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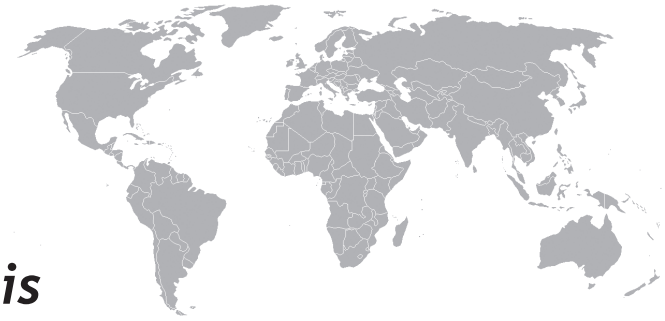

Renal dysfunctions in cirrhosis

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ABSTRACT
Kidney dysfunction is a common and potentially life-threating event in patients with cirrhosis, and underlying mechanisms for renal dysfunction are quite variable. Acute kidney injury (AKI) is relatively frequent encountered in approximately 20% of hospitalized patients with cirrhosis. Nevertheless, chronic kidney disease (CKD) occurs in almost 1% of all patients with cirrhosis. In this review various renal problems encountered in cirrhotic patients are discussed and strategies to prevent renal dysfunction are suggested.
Key Words: Liver Cirrhosis; Acute Kidney Injury; Chronic Kidney Failure.

INTRODUCTION

Physicians involved in the care of patients with cirrhosis recognize that the development of renal dysfunction is associated with significant morbidity and mortality (1). Methods for early and accurate diagnosis of acute renal failure may assist initiate specific treatment at earlier stage and improve the outcome. Despite improved understanding of the precipitants of and physiology underlying AKI in cirrhosis, considerable confusion continues to surround its diagnosis. This review will focus on conventional diagnostic criteria of AKI and on new criteria that have been recently proposed in order to diagnose and assess the severity of AKI. It will also address the pathophysiology, prevention of AKI in patients with cirrhosis.

PATHOGENESIS of KIDNEY DYSFUNCTİON in LIVER CIRRHOSIS

Cirrhosis is progressive liver disease characterized by destruction of hepatocytes and replacement of normal liver tissue with fibrosis (2). Cirrhosis can be considered in two stages, the compensated stage which is a dynamic process characterized by the destruction of normal histologic structure with fibrosis, nodule formation and development of portal hypertension and the decompensated stage following this in which clinical manifestations develop. The progression of portal hypertension is the main factor underlying decompensation. When the critical threshold of 12 mmHg is reached, systemic effects of portal hypertension ensues, affecting several organs and systems (3). Portal hypertension causes increased production of various vasodilator agents such as nitric oxide (NO), carbon monoxide and cannabinoid and their entry into splanchnic circulation. Among these substances NO is particularly paid attention. Nitric oxide and several other endogenious vasodilators cause decrease in effective blood volume and mean arterial blood pressure (4). In order to compensate this hemodynamic changes and to maintain adequate perfusion of vital organs such as brain and kidney, several counterregulatory mechanisms are activated such as increase in cardiac output, activation of sympathetic nervous system and renin-angiotensin-aldosteron cascade and increase in arginine vasopressin (5). These hemodynamic changes constitute hyperdinamic circulatory syndrome. Collateral circulation also contribute to these hemodynamic changes because portocaval collaterals decrease peripheral vascular resistance and also several vasoactive substances derived from intestines gain access into systemic circulation without being metabolized in the liver through these portosystemic shunts (6-7). As cirrhosis progresses these hemodynamic changes worsen and the cardiac output cannot compensate anymore, resulting in effective central hypovolemia. Endogenious vasoconstrictors are activated then, resulting in renal vasoconstriction, sodium and water retention (8). Decrease in renal perfusion causes decrease in glomerular filtration rate and sodium excretion. As expected urinary sodium excretion is usually below 10 mEq/L in patients with advanced cirrhosis. The end result of all these changes is impairment of renal functions. Hyponatremia and activated renin-angiotensin-aldosterone system also contribute to renal dysfunction. Some other risk factors frequently encountered in cirrhotic patients such as variceal bleeding, aggressive therapeutic paracentesis, use of diuretics and nephrotoxic drugs such as aminoglycosides or NSAID, contrast agents, spontaneous bacterial peritonitis and other infections and hypotension may also precipitate renal failure in these patients (9-10).

CLASSIFICATION OF RENAL INJURY IN CIRRHOSIS AND ITS CLINICAL SIGNIFICANCE

Renal dysfunction is associated with increased morbidity and mortality in cirrhotic patients. In a review of 118 studies analyzing factors associated with mortality, parameters of liver dysfunction (Child Pugh score and its components) and renal dysfunction (blood urea nitrogen and serum creatinin) were found to be strong predictors of mortality in decompansated cirrhotic patients (11). Better understanding of renal

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dysfunction types would aid in the management of different treatment strategies.

Diagnosis of Hepatorenal Syndrome (HRS) in Cirrhosis

HRS can be defined as renal dysfunction or insufficiency seen in advanced stages of cirrhosis due to decreased renal cortical blood flow associated with renal vasoconstriction. It is associated with high mortality rates. The major hemodynamic changes in HRS are splanchnic vasodilation associated with portal hypertension, decrease in the effective blood volume and the resultant decrease in renal perfusion. As renal perfusion decreases glomerular filtration rate and sodium (Na) excretion also decrease resulting in renal dysfunction (12). The diagnostic criteria for hepatorenal syndrome proposed by International Ascites Club in 2007 are shown in table 1.

Table 1: *The proposed criteria of International Ascites Club (IAC) for the diagnosis of hepatorenal syndrome (13)*

Cirrhosis with ascites
Serum creatinine >133 mmol/l (1.5 mg/dl)
No improvement in serum creatinine (decrease to a level of ≤133 mmol/l or 1.5 mg/dl) after at least 2 days of diuretic withdrawal and volume expansion with albumin. The recommended dose of albumin is 1 g/kg body weight/day; up to a maximum of 100 g/day
Absence of shock
No current or recent treatment with nephrotoxic drugs
Absence of parenchymal kidney disease as indicated by proteinuria >500 mg/day, microhaematuria (>50 red blood cells/high power field) and/or abnormal renal ultrasonography

There are two types of HRS. Type 1 or acute HRS is characterized by a rapidly progressive reduction of renal function as defined by a doubling of the initial serum creatinine to >220 µmol/l (2.5 mg/dl) or a 50% reduction in the initial 24 h creatinine clearance to <20 ml/min in less than 2 weeks. Type 2 or chronic HRS was defined as moderate renal failure that progressed gradually over weeks to months with serum creatinine concentration of 133–220 µmol/l (1.5–2.5 mg/dl). HRS-1 is usually associated with rapid deterioration of renal functions following a precipitating factor. HRS-2 usually develops slowly in patients with advanced stage cirrhotic patients with refractory ascites (13). Both but particularly HRS-1 is associated with poor prognosis. Alessandria et al reported the median survival for HRS-1 as 1 month and for HRS-2 as 6,7 months (14).

Definition of Acute Kidney Injury in Cirrhosis

Definition and classification of AKI is one of the most challenging subjects in critical care medicine. Clear and strict definitions are needed to understand the epidemiologic characteristics of AKI, to randomize the patients in controlled studies, to evaluate the results of various diagnostic tests and also to analyze the outcomes of different treatment strategies in studies conducted with special patient groups.

Diagnosis and classification of AKI in cirrhotic patients is of particular importance considering its strong association with morbidity and mortality. But it is also difficult to define and diagnose AKI in this particular patient group. One of the widely used criteria to diagnose AKI in cirrhotic patients is conventional criteria according to which serum creatinine value greater than 1,5 mg/dl is diagnostic for AKI. But serum creatinine and calculated glomerular filtration rate do not reflect renal functions accurately in these patients. Several factors contribute to this such as decreased creatinine production due to decreased hepatic synthesis of creatinine, decreased skeletal muscle mass and increased tubular secretion of creatinine in cirrhotic patients. Calculated creatinine clearance may also overestimate the real glomerular filtration rate due to stated reasons (15).

In order to meet the needs concerning early diagnosis of AKI and classification of AKI according to the severity of renal dysfunction, Acute Dialysis Quality Initiative (ADQI) Working group proposed the RIFLE Criteria in 2004 (16) (Table 2). RIFLE criteria are shown to predict in-hospital mortality in cirrhotic patients in several studies (17-18).

Table 2: *RIFLE Criteria (Within 7 days) (16)*

Category	Glomerular Filtration Rate (GFR)criteria	Urine Output (UO) criteria
R - Renal risk	Increased creatinine X 1.5 or	UO<0.5 ml/kg/hr X 6 h
	GFR decrease>25%	
I - Injury	Increased creatinine X 2 or GFR decrease >50%	UO<0.5 ml/kg/hr X 12 h
F - Failure	Increased creatinine X 3 or GFR decrease >75% or creatinine ≥4 mg/dl (acute rise of ≥0.5 mg/dl)	UO<0.3 ml/kg/hr (oliguria) X 24 h or anuria X 12h
L - Loss of kidney function	Persistant acute renal failure =complete loss of renal functions >4 weeks	
E - End stage renal disease	End stage renal disease (>3 months)	

But studies also showed that there are still some issues concerning RIFLE criteria. Mortality rates were shown to be increased even in risk stage (R stage). So Acute Kidney Injury Network (AKIN) modified the RIFLE criteria and the new criteria (AKIN criteria) were published in 2007. In AKIN criteria, the threshold of increase in serum creatinine was lowered, the GFR criteria were omitted and the time interval was shortened to 48 hours (Table 3). The urinary output criteria were kept the same. According to AKIN criteria AKI was classified in 3 stages; stage 1,2 and 3 corresponding to RIFLE stage R, I and F respectively. RIFLE stages L and E were omitted (19).

Table 3: *The Acute Kidney Injury Network (AKIN criteria) for the definition and classification of acute kidney ınjury (19)*

Stage	Serum creatinine criteria	Urine output criteria
1	Increased creatinine X 1.5 or≥0.3 mg/dL (within 48 h)	UO<0.5 ml/kg/hr X 6 h
2	Increased creatinine X 2-3	UO<0.5 ml/kg/hr X12 h
3	Increased creatinine X 3 or Serum creatinine>4mg/dl (with acute rise of ≥0.5 mg/dl) or renal replacement therapy	UO<0.3 ml/kg/hr (oliguria) X 24 h or anuria X 12 h

AKIN criteria had been validated both in hospitalized cirrhotic patients and in cirrhotic patients admitted to the intensive care unit (ICU) (20), in several prospective studies (21-23). In these studies AKI defined by AKIN criteria was found to be an independent predictor of mortality. The progression to higher AKI stages were also shown to be related to increased mortality. In the study conducted by Piano et al.(21) where they analyzed AKIN criteria to predict in-hospital mortality, the authors concluded that conventional criterion is more accurate than AKIN criteria in the prediction of mortality in patients with cirrhosis and ascites. The addition of either the progression of AKIN stage or the cut-off of sCr ≥ 1.5mg/dl to the AKIN criteria improved their prognostic accuracy.

In cirrhotic patients, renal dysfunction is mostly functional. Hemodynamic changes, cardiac dysfunction and the changes in

renal autoregulatory mechanisms contribute to renal failure. But in minority of the patients renal structural changes may also accompany. So in 2011 renal dysfunction classification system was proposed in cirrhotic patients by Acute Dialysis Quality Initiative (ADQI) and International Ascites Club (IAC) Working Group (24). The classification system covered both structural and functional diseases of kidneys. Three classes of renal injury were defined; AKI, chronic renal disease and acute on chronic kidney disease. One of the important aspects of this new classification to worth mention was that patients with acute renal failure that does not fulfill type 1 HRS or patients with chronic renal failure that does not fulfill type 2 HRS criteria were also covered. Oliguria criterion was not included in this classification because cirrhotic patients with refractory ascites can be oliguric even in the absence of AKI. The ADQI-IAC classification is summarized in table 4.Using ADQI-IAC criteria renal dysfunction prevalence in cirrhotic patients were reported to be 12,9% for AKI, 3,4% for CKD and 0,5% for AKI on CKD (25).

Table 4: *Proposed diagnostic criteria of kidney dysfunction in cirrhosis (24)*

Diagnosis	Definition
Acute kidney injury	Rise in serum creatinine of ≥50% from baseline or a rise of serum creatinine by ≥26.4 µmol/l (≥0.3 mg/dl) in <48 h HRS type 1 is a specific form of acute kidney injury
Chronic kidney disease	Glomerular filtration rate of <60 ml/min for >3 months calculated using MDRD6 formula HRS type 2 is a specific form of chronic kidney disease
Acute-on-chronic kidney disease	Rise in serum creatinine of ≥50% from baseline or a rise of serum creatinine by ≥26.4 µmol/l (≥0.3 mg/dl) in <48 h in a patient with cirrhosis whose glomerular filtration rate is <60 ml/min for >3 months calculated using MDRD6 formula

Both the acute deterioration in renal function and the background chronic renal dysfunction can be functional or structural in nature. HRS, hepatorenal syndrome; MDRD6, Modification of Diet in Renal Disease formula calculated using six variables of serum creatinine, age, gender, albumin, blood urea nitrogen and whether or not the patient is African-American.

The Kidney Disease Improving Global Outcomes (KDIGO) criteria were published in 2012 (26). The main difference between these new criteria over the conventional criteria in patients with cirrhosis are the following:(1) an absolute increase in sCr in considered; (2) the threshold of sCr ≥1.5 mg/dl is abandoned; and (3) a staging system of AKI, based on a change in sCr over a slightly longer time frame, arbitrarily set at 1 week to enable assessment for progression of stage (Table 5).

Table 5: *International Club of ascites (ICA-AKI) new definitions for the diagnosis and management of AKI in patients with cirrhosis (27)*

Definition of AKI	Increase in sCr≥0.3mg/dl within 48 hours A percentage increase sCr≥50% from baseline which is known, or presumed, to have occured within the prior 7 days
Staging of AKI	Stage 1: increase in sCr ≥ 0.3 mg/d Lor an increase in SCr≥1.5 fold to 2-fold from baseline Stage 2: increase in sCr>2-fold to 3 -fold from baseline Stage 3: increase in sCr>3-fold from baseline or sCr≥4 mg /dlwith an acute increase≥0.3 mg/d lor initiation of RRT
Baseline sCr	A value of sCr obtained in the previous 3 months, when available, can be used as baseline sCr.In patients with more than one value within the previous 3 months, the value closest to the admission time to the hospital should be used.In patients without a previous sCr value, the sCr on admission should be used as baseline.
Progression of AKI	Progression of AKI to a higher stage and/or need for renal replacement therapy
Regression of AKI	AKI Regression of AKI to a lower stage
No response	No regression of AKI
Partial response	Regression of AKI stage with a reduction of sCr to ≥ 0.3 mg/dL above the baseline value
Full response	Return of sCr to a value within 0.3 mg/dL of the baseline value

AKI, acute kidney injury; RRT, renal replacement therapy; sCr, serum creatinine

The new ICA-AKI criteria (27) give a new approach to the definition and staging of AKI, of the definition of AKI progression and response to treatment (Table 6). The major change was the exclusion of urine output as a parameter. Urine output in patients with cirrhosis and ascites is often an unreliable indicator because the GFR may be preserved in spite of the continuous sodium retention and oliguria and many patients are under diuretic therapy. This requirement is a major disadvantage of RIFLE, AKIN and KDIGO criteria.

Definition of Chronic Kidney Disease in Cirrhotic Patients

The definition of chronic kidney disease according to ADQI-IAC criteria is glomerular filtration rate of <60 ml/min for >3 months calculated using MDRD6 formula (24). Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group defined CKD is defined as abnormalities of kidney structure or function, present for >3 months, with implications for health (28).

In a prospective study using ADQI-IAC criteria, chronic kidney disease was investigated in cirrhotic patients with stable serum creatinine values for at least 3 months. Chronic kidney disease was diagnosed in 23,5% and HRS-2 in 8,3% of the patients. In this study 15,2% of the patients were diagnosed to have chronic kidney disease even they did not fulfill HRS diagnostic criteria (non-HRS CKD). The overall mortality rates were 52,2% for the patient with HRS and 33,3% for non-HRS CKD for a median follow up period of 9,8 months indicating that short term mortality rate was also high for non-HRS CKD patients (29).

The reported prevalence of chronic renal disease in cirrhotic patients is 1% (30). HRS-2 is the most common chronic renal disease seen in patients with advanced cirrhosis (31). Several other renal diseases are prevalent among patients with chronic liver diseases of various etiologies. Glomerulopathies can be seen in patients with hepatitis C. The most frequent glomerulonephritis encountered in hepatitis C patients is membranoproliferative glomerulonephritis which is associated with type 2 cryoglobulinemia. Membranous nephropathy, focal segmental fibrillary glomerulonephritis, immunotactoid glomerulopathy, immunoglobulin A nephropathy and renal thrombotic microangiopathy constitute other glomerular diseases that can be seen in hepatitis C patients (32). On the other hand chronic hepatitis B infection is associated with proteinuria. Membranous nephropathy is frequently encountered in renal biopsies. Spontaneous or on treatment viral clearance results in resolution of proteinuria (33). IgA nephropathy is prevalent among patients with alcoholic cirrhosis Considering the association of type 2 diabetes mellitus with hepatitis C, diabetic nephropathy is also one of the most important causes of chronic kidney disease in patients with chronic hepatitis C (34). Considering the impact of chronic kidney disease on the prognosis of patients with cirrhosis, patients with findings implicating renal impairment such as hematuria, proteinuria or hypertension should be prompted for further investigations

Acute on Chronic Kidney Disease in Cirrhosis

When renal dysfunction is classified according to ADQI-IAC criteria, AKI on CKD patients were found to be associated

with highest mortality rates. Therefore early diagnosis of AKI in patients with preexisting chronic renal dysfunction is of particular importance in cirrhotic population. Choi et al reported mortality rate as high as 66.7% in these patients. Mortality rates for patients with AKI and chronic kidney disease were 22.1% and 17.4% respectively in the same study (25). The reason of AKI in these patients can be structural or functional (24). Diagnosis of type-1 HRS in diabetic cirrhotic patients can also be challenging. ADQI-IAC classification may simplify the correct diagnosis in this particular clinical setting as well.

Differential Diagnosis

The identification of factors associated with AKI is sometimes difficult in cirrhotic patients because the same factors can trigger HRS, acute tubuler necrosis (ATN) or prerenal azotemia. International Ascites Club proposed a simple algorithm to overcome this problem. In the presence of dehydration, excessive diuretic usage or bacterial infections and if examination of the urine sediment is normal, proteinuria is less than 0,5 g/day and renal ultrasound examination is unremarkable, diuretic medications should be discontinued, albumin replacement therapy should be initiated to provide expansion of plasma volume. Renal functions will improve in patients with prerenal azotemia but not in in HRS patients. On the other hand, history of recent exposure to nephrotoxic drugs or contrast agents, the presence of granular and epithelial casts in the urine sediment or proteinuria >0,5 g/day favors the diagnosis of ATN (35). Urinary Na concentration is usually larger than 40 mEq/L and the fractional excretion of Na and urine osmolarity are also high in patients with ATN (36). Belcher et al studied several renal biomarkers for the differential diagnosis of prerenal azotemia, HRS and ATN in cirrhotic patients. Serum concentrations of neutrophil gelatinase-associated lipocalin (NGAL), interleukin -18 (IL-18), kidney injury molecule-1 (KIM-1), liver-type fatty acid binding protein (L-FABP) were found to be significantly higher in patients with ATN. The increases in the serum concentrations of these markers were specific for structural kidney damage and may aid in the differential diagnosis from other clinic conditions associated with functional renal impairment (37).

Pre-HRS is a new definition introduced recently and it is gaining popularity. It describes the very early phases of renal dysfunction in patients with possible progression to HRS where renal plasma flow is decreased but GFR is still normal, or low/normal. This stage of very early renal impairment is of clinical important because if appropriate measures are taken progression to HRS can be prevented with resultant improvement in mortality. Aggressive usage of diuretics, therapeutic large volume paracentesis, use of nephrotoxic drugs and angiotensin converting enzyme inhibitors should be avoided at this stage and other precipitating factors such as SBP and other infections should be treated vigorously. The diagnosis of pre-HRS is quite difficult because methods to measure renal plasma flow are expensive and they are not easily applicable in routine daily practice. Development of more practical and less expensive methods to measure renal plasma flow would aid early diagnosis of patients at this preventable stage (38).

PRECAUTIONS TO PREVENT RENAL INJURY IN CIRRHOTIC PATIENTS

Spontaneous Bacterial Peritonitis (SBP):

SBP is defined as the presence of > 250 neutrophyles per mm3 of ascitic fluid. The annual incidence of SBP in cirrhotic patients is approximately 10% (39). The increase in intraabdominal pressure in patient with SBP may cause compartment syndrome increasing the risk of development of acute kidney injury (40). Follo et al reported AKI prevalence as 33% in a study of 197 patients with 252 hospitalizations due to SBP (41). AKI is one of the most important factors related to prognosis in patients with SBP (42-43). SBP should be investigated in all cirrhotic patients with ascites presenting with fever, abdominal pain, hepatic encephalopathy and AKI and early empiric antibiotic therapy should be instituted if SBP is present without waiting for the results of the ascites and blood cultures. Nephrotoxic drugs such as aminoglycosides should be avoided in patients with SBP as well (44-45). Long term prophylactic antibiotic therapy is advised in patients with ascitic albumin concentration below 15 g/L to prevent recurrences (46).

Infections other than SBP:

Since immune system is compromised in cirrhosis bacterial infections are common and they are responsible up to 30% of total mortality and morbidity in cirrhotic patients (47). Urinary infections, pneumonia and soft tissue infections are the most common infections following SBP (48). Bacterial infections aggravate splanchnic arterial vasodilation and they compromise liver functions via endotoxemia and various cytokines triggering AKI (31). Therefore prophylactic antibiotic therapy is advised in cirrhotic patients before various surgical procedures or in patients with gastrointestinal bleeding to prevent infections (49). Vaccination against hepatitis A and B viruses, pneumococci and Haemophilus influenzae are also advisable (50).

Variceal bleeding:

Gastroesophageal varices are seen up to 50% in patients with cirrhosis and the annual incidence of variceal bleeding in these patients is 15-20% (51). The prevalence of AKI in cirrhotic patients with variceal bleeding is reported to be 11% (52). The use of vasoactive agents such as terlipressin together with appropriate volume repletion, endoscopic treatment of bleeding varices and the use of prophylactic antibiotic therapy significantly decrease renal dysfunction and mortality rates in these patients (53).

Paracentesis:

Ascites is one of the most common complications of cirrhosis and it is associated with bad prognosis (11, 54). Large volume paracentesis is widely used for the treatment of grade 3 or refractory ascites in cirrhotic patients (55). Increased mortality rate and renal dysfunction had been reported after large volume paracentesis and were thought to be associated with the decrease of effective arterial volume (56). Since albumin replacement therapy decreases such complications, 8 g of albumin replacement is advised for each liter of fluid above 5 liters when large volume paracentesis is performed (57).

Diuretics:

Diuretic drugs particularly spironolactone and furosemide are also frequently prescribed to cirrhotic patients for the treatment of ascites. The regulation of diuretic dose in these patients is done primarily by following body weight. The aimed weight loss with diuretic therapy in these patients is 1 kg/day if peripheral edema is present and 0,5 kg/day if edema is absent. Diuretic drugs should be discontinued when serum creatinine rises above 2 mg/dL.

Drugs with potential nephrotoxicity such as non-steroidal anti-inflammatory drugs or angiotensin converting enzyme inhibitors should be avoided in these patients and contrast agents should be used with extreme caution as well (57).

CONCLUSION

Renal dysfunction is common in cirrhotic patients. It may be in a form of AKI or chronic renal failure. Knowledge of the exact nature of renal disease is important for appropriate planning of the therapeutic approach. Some factors can trigger renal dysfunction. With careful management of the risk factors, HRS development can be prevented in selected patients. Even small changes in serum creatinine are very important in cirrhotic patients. So several different criteria are suggested for early detection and appropriate classification of AKI in cirrhotic patients. Early diagnosis and proper management of renal dysfunction in vulnerable patient groups will contribute to the reduction of mortality and morbidity.

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