

REFERENCES


B. Teneva