

Renal Dysfunction in Liver Transplant Candidates: Evaluation, Classification and Management in Contemporary Practice

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Abstract

Renal dysfunction is a common comorbidity in patients with liver failure and is a well-established predictor of both morbidity and mortality among patients awaiting liver transplantation. The etiology of renal failure in patients with cirrhosis can be functional, structural, or represent a combination of potentially reversible physiologic changes and permanent histologic damage. Diagnostic criteria for acute and chronic kidney disease have been established, but cirrhosis poses challenges for accurate assessment of renal function with conventional clinical methods such as serum creatinine and creatinine-based estimating equations. Renal biopsies can have an important role for defining permanent structural damage as part of the pre-transplant evaluation of patients with liver disease; however, coagulopathy, portal hypertension and ascites increase the risk of biopsy-associated complications in cirrhotic patients. While renal dysfunction due to hepatorenal physiology is potentially reversible after liver transplantation, simultaneous kidney liver transplantation and kidney after liver transplant can also improve outcomes in a subset of patients with irreversible renal injury.

Keywords: Acute kidney injury; Cirrhosis; Glomerular filtration rate; Hepatorenal syndrome; Simultaneous; liver-kidney transplantation

Abbreviations: ADQI: Acute Dialysis Quality Initiative; AKIN: Acute Kidney Injury Network; CKD: Chronic Kidney Disease; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; CrCl: Creatinine Clearance; eCrCl: Estimated Creatinine Clearance; eGFR: Estimated Glomerular Filtration Rate; GFR: Glomerular Filtration Rate; HBV: Hepatitis B Virus; HCV: Hepatitis C Virus; HRS: Hepatorenal Syndrome; IAC: International Ascites Club; K/DOQI: Kidney Disease Outcomes Quality Initiative; MELD: Model for End-Stage Liver Disease; MDRD: Modification of Diet in Renal Disease; RRT: Renal Replacement Therapy; SBP: Spontaneous Bacterial Peritonitis; SLK: Simultaneous Liver-Kidney; TIPS: Transjugular Intra-Hepatic Portosystemic Shunt

Introduction

While the incidence of renal dysfunction in patients with liver failure is not precisely known, renal failure is a significant source of morbidity in patients with liver disease. Acute renal failure complicates approximately 20% of the admissions for cirrhosis [1,2]. Chronic kidney disease (CKD) occurs in 1% of all cirrhotic patients. In 2007, approximately 7% of transplant candidates were on renal replacement therapy (RRT) listed for simultaneous liver-kidney transplant (SLK) or both [3]. Likewise, renal dysfunction is a well-established predictor of mortality and healthcare costs while on the waiting list for liver transplantation [4]. Serum creatinine is one of the three variables used to calculate the Model for End-Stage Liver Disease (MELD) score, which has been shown to predict short-term mortality in 83%-87% of wait-listed candidates and predict resource utilization and length of stay at time of transplantation [5]. The adoption of a severity of illness-based allocation system in 2002 using the MELD score, such that patients with higher acuity of illness as defined by MELD have priority for deceased donor organs within the geographic boundaries that direct organ distribution, resulted in an approximately 15% reduction in mortality on the liver transplant waiting list [6].

Etiology of Renal Failure

Risk factors for the development of renal failure in patients with cirrhosis are multifactorial, and include ascites, spontaneous bacterial peritonitis (SBP), hepatic encephalopathy and the use of diuretics or

other nephrotoxic medications [7]. Ascites is the factor most strongly associated with the development of acute renal dysfunction, especially in the setting of SBP [7,8].

Kidney dysfunction in patients with end-stage liver disease can be caused by functional changes, structural changes or a combination of both. Acute renal impairment is usually caused by pre-renal failure secondary to hypovolemia (i.e. aggressive diuretic therapy) or hepatorenal syndrome (HRS). Both result from decreased renal perfusion and are therefore functional and potentially reversible. However, persistently reduced renal blood flow may result in acute tubular necrosis and eventual irreversible changes characterized by glomerular and interstitial fibrosis [9]. Other causes of acute renal dysfunction include conditions that are also common in other patient populations, such as nephrotoxicity induced by drugs (i.e. aminoglycosides, non steroidal anti-inflammatory drugs) or by intravenous contrast. Treatment with aminoglycosides is associated with a four to six-fold increase in the risk of renal dysfunction independent of the severity of the liver disease, and should be avoided unless mandated by bacterial sensitivities and resistance [7,10].

CKD in cirrhotic patients can result from prolonged acute injury or concomitant systemic co-morbidities, such as diabetes and hypertension. CKD can also result as a direct complication of liver disease, as in prolonged (type 2) HRS or secondary IgA nephropathy. Further, Hepatitis C virus (HCV) and Hepatitis B virus (HBV) are common causes of cirrhosis that may also cause renal injury in the form of glomerulonephritis or glomerulopathies [11]. Impairment

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Received February 23, 2012; Accepted March 28, 2012; Published March 30, 2012

Citation: Gleisner AL, Jung HS, Lentine KL, Tuttle-Newhall J (2012) Renal Dysfunction in Liver Transplant Candidates: Evaluation, Classification and Management in Contemporary Practice. J Nephrol Therapeutic S4:006. doi:10.4172/2161-0959.S4-006

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in immune complex clearance by the Kupffer cells and hepatocytes with resnet deposition in the glomeruli is thought to be the common underlying mechanism for the development of glomerulonephritis in HCV, HBV and secondary IgA nephropathy [12].

Hepatorenal syndrome

The hepatorenal syndrome (HRS) is a functional cause of renal failure associated with advanced cirrhosis [1,13]. HRS is a consequence of reduced effective arterial blood volume secondary to severe splanchnic arterial vasodilation in the setting of portal hypertension [14]. Splanchnic vasodilation is a result of increased production of vasodilators such as nitric oxide (NO) and endogenous cannabinoids [14,15]. In earlier stages of cirrhosis, there is a compensatory increase in cardiac output as systemic vascular resistance decreases [16]. With disease progression, however, compensation by cardiac output becomes insufficient. Subsequently, the sympathetic nervous system and the renin-angiotensin system are activated. Along with a hypersecretion of arginine vasopressin, these mechanisms seek to maintain an effective arterial blood volume [16]; however, they also lead to renal vasoconstriction, hypoperfusion, ascites and edema. Renal failure associated with refractory ascites can develop slowly within several weeks or months (type 2 HRS), or it can develop abruptly in less than 2 weeks when it is often associated with SBP (type 1 HRS). Peritonitis causes a severe inflammatory response with production of vasoactive mediators, worsening the circulatory dysfunction and precipitating acute renal failure [17]. This mechanism explains the strong association between ascites and acute renal failure, especially in the setting of SBP [8]. The International Ascites Club (IAC) working group proposed the revised diagnostic criteria for HRS in 2007 (Table 1) [13]. Both type 1 and type 2 HRS are potentially reversible with liver transplantation that occurs before the development of substantial renal fibrosis.

Diagnosis of Kidney Disease

Renal function changes can be accessed through the direct measurement of the glomerular filtration rate (GFR) by the infusion of exogenous markers that are freely filtered by the glomerulus. They can also be estimated through the measurement of the clearance of endogenous compounds that are freely filtered but minimally secreted by tubular cells. Structural abnormalities are suggested by abnormal urinary markers such as hematuria and proteinuria, but the type (i.e. glomerular, tubulo-interstitial or vascular) and severity of the lesion can only be determined by histological examination of a biopsy specimen.

Direct measurement of the GFR with exogenous markers

The gold standard for the measurement of GFR is inulin clearance.

Cirrhosis with ascites

Serum creatinine >133 $\mu\text{mol/l}$ (1.5 mg/dl)

No improvement of serum creatinine (decrease to a level of $\leq 133 \mu\text{mol/l}$) after at least 2 days with diuretic withdrawal and volume expansion with albumin. The recommended dose of albumin is 1 g/kg of body weight per 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, microhematuria (>50 red blood cells per high power field) and/or abnormal renal ultrasonography

Table 1: International Ascites Club (IAC) proposed diagnostic criteria for hepatorenal syndrome [13].

Inulin is freely filtered by the glomerulus. It is not secreted, reabsorbed, synthesized or metabolized by the kidney. Measurement of inulin clearance is time consuming and costly because it requires continuous intravenous infusion with timed urine collections. Other techniques requiring a single injection of markers have been developed. These include measured clearances of radiolabeled markers such as $^{51}\text{Cr-EDTA}$, $^{99\text{mTc-DPTA}}$ and $^{125}\text{I-iodohalamate}$ and non-radioactive agents such as iohexol or iohalamate [18,19]. Using these tests, the GFR is based on the area under the curve of the plasma concentration of the marker. This obviates the need for urine sampling. Unfortunately, these are also costly and time consuming, and are not easily accessible in the clinical setting. There are also concerns for exposing the patient to additive doses of radiation. Direct measurement of the GFR based on the clearance of exogenous markers is difficult in routine clinical practice and is unsuitable for assessing changes in renal function in short intervals.

Creatinine and creatinine-based equations

Creatinine, an endogenous compound derived from the creatine in the muscle that is freely filtered by the glomerulus, is the most widely used surrogate marker of renal function. Because creatinine is secreted by proximal tubular cells, creatinine clearance (CrCl) exceeds GFR. Creatinine clearance can be measured from a timed urine collection and a blood sample or estimated based on the serum level, which is related to the reciprocal of GFR in the steady state [20]. In addition to its relationship with GFR, steady state serum creatinine levels vary with age, gender, geographic, ethnic and racial groups. Several factors are involved, including differences in muscle mass, dietary intake, tubular secretion and extra-renal elimination [18]. Some drugs, such as trimethoprim and cimetidine, inhibit tubular secretion and can result in decreased CrCl despite no real changes in the GFR [18,21].

Several formulas used in estimating GFR from serum creatinine level include adjustments for age, sex, race and weight to improve accuracy of estimation (Table 2). The popular Cockcroft-Gault formula was developed in 1973 [22] to compute estimated creatinine clearance (eCrCl) using adjustment for weight, gender and age, and is expressed in milliliters per minute. The Modification of Diet in Renal Disease (MDRD) study equation was developed in 1999 and revised in 2005 for use with a standardized creatinine assay [23,24]. This formula adjusts for age, gender and race and provides estimated GFR (eGFR) in milliliters per minute per 1.73 m^2 body surface area. The MDRD equation was found to be more accurate than the Cockcroft-Gault formula in a population with kidney dysfunction from multiple causes, even after adjustment of the Cockcroft-Gault formula for the body-surface area [24]. Because the MDRD study equation was developed in with a cohort of patients with CKD, it underestimates measured GFR at higher levels [25]. The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation was developed in 2009 to correct this bias while maintaining the precision of the GFR estimation in lower levels of kidney function [26]. The CKD-EPI equation has been validated in different populations and has shown to improve the accuracy of eGFR in the general population [18,27].

The use of serum creatinine levels and creatinine-based estimating equations is problematic in the setting of cirrhosis. Creatine production by the liver is impaired and protein-calorie malnutrition is common [28,29]. Body weight can be greatly affected by edema and ascites. In addition, techniques routinely applied to determine serum creatinine are based on spectrophotometry. Bilirubin is a chromogen that interferes with the creatinine measurement and high levels can

Equation	
Cockcroft–Gault formula [22]	$Ccr = [(140 - \text{age}) \times \text{weight}] / 72 \times Scr \times 0.85$ if the subject is female, in milliliters per min
MDRD study equation [24]	$GFR = 175 \times (\text{standardized } Scr)^{-1.154} \times (\text{age})^{-0.203} \times 0.742$ if the subject is female $\times 1.212$ if the subject is black, in milliliters per minute per 1.73 m ²
CKD-EPI equation [25]	$GFR = 141 \times \min(Scr/\kappa, 1)^\alpha \times \max(Scr/\kappa, 1)^{-1.209} \times 0.993$ Age $\times 1.018$ if female $\times 1.159$ if black

*where Scr is serum creatinine, κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -

0.411 For males, min indicates the minimum of Scr/ κ or 1, and max indicates the maximum of Scr/ κ or 1

Table 2: Equations for estimation of renal function.

lead to falsely low creatinine measurements based on this interference. Techniques have been developed to minimize this interference but are not widespread [30,31]. As a result, serum creatinine and creatinine-based equations tend to overestimate the GFR in cirrhotic patients [32-34].

The direct measurement of the CrCl through timed urine collections could potentially be more precise in the determination of the GFR; however, the increase in tubular secretion of creatinine with lower levels of GFR results in overestimation of the GFR in cirrhosis [35,36]. The logistics of modern in-hospital care and self-collections can also skew the results based on inadequate collections. A recent systematic review and meta-analysis by Proulx et al. [37] comparing measured CrCl with inulin clearance found that CrCl overestimated GFR by a mean of 13 ml/min/1.73 m². In-house measurements require well-educated care team.

Cystatin C

Other endogenous markers have been proposed in order to provide more precise, yet still practical, GFR estimation. Cystatin C is a low molecular protein produced at a constant rate by all nucleated cells. Serum levels of cystatin C are less variable than serum creatinine and independent of muscle mass. Cystatin C is freely filtered by the glomerulus and is reabsorbed and catabolized by the tubular epithelial cells [38]. This precludes the direct measurement of the cystatin C clearance through measurement of urinary levels. GFR is instead estimated based on the reciprocal of the serum level. Studies comparing cystatin C with creatinine or creatinine-based estimating equations show heterogeneous results, and while Cystatin C shows promise as an alternative to serum creatinine, it has not yet been adopted into routine clinical practice [39,40]. In patients with cirrhosis, Cystatin C detected a decrease in GFR defined as $GFR < 72$ ml/min/1.73 m² measured by inulin clearance with sensitivity similar to that achieved among patients without cirrhosis (73% and 88%, respectively). The sensitivity of serum creatinine levels and eCrCl (Cockcroft–Gault formula) for reduced GFR was much lower (23% and 53% respectively) [41]. Nonetheless, the overall accuracy of the serum creatinine for detection of reduced GFR, as measured by the receiver operating characteristic (ROC) curve, was similar to that of the cystatin C. This suggests that sensitivity of plasma creatinine and eCrCl could be improved if lower reference levels for abnormal function were adopted. According to Orlando et al. [41], the sensitivity and specificity for impaired GFR in patients with cirrhosis is 76% and 89% respectively for a serum creatinine threshold of 87 μ mol/L (0.98 mg/L). Nonetheless, this threshold would likely need to

be adjusted by the severity of liver dysfunction in order to maintain its accuracy in a heterogeneous population of patients with cirrhosis.

Urinary markers

Urinary markers such as urinary sodium, fractional excretion of sodium, and urine osmolality are often also used in patients with acute kidney dysfunction to aid in the diagnosis of cause. In end-stage liver disease, the utility of these tests are limited by the activation of water and sodium retention, vasoconstrictor systems, and by the use of diuretics. Other markers, including hematuria and proteinuria, indicate the presence of glomerular injury. In one study, prevalence of proteinuria and hematuria was higher in patients with membranoproliferative glomerulonephritis than in patients with minimal findings or predominant histological diagnosis of acute tubular necrosis, interstitial fibrosis or glomerulosclerosis, but there was no correlation of proteinuria or hematuria with the degree of renal damage in patients with liver disease. The prevalence of hematuria and proteinuria was similar when transplant candidates accepted for liver transplant alone where compared to those with extensive interstitial fibrosis, glomerulosclerosis and/or diffuse membranoproliferative glomerulonephritis recommended for SLK [42]. In addition, the absence of proteinuria and hematuria do not exclude glomerular changes [42,43].

Renal biopsy

Renal biopsy and pathological examination is the gold standard for the evaluation of structural changes in the kidney and autopsy studies suggest a high prevalence of structural abnormalities in patients with cirrhosis. Wagrowska-Danilewicz et al. [44] investigated cirrhotic patients with reportedly normal renal function and no renal changes on gross examination during autopsy. They found several abnormalities upon histological evaluation, including increased glomerular cellularity, thickening in the mesangial matrix, and glomerular sclerosis. These results highlight the discrepancy of biopsy findings when compared to clinical and laboratory (serum or urine) abnormalities. While some patients with severe renal dysfunction in the setting of HRS may have normal biopsy results, others will have severe renal lesions despite normal or near normal serum creatinine levels due to the overestimation of the GFR by the routine methods.

Concerns with bleeding risk have historically limited the use of renal biopsy in cirrhotic patients until the recent introduction of the transjugular renal biopsy as an alternative to the conventional percutaneous technique. Transjugular biopsy is safe and has similar diagnostic yield when a percutaneous biopsy is contraindicated [45]. Several studies have described the feasibility of transjugular renal biopsies in cirrhotic patients. Jouet et al. [46] described a success rate for obtaining adequate specimen approaching 80% with acceptable complication rates in a cohort of cirrhotic patients with abnormal renal function undergoing evaluation for liver transplantation. Most patients had findings suggestive of glomerulopathy, including focal segmental sclerosis and membranoproliferative glomerulonephritis. A Mesangial IgA deposit in immunofluorescence was the most common abnormality found among those biopsies studied. Among 11 transplant candidates, in this series, those with normal renal biopsy results were considered to have HRS and were offered liver transplantation alone. SLK was offered to patients with moderate to severe lesions in the kidney biopsy. Clinically significant complications of renal biopsy included hematuria and hematoma. Despite all patients having clotting disorders precluding percutaneous renal biopsy, only 3 out of 55 cases

required blood transfusion and there were no deaths. In a subsequent series, Sam et al. [47] described no major bleeding events, even in those with concomitant liver biopsy. Another study by Misra et al. [48] reported only one patient out of 39 patients with severe bleeding necessitating hemodynamic support after the transjugular approach [48]. Contrast medium-induced nephropathy was present in 3 of these patients (7.8%). Perirenal hematomas were identified in up to 52% of patients, which is comparable to rates reported with the percutaneous route in patients with normal coagulation parameters. Transfusion was often required but not necessarily related to the size of the perirenal hematoma. Our institution recently described a series of 23 patients who underwent transjugular kidney biopsy by interventional nephrologists in 2002–2009, whose contraindication for percutaneous kidney biopsy was mainly coagulopathy [49]. Sufficient tissue for adequate diagnosis was obtained in 20 patients (87%). The only major complication was blood transfusion, required by 3 patients. These results reinforce the safety and the specificity of the transjugular approach for biopsying the kidney in patients with liver disease.

On the other hand, percutaneous kidney biopsy has been used successfully used in some centers. In a series of 44 patients with cirrhosis, Wadei et al. [42] described a 30% percutaneous biopsy complication rate with 11% requiring fluoroscopic guided embolization. There were no surgical interventions or deaths associated with this procedure. An international normalized ratio (INR) greater than 1.5 increased the risk of complication by five times. There were no other factors associated with an increased risk of complications, including serum creatinine and platelet count.

Definition of Acute And Chronic Kidney Disease

Definition of acute kidney disease

In 2004, the Acute Dialysis Quality Initiative (ADQI) Working Group developed a consensus definition and classification for acute kidney injury known as the RIFLE criteria (R: renal risk, I: injury, F: failure, L: loss of kidney function, E: end-stage renal disease) (Table 3). These criteria stratify acute renal dysfunction into grades of increasing severity based on changes in serum creatinine and/or urine output [50]. The RIFLE criteria have been shown to be a valid predictor of mortality in several patient populations, including those with cirrhosis admitted to the intensive care unit [51,52]. Recently, the Acute Kidney Injury Network (AKIN) broadened the definition of AKI to include an absolute increase in serum creatinine of ≥ 0.3 mg/dl when documented to occur within 48 hours of admission. Such increases have been shown to be associated with increased morbidity and mortality [53].

Definition of chronic kidney disease

The current definition and staging of CKD (Table 4) was developed by the Kidney Disease Outcomes Quality Initiative (K/DOQI) Workgroup in 2002 [54]. This definition includes patients with GFR < 60 ml/min/1.73m² and patients with structural/functional abnormalities of the kidney regardless of the GFR. It defines the presence of the kidney injury for ≥ 3 months to infer chronicity; although, both documentation and presumption of the abnormality are acceptable [55]. Of note, this definition does not include values of the serum creatinine alone but it does allow the use of current equations based on serum creatinine to estimate the GFR [55].

In March of 2010, members of the ADQI and the IAC formed a working group to discuss the definition of acute and chronic renal dysfunction as applied to patients with cirrhosis [1]. The proposed

	Creatinine/GFR criteria	Urine output criteria
RIFLE classification by the ADQI		
Risk	50-100% or GFR decrease $> 25\%$	< 0.5 ml/kg/h for > 6 h
Injury	50-100% or GFR decrease $> 50\%$	< 0.5 ml/kg/h for > 12 h
Failure	$> 200\%$ or GFR decrease $> 75\%$	< 0.3 ml/kg/h for > 24 h or anuria for > 12 h
Loss	Complete loss of kidney function; > 4 weeks dialysis	
ESRD	End stage renal disease; > 3 months dialysis	
Stage 1 (risk)	Increase in serum creatinine of ≥ 0.3 mg /dl within 48 h or any increase ≥ 1.5 to 2-fold from baseline	< 0.5 ml/kg/h for > 6 h
Stage 2 (injury)	Increase in serum creatinine to > 2 to 3-fold from baseline	< 0.5 ml/kg/h for > 12 h
Stage 3 (failure)	Increase in serum creatinine to > 3 -fold from baseline or serum creatinine ≥ 4 mg/dl	< 0.3 ml/kg/h for > 24 h or anuria for > 12 h

Table 3: Classification of Acute Kidney Injury (AKI) according to the Acute Dialysis Qualitative Initiative (ADQI) [50] and to the Acute Kidney Injury Network (AKIN) [53].

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: either kidney damage or glomerular filtration rate (GFR) < 60 ml/min/1.73 m²

for > 3 months. Kidney damage is defined as pathological abnormalities or markers of damage including abnormalities in blood or urine tests or imaging studies

Table 4: Definition and stages of chronic kidney disease* based on kidney disease outcomes quality initiatives (K/DOQI) guidelines [54].

diagnostic criteria for acute kidney injury (Table 5) contained a serum creatinine component but excluded urine output, since patients with refractory ascites may maintain a low urine output even in the absence of kidney dysfunction. The consensus also recommends the use of the MDRD formula [23] when estimating the GFR for the diagnosis of CKD and introduces a third diagnostic criteria, acute-on-chronic kidney disease, to allow the identification of those patients who have an acute deterioration of the kidney function in the setting of background CKD, regardless of whether the cause of the acute impairment is structural or functional. The classic diagnostic criteria of HRS exclude those patients with structural renal damage, but it is reasonable to assume that a sudden deterioration in patients with known structural kidney damage may have a functional component. These patients could potentially benefit from therapeutic interventions that are often reserved for those who meet the diagnosis of HRS. Finally, the ADQI/IAC working group recognizes that functional abnormalities may

Diagnosis*	
Acute kidney injury	Rise in serum creatinine of $\geq 50\%$ from baseline or a rise of serum creatinine by 0.3 mg/dl in 48h
Chronic kidney disease	Glomerular filtration rate of < 60 ml/min for > 3 months calculated using the MDRD formula
Acute-on-chronic kidney disease	Rise in serum creatinine of $\geq 50\%$ from late baseline or a rise of serum creatinine by 0.3 mg/dl in 48h in a patient with cirrhosis whose glomerular filtration rate is < 60 ml/min for > 3 months calculated using the MDRD formula

*both the acute deterioration in renal function in the background chronic renal dysfunction can be functional or structural in nature

Table 5: Proposed diagnostic criteria of kidney dysfunction in cirrhosis [1].

result in structural changes (i.e. acute tubular necrosis), but the precise timing for the development of structural renal changes and for the setting of irreversible dysfunction remains undefined.

Prevention and Treatment

Treatment aims at recognizing and managing reversible causes of acute renal failure and acute deterioration of CKD. Progression to acute tubular necrosis can be avoided with the prompt recognition and treatment of hypovolemia secondary to variceal bleeding or excessive response to diuretics. If contrast medium needs to be used, hydration should be implemented prior to and after the procedure to minimize risk of contrast-induced nephrotoxicity [56]. Drugs associated with nephrotoxicity such as non steroid anti-inflammatory agents and aminoglycosides should be discontinued and avoided [10]. Infection, especially SBP, should be diagnosed and treated without delay. Severe sepsis associated with renal insufficiency may respond to steroids [57]; however steroid use in some populations is controversial. Refractory ascites should be treated with repeat paracentesis and intravenous albumin replacement [58] or placement of a transjugular intrahepatic portosystemic shunt if the MELD score allows it. Albumin has been shown to decrease the incidence of HRS and resulted in improved hospital and 3-month survival in patients diagnosed with SBP and evidence supports its use in these circumstances [59].

Vasoconstrictors such as terlipressin, midodrine or norepinephrine are promising therapies for HRS [13]. Terlipressin, a vasopressin analogue, is the most widely studied vasoconstrictor in patients with HRS syndrome and its effectiveness has been demonstrated in randomized controlled trials [60,61], with improvement in renal function in approximately 40 to 65% of patients. Patients with type 2 HRS are at higher risk of recurrent renal failure with discontinuation of vasoconstrictor agents but retreatment can be effective. Adverse events included headache, abdominal pain, cardiac arrhythmia, and hypertension [62]. A recent systematic review evaluated the effect of the treatment with vasoconstrictors (terlipressin, octreotide and noradrenaline) in patients with HRS type 1 or 2 and found a significant overall reduction in the mortality (RR 0.82; 95% CI, 0.70-0.96). In subgroup analysis, significant reduction in the mortality was seen at 15 days (40% reduction) but not at longer periods. The trials were small, and only two included noradrenaline and one octreotide, which limit the power of subgroup analysis for these therapies [63]. Of note, Terlipressin has not been approved by the FDA at this time. For this reason, in the United States, HRS has been treated with midodrine, often in conjunction with albumin and octreotide. This strategy appears

effective in non-randomized trials [64-66], with reports of significant increases in the GFR and renal sodium excretion after treatment for 2-3 weeks. Skagen et al. [66] evaluated the effect of midodrine, octreotide and albumin in patients with HRS type 1 and 2 and found a significant improvement in survival when compared to historical controls (median survival 101 vs 18 days, respectively). These strategies have not been evaluated in randomized controlled trials. Transjugular intra-hepatic portosystemic shunts (TIPS) have also been found to improve renal function in limited studies with patients with HRS type 1 and 2 [13]. Both vasoconstrictors and TIPS suppress the endogenous vasoconstrictor systems and improve circulatory dysfunction in cirrhosis. TIPS improve splanchnic vasodilation through relief of portal hypertension. In addition, it helps with the control of the ascites in most patients. Both use of vasoconstrictors and TIPS in selected patients have been recommended as treatment strategies for patients with HRS by the IAC in their 2007 consensus on the diagnosis, prevention and treatment of HRS, although the limitation of evidence was noted [13].

In cirrhotic patients with functional renal dysfunction, the definitive treatment is liver transplantation. Treatment of liver failure resolves kidney dysfunction although the duration of RRT after transplantation is variable. Hemodynamic abnormalities associated with HRS disappear within the first month after transplantation [67]. If there is significant structural kidney disease, simultaneous liver-kidney (SLK) transplant assures treatment of both liver and kidney failure.

Nevertheless, because renal dysfunction is often a combination of functional and structural abnormalities, recovery is hard to predict. It can be influenced by perioperative conditions such as intra-operative bleeding, blood transfusion, vasopressors and calcineurin inhibitors. The largest decline in renal function occurs during the transplant and in the immediate post-operative period [68]. Northup et al. [69] recently reviewed 1041 liver transplant recipients from the UNOS database who were on dialysis for acute renal failure at the time of their transplant. Of these, 707(68%) patients recovered their renal function and were removed from dialysis following liver transplant alone.

Prognosis and Implications

It is clear that renal dysfunction is associated with high mortality in cirrhosis. Mortality while on the liver transplant wait-list can be associated with increasing MELD scores, which heavily relies on the creatinine [6]. A score that includes the direct measurement of the renal function is even more accurate in predicting short-term mortality in these patients, reinforcing the importance of the renal function on wait-list mortality [32]. Estimated median survival is about 6 months for those with HRS type 2 and less than 2 weeks for those with untreated HRS type 1 [16].

In addition to pre-transplant renal dysfunction, post-transplant acute renal failure, age, diabetes, coronary artery disease and hepatitis C have been associated with the development of chronic renal failure after liver transplant [69-72]. End-stage renal disease (ESRD) has been described to occur in 18% of liver transplant recipients at 5 years [72]. Besides detrimental effects on quality of life and cost, chronic renal failure was associated with a four-fold increased in the risk of death after non-renal transplantation [72]. Kidney transplantation for transplanted patients of other solid organs resulted in a significant improvement in mortality when compared to dialysis. Kidney after liver transplantation is an alternative to SLK when renal recovery is unclear. However, because both organs are from the same donor in SLK transplants, rejection-free graft survival is superior at 1 and 3

years (85% and 78%, respectively) as compared with kidney after liver transplant (77% and 67%, respectively) [73]. This highlights the importance of predicting post-transplant progression to ESRD while on the waiting list.

Prediction of renal recovery and progression to end-stage renal disease after transplant

Two pre-transplant factors have been used for the prediction of renal recovery and to aid in the decision for the indication of SLK: duration of kidney dysfunction and histological findings. The duration of the kidney dysfunction has been shown to be associated with post-transplant renal failure and recovery [69,74]. In a recent study by Northup et al. [69], recovery was observed in 70.8% patients on RRT for less than 30 days but in only 11.5% of those for more than 90 days. Although there is no clear cuff off, an American consensus conference suggested 6 weeks as a threshold after which SLK transplant should be considered [3]. Patients with liver disease and concomitant CKD with GFR <30 ml/min (stage 4 and 5) should be offered SLK transplant. For patients with CKD stage 1 through 3, survival benefit of SLK over liver transplant alone is unknown.

Because renal biopsy has been shown to be safe and effective in patients with liver failure, it has been utilized for SLK transplant evaluation in some centers [42,75] and recommended by the UNOS guidelines for dual listing. In a study by Tanriover et al. [75], patients with prolonged renal dysfunction, as estimated by serum creatinine and confirmed by direct measurement of the GFR using the iodine-125 iothalamate test, was recommended for renal biopsy. Patients with findings of advanced intrinsic kidney disease (interstitial fibrosis greater than 30%, glomerular sclerosis greater than 40%, or moderate to severe arteriosclerosis) were recommended for SLK transplant. Follow-up results confirmed acceptable outcomes in kidney function for those patients with favorable renal biopsy findings despite significant clinical renal dysfunction who underwent liver transplant alone. Wadei et al. [42], retrospectively analyzed the outcomes of 44 liver transplant candidates with impaired renal function of unknown origin that underwent a percutaneous native kidney biopsy. A decision to proceed with SLK transplant was made if the biopsy showed >40% global glomerulosclerosis, >30% interstitial fibrosis, and/or diffuse (involving 50% of glomeruli) membranoproliferative glomerulonephritis (MPGN). No clinical criteria correlated with fixed renal damage found on renal biopsy. Twenty-seven (61%) candidates, including 5 patients on RRT, were recommended liver transplant alone despite significant renal dysfunction. The results showed similar outcomes between those who received liver transplant alone versus those who received simultaneous kidney-liver transplants, with no difference in the mean GFR at 1 year and last follow-up. The five patients on RRT prior to the transplant had dialysis discontinued within the first month after transplant.

Kidney biopsy should therefore be considered in the evaluation of patients with acute kidney dysfunction for whom recovery after transplant is unclear, including those with RRT duration between 6 and 12 weeks and those with acute or chronic presentation of suspected intrinsic disease [68]. Biopsy is also recommended for CKD patients with a GFR greater than 30 but less than 60 ml/min/1.73 m² who are at significant risk of progression to ESRD post-liver transplantation [76]. Those with significant structural kidney disease (>40% global glomerulosclerosis, >30% interstitial fibrosis, moderate or severe arteriosclerosis) should be offered SLK transplant as opposed to liver alone [77]. Given the low probability of renal recovery, those with

acute kidney failure for greater than 12 weeks should be considered for SLK without renal biopsy [68]. This management strategy aims to prevent post-transplant renal failure and its associated mortality while appropriately utilizing scarce donor kidney resources. Nonetheless, there is still reluctance to perform renal biopsies routinely in liver failure patients in practice due to the concern for bleeding risk despite demonstration that risks can be managed when the procedure is performed by experienced internationalists. With the use of the MELD score to prioritize organ allocation, an increased proportion of patients are being transplanted with acute or chronic renal disease [78]. This could lead to decreased post-transplant survival and raise concerns regarding the best use of organs. In fact, comparing the pre-MELD to MELD era, there has been a 41% increase in patients on dialysis and a 117% increase in SLK transplants [79]. It is clear indeed that pre-transplant renal dysfunction has been associated with increased risk of infection and death [76, 80-82]. Patients with HRS have more complications and decreased survival after transplant, with a 60% 3-year survival rate. The actual impact of SLK in the survival after transplantation is controversial. Survivals for patients who have undergone SLK have been reported to be similar to those with normal pre-operative creatinine who received liver transplant alone [82]. Nonetheless, when patients who underwent SLK in the U.S. in the MELD era were compared with matched- controls who underwent liver transplant alone using national registry data, there was no survival benefit for SLK, except for patients on long-term dialysis, for whom there was a 43% reduction in the mortality with SLK [83]. The data suggest that kidney grafts may be overused in some liver failure patients in recent practice.

Conclusion

While the frequency of renal dysfunction in patients with liver failure is not precisely known, renal dysfunction is a significant source of morbidity in patients with liver disease. Understanding the etiology, indications for diagnostic tools, classification of disease and therapies impact not only patient survival, but improve graft allocation and utilization. Historically, concomitant kidney failure in patients with end stage liver disease was a contra- indication for liver transplant, but with current diagnostic techniques guiding therapy, patient survival has increased.

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This article was originally published in a special issue, **Kidney Transplantation** handled by Editor(s) Dr. Gagangeet Sandhu, Columbia University College of Physicians and Surgeons, USA; Dr. Krista Lentine, Saint Louis University School of Medicine, USA