EDITOR'S CHOICE

Working Party proposal for a revised classification system of renal dysfunction in patients with cirrhosis

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ABSTRACT

Objectives To propose an improvement on the current classification of renal dysfunction in cirrhosis. Clinicians caring for patients with cirrhosis recognize that the development of renal dysfunction is associated with significant morbidity and mortality. While most cases of renal dysfunction in cirrhosis are functional in nature, developed as a result of changes in haemodynamics, cardiac function, and renal auto-regulation, there is an increasing number of patients with cirrhosis and structural changes in their kidney as a cause of renal dysfunction. Therefore, there is a need for a newer classification to include both functional and structural renal diseases.
Design A working party consisting of specialists from multiple disciplines conducted literature search and developed summary statements, incorporating the renal dysfunction classification used in nephrology. These were discussed and revised to produce this proposal.
Setting Multi-disciplinary international meeting.
Patients None.
Interventions Literature search using keywords of cirrhosis, renal dysfunction, acute kidney injury (AKI), chronic kidney injury (CKD), and hepatorenal syndrome.
Results Acute kidney injury will include all causes of acute deterioration of renal function as indicated by an increase in serum creatinine of >50% from baseline, or a rise in serum creatinine of ≥26.4mol/L (≥0.3mg/dL) in <48hours. Chronic renal disease will be defined as an estimated glomerular filtration rate (GFR) of <60ml/min calculated using the Modification of Diet in Renal Disease 6 (MDRD6) formula, recognising that the MDRD6 formula is not perfect for the cirrhotic patients and this may change as improved means of estimating GFR becomes available. Acute on chronic kidney disease will be defined as AKI superimposed on existing chronic renal disease using the above definitions for AKI and CKD.
Conclusions Accepting this new classification will allow studies into the epidemiology, incidence, prevalence, natural history and the development of new treatments for these subtypes of renal dysfunction in cirrhosis.

Significance of this study

What is already known about this subject?

- Hepatorenal syndrome is a severe complication of advanced cirrhosis with a poor prognosis if left untreated.
- The diagnosis of hepatorenal syndrome requires the patient fulfilling a set of diagnostic criteria.
- Once a diagnosis of hepatorenal syndrome is made, treatments are available and these are effective in up to 40% of patients.

What are the new findings?

- A proposal to broaden the diagnosis of renal dysfunction in cirrhosis to include cases of acute and chronic renal failure not meeting the diagnostic criteria of hepatorenal syndrome types 1 and 2, respectively.
- Acute kidney injury will include all causes of acute deterioration of renal function as indicated by an increase in serum creatinine of >50% from baseline or a rise in serum creatinine of ≥26.4 μmol/l (≥0.3 mg/dl) in <48 h.
- Chronic renal disease will be defined as an estimated glomerular filtration rate of <60 ml/min for more than 3 months calculated using the Modification of Diet in Renal Disease 6 formula.
- Acute on chronic kidney disease will be defined as an acute kidney injury superimposed on existing chronic renal disease using the above definitions for acute kidney injury and chronic kidney disease.

How might it impact on clinical practice in the foreseeable future?

- The recognition of cases of renal dysfunction outside the traditional definition of hepatorenal syndrome will allow patients with lesser degrees of renal dysfunction to receive treatment.
- The acceptance of these broadened definitions of renal dysfunction in cirrhosis will help to design studies to assess the pathophysiology, and thence to devise treatment strategies for these patients.
- A better classification system may also secure more correct diagnoses leading to earlier and better treatment.
- This potentially could have a positive impact on patient outcome, as patients will be treated earlier in the natural history of renal dysfunction.

Acute kidney injury (AKI) is common in patients with cirrhosis and ascites, occurring in up to 19% of cirrhotic patients admitted to hospital. In addition, chronic kidney disease (CKD) occurs in approximately 1% of all patients with cirrhosis.[1]

The combination of liver disease and renal dysfunction can occur as a result of systemic conditions that affect both the liver and the kidney simultaneously. However, renal dysfunction complicating primary disorders of the liver are much more common. These may include structural

renal diseases such as IgA nephropathy, membranous nephropathy and cryoglobulinaemia, or renal dysfunction without significant histopathological changes such as hepatorenal syndrome (HRS). These episodes of renal dysfunction may occur acutely and are associated with significant morbidity and mortality. With improved understanding of renal complications in cirrhosis and the advent of treatment options, there is now a greater need to diagnose renal dysfunction in cirrhosis accurately.

The Acute Dialysis Quality Initiative (ADQI) is an ongoing process that seeks to produce evidence-based recommendations for the prevention and management of AKI.[2] As AKI has not been formally defined in patients with cirrhosis, members of the ADQI and the International Ascites Club (IAC) formed a Working Group in March 2010 to discuss the definition of renal dysfunction (both acute and chronic) in patients with cirrhosis. Members of the Working Group included specialists who are experts in the pathophysiology and management of renal dysfunction in cirrhosis and were selected from the membership of the ADQI and IAC. They conducted a literature search and developed summary statements which were discussed and revised at the meeting. The participants of the joint ADQI–IAC meeting are shown in appendix 1. The final summary statements and directions for future research are the basis for this paper.

HISTORICAL PERSPECTIVE

The clinical entity we now know as HRS was originally described by Flint in 1963.[3] In 1959, Papper *et al* reported intense renal vasoconstriction in an otherwise normal kidney in such patients, paving the way for the understanding of the pathogenesis of HRS.[4] Epstein *et al* later confirmed renal vasoconstriction using renal angiography in a patient with cirrhosis dying from renal failure and demonstrated post-mortem filling of all renal vessels to the periphery of the cortex, thus establishing the 'functional nature' of HRS.[5]

Rodes *et al* next identified three different outcome patterns in cirrhotic patients with renal dysfunction[6]: (1) a rapidly progressive course with a history of a complication closely related to the onset of renal failure (this group was later classified as type 1 HRS); (2) patients with stable renal dysfunction during hospitalisation but no obvious cause for renal failure (type 2 HRS); and (3) patients with an initial similar course as those in group 2 until some complication occurred that hastened the course of renal failure. The outcome was worst for patients in the first group and best for patients in the second group.

DEFINITION OF HEPATORENAL SYNDROME

In 1979, a group of international investigators defined HRS as a progressive form of renal dysfunction that occurred in cirrhosis and other severe parenchymal liver diseases,[7] with features of prerenal renal failure (low urine sodium concentration and hyperosmolar urine) but without any improvement following volume expansion. However, they recognised that some cases do progress to acute tubular necrosis. Despite setting guidelines, there continued to be confusion over what truly constituted HRS. This led to an editorial in the *Lancet*[8] suggesting the term 'hepatic nephropathy' to distinguish functional renal failure from any combination of renal failure occurring with liver failure, such as paracetamol overdose causing combined liver and renal failure.

In 1996, the IAC defined HRS as a syndrome that occurs in patients with cirrhosis, portal hypertension and advanced liver failure, characterised by impaired renal function with marked abnormalities in the arterial circulation and activity of endogenous vasoactive systems.[9] Clinically, HRS was divided into two types: type 1 or acute HRS was characterised 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 <2 weeks; type 2 or chronic HRS was defined as moderate renal failure that progressed gradually over weeks to months with a serum creatinine of 133–220 μmol/l (1.5–2.5 mg/dl).

The IAC updated the definition and diagnostic criteria for HRS in 2005 (box 1).[10] This came about because of an improved understanding of the pathophysiology of HRS, the recognition that it frequently follows bacterial infections (especially spontaneous bacterial peritonitis), the development of effective treatments and improved survival for patients with HRS, especially type 1. HRS is therefore no longer necessarily a fatal condition without liver transplantation.

PATHOPHYSIOLOGY OF HEPATORENAL SYNDROME

The following is a summary of the current understanding of the pathophysiology of HRS (figure 1).

Portal hypertension as the initiator of haemodynamic changes

The development of cirrhosis is associated with distortion, compression and even obliteration of the liver vasculature. In addition, there is decreased intrahepatic production of vasodilators and activated hypercontractile stellate cells.[11] This overall increased resistance to portal inflow—or portal hypertension[12]—will increase the shear stress on the splanchnic vessel walls leading to increased production of various vasodilators such as nitric oxide, causing splanchnic vasodilation.[13] Several other factors including increased bacterial translocation, increased mesenteric angiogenesis and hyporesponsiveness of the splanchnic vessels to vasoconstrictors also contribute to the splanchnic vasodilation.[14] The end result is a pooling of blood in the splanchnic vascular bed, akin to a splanchnic steal syndrome.[15] The shunting of blood and excess vasodilators from the splanchnic to the systemic circulation following the opening of portal-systemic shunts related to increased portal pressure also leads to systemic arterial vasodilation.[16] The combined effect causes a relative inadequacy of the systemic circulation, the so-called 'reduction in the effective arterial blood volume', thereby triggering a hyperdynamic circulation in these patients.[17 18]

Independent of these haemodynamic changes, portal hypertension per se can lead to renal vasoconstriction via increased

Box 1 International Ascites Club (IAC) proposed diagnostic criteria for hepatorenal syndrome[10]

- Cirrhosis with ascites
- Serum creatinine >133 μmol/l (1.5 mg/dl)
- No improvement in serum creatinine (decrease to a level of ≤133 μmol/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

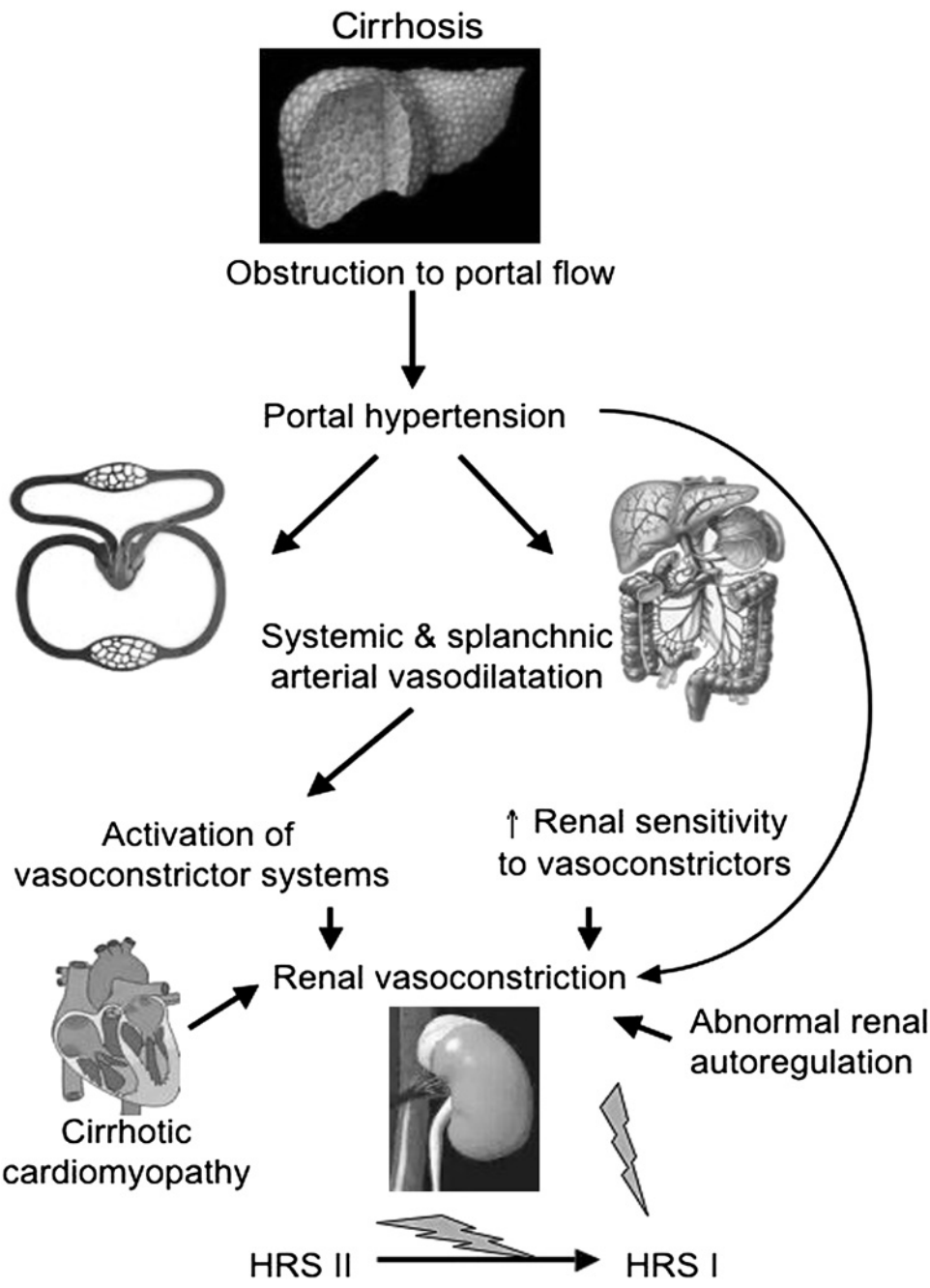

Figure 1 Pathophysiology of hepatorenal syndrome: \ acute precipitating event. HRS, hepatorenal syndrome.

sympathetic nervous activity. For example, the elimination of portal hypertension with the insertion of a transjugular intrahepatic portosystemic shunt (TIPS) is able to improve renal blood flow[19] associated with a reduction in sympathetic nervous activity.[20] The infusion of glutamine which increases hepatic sinusoidal pressure, mimicking portal hypertension, reduces the glomerular filtration rate (GFR).[21] Finally, lumbar sympathetic blockade in patients with HRS increases renal blood flow, suggesting that the renal sympathetic activity is implicated in the efferent arm of this hepatorenal reflex.[22]

Excess renal vasoconstriction

A reduced effective arterial blood volume results in the compensatory activation of various vasoconstrictor systems. In response, renal blood flow decreases with consequent reduction in GFR. Normally, the kidneys maintain blood flow by increasing production of renal vasodilators such as prostaglandins and kallikrein. However, in patients with cirrhosis there is an overall reduction in renal vasodilator production,[15 23] thereby favouring renal vasoconstriction.[24] This renal hypoperfusion further increases the production of various intrarenal vasoconstrictors including angiotensin II and endothelin, causing further deterioration of renal haemodynamics and renal function, occasionally with glomerular ischaemia and mesangial constriction.[25]

Abnormal renal autoregulation

Renal autoregulation is the process whereby regulatory mechanisms ensure that the kidneys receive a relatively constant blood supply regardless of fluctuations in blood pressure. Below a critical threshold of 65 mm Hg, renal blood flow decreases in proportion to renal perfusion pressure which, in turn, is dependent on mean arterial pressure. In cirrhosis, there is a progressive rightward shift of the renal autoregulation curve as liver disease progresses—that is, for every given renal perfusion

pressure, there is a gradual reduction of renal blood flow as liver disease advances.[26] The patient with cirrhosis is therefore poised to develop renal failure simply because of the presence of advanced cirrhosis.

Abnormal cardiocirculatory function

The high cardiac output state of the hyperdynamic circulation in decompensated cirrhosis means that there is limited cardiac reserve in these patients, and further reductions in systemic vascular resistance cannot be met with further increases in cardiac output. Failure to maintain blood pressure further compromises renal perfusion. In cirrhotic patients with ascites and spontaneous bacterial peritonitis, and therefore further arterial vasodilation as a result of the infection, those who went on to develop HRS at infection resolution had significantly lower cardiac output compared with baseline and also compared with those who did not develop HRS. A relative inability to increase cardiac output during stress, a condition known as cirrhotic cardiomyopathy,[27 28] may therefore be a risk factor for the development of HRS.[29] Indeed, a relative low cardiac output and high plasma renin activity were significant predictors for the development of HRS in cirrhosis with ascites.[30] The fact that blockage of a TIPS shunt with an angioplasty balloon instantly reduces renal blood flow, which reverses upon deflation of the balloon, confirms that a reduction or increase in venous return and hence cardiac output has a direct bearing on renal haemodynamics.[31] Recently, the relationship between cardiac systolic dysfunction and the risk of developing renal dysfunction in cirrhosis was also confirmed, as well as the negative impact of cardiac dysfunction on patient survival.[32]

All the above factors contribute to the gradual deterioration in renal function as cirrhosis advances. Any event that causes an abrupt deterioration in haemodynamics can lead to a rapid decline in renal function, precipitating type 1 HRS (figure 1).

CURRENT DIAGNOSTIC CRITERIA FOR HEPATORENAL SYNDROME: ADVANTAGES AND DISADVANTAGES

The most recent diagnostic criteria for HRS clearly delineated which patients should be regarded as having HRS and therefore receive specific treatment. However, the rigid cut-off value of a serum creatinine level of 133 μmol/l (1.5 mg/dl) may limit treatment to patients with the most severe degree of renal dysfunction. The changes that predispose to the development of HRS are not an 'all-or-none' phenomenon, but rather evolve progressively with the natural history of cirrhosis (figure 2). It is unclear whether patients who have milder degrees of renal dysfunction will also experience adverse outcomes. If so, they should also be offered treatment early rather than waiting until the diagnostic criteria of HRS are reached. Additionally, serum creatinine is notoriously inaccurate in the diagnosis of renal dysfunction in cirrhosis.[33] Although serum creatinine reflects renal function in patients with compensated cirrhosis fairly accurately, patients with decompensated cirrhosis often have low serum creatinine levels relative to their GFR owing to reduced production of creatinine from creatine in the liver and significant muscle wasting.[34] Thus, serum creatinine in patients with decompensated cirrhosis can still be within the normal range despite significant renal dysfunction.[35]

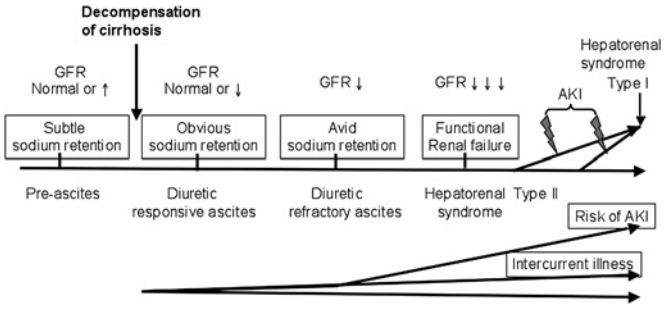

Figure 2 Natural history of cirrhosis: ↯ acute precipitating event. AKI, acute kidney injury; GFR, glomerular filtration rate.

The use of creatinine clearance in cirrhosis to assess renal function is also unreliable because of the falsely low serum creatinine in these patients coupled with a relatively increased renal tubular creatinine secretion compared with filtered creatinine. Furthermore, it requires a 24-h urine collection which is often incomplete. Formulae such as the Cockcroft–Gault and Modification of Diet in Renal Disease (MDRD)—which are based on serum creatinine concentrations—will also overestimate the GFR in cirrhosis.[36 37] Clearance techniques using exogenous markers such as inulin or iothalamate provide a more accurate measurement of GFR but are labour-intensive and expensive.[38] The use of a one-sample ^{51}Cr-EDTA clearance technique is much simpler. However, this method tends to overestimate true renal function in patients with both volume overload and ascites due to redistribution of tracer into the ascitic and interstitial fluid. These problems in the estimation of GFR are compounded by correcting for body surface area.[39]

Other biological markers such as cystatin C[40] and neutrophil gelatinase associated lipocalin (NGAL),[41] although promising, have not been validated in patients with advanced liver disease. Therefore, until better measurements of GFR can be found and validated, serum creatinine measurement remains the most widely used method for estimating renal function in clinical practice in patients with cirrhosis.[42]

Recognising the inadequacy of serum creatinine as an index of renal function in cirrhosis, patients with milder degrees of renal dysfunction may not be diagnosed until advanced renal failure sets in. The ADQI–IAC Working Group therefore proposes the following definitions for the diagnosis of renal dysfunction in cirrhosis in order to help identify patients with milder renal dysfunction for possible treatment. Since no studies have been performed in cirrhosis using these proposed definitions, they can best be regarded as expert opinions or level D evidence, but they represent an important first step in the process of standardising nomenclature and definitions in patients with cirrhosis and renal dysfunction. It is planned that this empirical proposed classification will be validated in prospective trials.

DEFINITION OF ACUTE KIDNEY INJURY IN CIRRHOSIS

In 2004 the ADQI Working Group developed a consensus definition and classification for AKI known as the RIFLE criteria (R: renal risk, I: injury, F: failure, L: loss of kidney function, E: end-stage renal disease) which stratified acute renal dysfunction into grades of increasing severity based on changes in serum creatinine and/or urine output (figure 3).[43] To date, the RIFLE criteria have been validated in over 500 000 patients with AKI[44 45] and have been shown to predict clinical outcomes with a progressive increase in mortality with worsening RIFLE class.[46] The Acute Kidney Injury Network (AKIN), an independent collaborative network consisting of experts from ADQI and several nephrology and intensive care medicine societies, broadened the definition of AKI to include an absolute increase in serum creatinine of ≥26 μmol/l (≥0.3 mg/dl) when documented to occur within 48 h,[47] since smaller increases in serum creatinine than those considered in the RIFLE classification have been

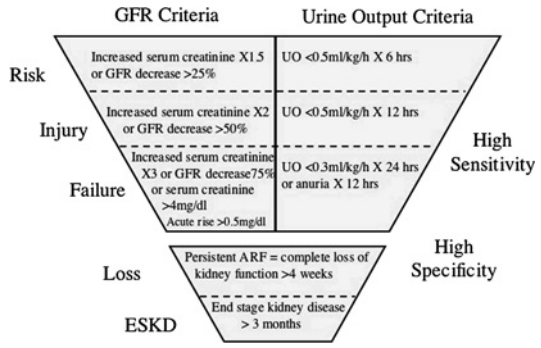

Figure 3 The RIFLE (R: renal risk, I: injury, F: failure, L: loss of kidney function, E: end-stage renal disease) diagnostic criteria.[43] ARF, acute renal failure; GFR, glomerular filtration rate; UO, urine output.

shown to be associated with an adverse outcome.[48] Once established, a staging system then defines the severity of the AKI (table 1).

The spectrum of kidney disease in cirrhosis includes acute and chronic conditions. Nephrologists distinguish acute and chronic renal disease by an artificial timeline of 3 months. Using the RIFLE/AKIN criteria for AKI, only a few patients with cirrhosis and acute kidney dysfunction will meet the criteria for type 1 HRS and therefore the remainder will have to be regarded as having AKI, be it structural or functional. Similarly, some patients with cirrhosis will have CKD such as diabetic nephropathy or mild renal dysfunction not reaching a serum creatinine of 133 μmol/l (1.5 mg/dl), and therefore not meeting the criteria for a diagnosis of type 2 HRS. HRS therefore only describes a portion of cirrhotic patients with renal dysfunction. The ADQI–IAC proposed that the term 'hepatorenal disorders' (HRD) be used to describe all concurrent kidney dysfunction in patients with advanced liver disease—whether functional or structural in nature—which fulfils the diagnostic criteria of AKI or CKD or HRS (figure 4). Such a definition is not meant to replace the current definition of HRS, but rather to be inclusive of all patients with renal dysfunction so that a proper classification of renal dysfunction and appropriate studies can be conducted to define their prognosis and to devise treatment options.

Using the creatinine criteria for AKI in patients with cirrhosis will certainly identify many patients with acute renal dysfunction and normal serum creatinine but low GFR. The urine output criteria for AKI may not be applicable in cirrhosis since patients with refractory ascites may maintain a urine output of <0.5 ml/kg/h even in the absence of AKI. The final consensus proposal of the Working Party was to accept the definition of AKI in cirrhosis as an increase in serum creatinine of >50% from baseline or a rise in serum creatinine of ≥26.4 μmol/l (≥0.3 mg/dl) in <48 h, irrespective of whether the cause of the acute deterioration in renal function is related to a functional or structural disorder (table 2). Type 1 HRS can be regarded as a specific form of AKI. It was further agreed that these empirical new diagnostic criteria of AKI for cirrhosis will be validated to determine whether these smaller increases in serum creatinine are associated with poor outcomes. Two studies involving critically ill patients with cirrhosis admitted into an intensive care unit already showed that the RIFLE criteria for AKI was a good predictor of hospital survival.[49 50]

Once confirmed, the serum creatinine threshold for the diagnosis of type 1 HRS may need to be revised to a lower target value. This has the potential to allow patients with a smaller rise in creatinine to benefit from treatments currently reserved for patients with classical HRS. This new classification will also allow studies of the epidemiology, incidence, prevalence and natural history of various subtypes of AKI in cirrhosis, thereby allowing the development of potential preventive and treatment strategies.

DEFINITION OF CHRONIC KIDNEY DISEASE IN CIRRHOSIS

Patients with chronic renal impairment related to cirrhosis may not fit the definition and staging of CKD (table 3) as set out by the practice guidelines from the Kidney Disease Outcomes Quality Initiatives (K/DOQI) Workgroup,[51] since it requires a GFR of <60 ml/min/1.73 m^2 for >3 months, irrespective of the presence or absence of structural kidney damage. As mentioned above, estimation of GFR in cirrhosis using various formulae is problematic and actual measurement of GFR using iothalamate or inulin clearance techniques are cumbersome and essentially only performed for research purposes. Therefore, the application of the definition of CKD in cirrhosis is challenging. When the serum creatinine reaches the threshold of 133 μmol/l (1.5 mg/dl), the patient is said to have type 2 HRS.

The prognosis of patients with cirrhosis and CKD—whether type 2 HRS or structural renal disease—is worse than the corresponding stage of CKD in non-cirrhotic patients because of coexisting liver disease. Therefore, unlike non-cirrhotic patients, these patients usually do not survive long enough for the CKD to slowly deteriorate, nor will their CKD typically decline to the point of requiring dialysis unless AKI supervenes. Nevertheless, to be useful, a HRD classification system must include all potential scenarios where CKD and advanced liver disease coexist, either as independent entities or as the result of complex organ interactions. For example, a patient with cirrhosis due to non-alcoholic steatohepatitis may also have CKD on the basis of diabetes. Similarly, a patient with cirrhosis and ascites and mild renal dysfunction below the level defined by type 2 HRS may develop other forms of CKD such as IgA nephropathy related to his alcoholic liver disease. Finally, patients in both of these examples are likely to be at increased risk for AKI with various precipitants such as radiocontrast dye or sepsis.

Further research is required to understand the clinical significance of reaching K/DOQI criteria for CKD in a patient with cirrhosis. Nevertheless, the Working Group proposed the definition of CKD as an estimated GFR of <60 ml/min calculated

Table 1 The Acute Kidney Injury Network (AKIN) criteria for the definition and classification of AKI (modified RIFLE criteria)[43 47]

AKI stage	Serum creatinine criteria	Urine output criteria
1 (Risk)	Increase in serum creatinine of ≥26.4 μmol/l (≥0.3 mg/dl) within 48 h or an increase of ≥150–200% (1.5–2-fold) from baseline	<0.5 ml/kg/h for >6 h
2 (Injury)	Increase in serum creatinine to 200–299% (>2–3-fold) from baseline	<0.5 ml/kg/h for >12 h
3 (Failure)	Increase in serum creatinine to ≥300% (>3-fold) from baseline or serum creatinine of ≥354 μmol/l (≥4.0 mg/dl) with an acute increase of ≥44 μmol/l (≥0.5 mg/dl) or initiation of renal replacement therapy	<0.3 ml/kg/h for 24 h or anuria for 12 h

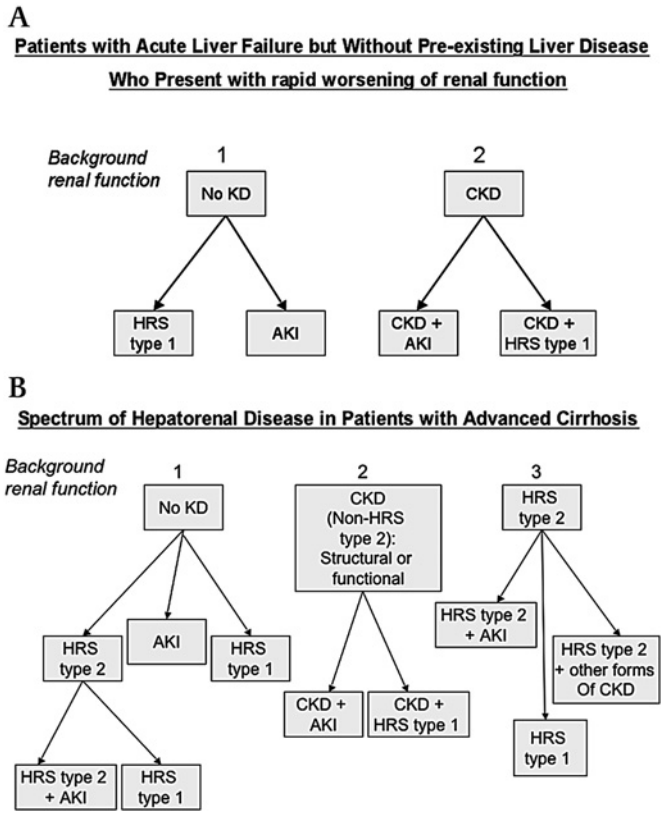

Figure 4 Classification of hepatorenal disorder (HRD). (A) Patients with acute liver failure without pre-existing liver disease who present with rapid worsening of renal function. (B) Spectrum of hepatorenal disorders in patients with advanced cirrhosis. AKI, acute kidney injury; CKD, chronic kidney disease; KD, kidney disease; HRS, hepatorenal syndrome.

using the MDRD6 formula[52] for >3 months for patients with cirrhosis (table 2) rather than a serum creatinine-based definition, to be in line with the definition of CKD in other subspecialties. The group also recognises that the MDRD6 formula tends to overestimate the GFR, but this is the formula that approximates most closely to GFR measurement using ^{125}I iothalamate clearance, especially in patients with low GFR of <40 ml/min.[36] Future studies are therefore needed to formulate a specific equation for the calculation of GFR with an acceptable accuracy for patients with advanced cirrhosis and to determine what threshold represents an increased risk in this population. The use of imaging criteria or histology to diagnose CKD was not considered by the group, as chronic renal damage may well precede the appearance of small sized kidneys on imaging and renal biopsy in patients with cirrhosis and coagulopathy is associated with an increased risk of bleeding. Furthermore, large volume ascites may preclude this technique.[42]

Table 2 Proposed diagnostic criteria of kidney dysfunction in cirrhosis

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.

Table 3 Definition and stages of chronic kidney disease based on kidney disease outcomes quality initiatives (K/DOQI) guidelines[51]

Stage	Description	GFR (ml/min/1.73 m^2)
I	Kidney damage with normal or increased GFR	≥90
II	Kidney damage with mildly decreased GFR	60–89
III	Moderately decreased GFR	30–59
IV	Severely decreased GFR	15–29
V	Kidney failure	<15 (or dialysis)

Chronic kidney disease is defined as either kidney damage or glomerular filtration rate (GFR) <60 ml/min/1.73 m^2 for >3 months. Kidney damage is defined as pathological abnormalities or markers of damage including abnormalities in blood or urine tests or imaging studies.

DEFINITION OF ACUTE-ON-CHRONIC KIDNEY DISEASE IN CIRRHOSIS

Finally, it is important to recognise that AKI may also occur in patients with cirrhosis and pre-existing renal dysfunction. The clinician should not have any problem identifying the precipitation of type 1 HRS with spontaneous bacterial peritonitis in a patient with type 2 HRS as the definitions of types 1 and 2 HRS are well established. However, type 1 HRS may also superimpose on CKD that does not fulfil type 2 HRS criteria, either because the renal dysfunction is not severe enough or because it is due to other forms of kidney disease (eg, diabetic nephropathy). Under the current diagnostic criteria for HRS, this scenario poses a diagnostic dilemma as the classical definition of HRS does not permit the presence of any evidence of structural renal damage. This may have potential clinical implications as therapeutic interventions, such as a TIPS shunt, may not be inserted into patients with mixed HRD when such interventions are actually beneficial.[53 54] We recognise that acute-on-chronic renal failure does occur in cirrhosis, although much work is needed to understand this entity better, particularly when forms of HRD are mixed (eg, AKI superimposed on CKD in a patient with advanced liver disease). The Working Group agreed that, at present, an empirical definition of acute-on-chronic kidney disease as an increase in serum creatinine of >50% from baseline or a rise in serum creatinine of ≥26.4 μmol/l (≥0.3 mg/dl) in <48 h in a patient with cirrhosis whose baseline GFR is <60 ml/min calculated with the MDRD6 formula for >3 months will be adopted. Once again, both the acute deterioration in renal function and the background chronic renal dysfunction can be functional or structural in nature (table 2).

SUMMARY

Renal complications are common in cirrhosis, especially in patients with refractory ascites, and they can negatively impact survival. The IAC has set out clear diagnostic criteria for both acute and chronic forms of HRS, but has not delineated guidelines for the diagnosis of other forms of renal impairment in cirrhosis,

whether acute or chronic. Well-accepted definitions and staging systems for CKD and AKI exist but have not been consistently applied to patients with advanced liver disease. Working together, the ADQI and IAC have proposed uniform standards for the diagnosis of AKI and CKD in cirrhosis adapted from these established definitions. These new diagnostic criteria are not meant to replace the well-established diagnostic criteria of HRS, but rather to broaden the scope to include other forms of renal disease in cirrhosis. The Working Group recognises that these diagnostic criteria will need to be validated in large cohorts of patients and may need to be modified depending on the outcome of these studies. Once confirmed, these diagnostic criteria will be applied to the development of clinical trials to evaluate potential treatment options for patients with HRD.

RECOMMENDATIONS FOR FUTURE RESEARCH

Future research will have to concentrate on improving our understanding of renal dysfunction in cirrhosis. To achieve this, the Working Group has suggested the following broad research areas.

1. To collect data on the epidemiology in terms of incidence, prevalence and basic demographics of patients with HRD including AKI, CKD and acute-on-chronic HRD.
2. To study the natural history of HRD, especially to search for precipitating factors for AKI, and to describe the rate of decline of renal function in patients with CKD.
3. To find better markers for renal dysfunction in cirrhosis such as cystatin C or NGAL. Alternatively, to determine the test characteristics including cut-off values for serum creatinine that define an increased risk for patients with HRD.
4. To determine whether the pathophysiology of type 2 HRS is different or the same as that of type 1 HRS, but only a matter of extent.
5. To investigate whether patients with various forms of CKD are at risk of developing type 2 HRS, and to determine whether the development of type 1 HRS from pre-existing type 2 HRS is the same as from pre-existing non-functional CKD.
6. To determine novel risk factors including cardiac dysfunction for the development of renal dysfunction and their impact on prognosis.

Once the various aspects of the different types of HRD are defined, we will be in a better position to refine the treatment for renal dysfunction in cirrhosis. The questions that will need to be answered include:

1. Are the diagnostic criteria for HRS too restrictive? Should the cut-off value of serum creatinine of 133 μmol/l (1.5 mg/dl) and 220 μmol/l (2.5 mg/dl) be lowered so that cirrhotic patients with milder renal failure can be identified and given treatment earlier?
2. Are treatments for type 1 HRS in patients with underlying CKD equally efficacious as in those without?
3. In case of non-responsiveness to vasoconstrictors and albumin, how long does type 1 HRS remain a functional disease before acute tubular necrosis develops?

Achieving these research goals will go a long way towards improving the outcome in patients with cirrhosis with renal dysfunction.

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APPENDIX 1

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Working Party proposal for a revised classification system of renal dysfunction in patients with cirrhosis

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