11 Preoperative Assessment and Optimisation of Liver Transplant Patients: Renal Issues

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11.1 Introduction

The first successful human liver transplant was performed in 1969; since then liver transplant has evolved rapidly becoming the standard therapy for the acute and chronic liver failure of all aetiologies. The success has been attributed to several advances such as improvements in surgical techniques, the introduction of new immunosuppressants and preservative solutions and early diagnosis and management of complications [1]. Cirrhosis (57%) remains the most common cause for liver transplant followed by cancers (15%), cholestatic diseases (10%), acute hepatic failure (8%) and metabolic disorders (6%) [1].

Patients with liver pathology are susceptible to renal impairments due to pre-existing hormonal and circulatory imbalances or due to precipitating factors. Acute renal failure (ARF) is caused mainly by renal hypoperfusion and tubular necrosis. Haemorrhage, fluid loss due to the use of diuretics, sepsis and hepatorenal syndrome are the main causes of prerenal failure [2]. Liver disease and renal dysfunction can occur simultaneously as a result of a systemic condition affecting both these organs; however, renal dysfunction complicating primary disorders of the liver such as IgA nephropathy, cryoglobulinemia, membranous nephropathy and hepatorenal syndrome is much more common [3]. In 19% of cirrhotic patients awaiting a liver transplant, acute kidney injury is frequently developed during hospitalisation due to nephrotoxic drugs, diuretics and contrast dyes used in perioperative period [4–6] and approximately 1% of the patients develop chronic renal failure (CRF) [2–4]. In patients without renal impairment, acute kidney injury is diagnosed when serum creatinine level increases by more than 50% of the base value, to above 1.5 mg/dl [7]. It is imperative to assess and diagnose renal dysfunction early in patients with liver disease awaiting transplant. There has been an improvement in the understanding of renal complications in liver disease and the treatment options for the same. A thorough preoperative examination of all the systems is crucial and mandatory. Hemodynamic derangements and insults during the perioperative period are somewhat predictable based on the preoperative assessment of the patient and this is the time when preventive therapy can be initiated if the risk is aptly determined [8]. Anaesthetists play a pivotal role in identifying patients at risk for acute renal failure, optimising anaemia and treating hypovolemia in the preoperative period.

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11.2 Definition of Acute Kidney Injury

Comparison of the criteria for staging of AKI by three systems is tabulated in Table 11.1.

RIFLE (risk, injury, loss of kidney function, end-stage renal failure) system used serum creatinine and urine output to define adult kidney injury, the first-ever criterion for adult kidney injury to be published in 2004 [6].

A modification of RIFLE criteria was published by the Acute Kidney Injury Network (AKIN) in 2007 [9] AKIN criteria evolved from RIFLE criteria but with the understanding that smaller changes in concentration of serum creatinine are associated with morbidity and mortality [10]. AKIN criteria failed to define adult kidney injury without knowledge of baseline serum creatinine [6, 10, 11].

In 2012, the Kidney Disease: Improving Global Outcome (KIDGO) foundation proposed a clinical and practice guidelines of acute kidney injury. The guidelines included a comprehensive review of acute kidney injury definition, risk assessment, diagnosis, prevention, treatment and renal replacement therapy [12, 13]. The KIDGO criteria included absolute change in serum creatinine and accepted 48 hours and an extended 7-day time frame for diagnosis of acute kidney injury [12].

To define acute kidney injury based on serum creatinine levels would be flawed as it is influenced by [6] by overall nutrition state, volume overload, drugs especially steroids, muscle injury

Table 11.1 Comparison of RIFLE, AKIN and KIDGO criteria in the staging of acute injury [6, 9, 11, 13, 14]

Definition system	RIFLE 7 Days	AKIN 48 h	KIDGO
Staging	**Risk** Increased sCr × 1.5 or GFR decrease >25% or urine output <0.5 ml kg^{-1} h^{-1} for 6 h	**Stage 1** Increased sCr × 1.5–2 or sCr increase ≥0.3 mg dl^{-1} or urine output <0.5 ml kg^{-1} h^{-1} for >6 h	**Stage 1** Increased sCr × 1.5–1.9 that is known or presumed to have occurred within the preceding 7 days or sCr increase ≥0.3 mg dl^{-1} within 48 h or urine output <0.5 ml kg^{-1} h^{-1} for 6–12 h
	Injury Increased sCr × 2 or GFR decease >50% or urine output <0.5 ml kg^{-1} h^{-1} for 12 h	**Stage 2** Increased sCr × 2–3 or urine output <0.5 ml kg^{-1} h^{-1} for >12 h	**Stage 2** Increased sCr × 2–2.9 or urine output <0.5 ml kg^{-1} h^{-1} for ≥12 h
	Failure Increased sCr × 3 or GFR decrease 75% or sCr ≥ 4 mgdl−1 when sCr is in acute increase (≥0.5 mg dl^{-1}) or urine output <0.3 ml kg^{-1} h^{-1} for 24 h or anuria for 12 h	**Stage 3** Increased sCr × 3 or more or sCr ≥4 mg dl^{-1} when sCr is in acute increase (≥0.5 mg dl^{-1}) or urine output <0.3 ml kg^{-1} h^{-1} for >24 h or anuria for 12 h	**Stage 3** Increased sCr × 3 Or sCr ≥4 mg dl^{-1} or initiation of RRT or GFR decreases to <35 ml min^{-1} $(1.73\ m)^{-2}$ in patients <18 years old or urine output <0.3 ml kg^{-1} h^{-1} for ≥24 h or anuria for ≥12 h

sCr serum creatinine, *GFR* glomerular filtration rate, *RIFLE* risk; injury; failure; loss of kidney function; end-stage renal failure, *AKIN* Acute Kidney Injury Network, *KIDGO* Kidney Disease: Improving Global Outcome, *RRT* renal replacement therapy

and fluid overload. Over the last few years study in the field of acute kidney injury has expanded with identifying different molecules excreted from the injured kidney; these molecules have ranged from constitutive proteins released from the damaged kidney to molecules upregulated in response to injury or non-renal tissue products that are filtered, reabsorbed or secreted by the kidney. These biomarkers are proteins that can be found in urine exosomes and free filtered urine [15] and can be utilised to predict the nature, magnitude and site of injury based on their specificity. Biomarkers such as Cystatin C, Microalbumin, N-Acetyl-beta-d glucosaminidase, Neutrophil Gelatinase-associated lipocalin (NGAL) and Interleukin 18 have been used to detect early renal impairment [16].

Cystatin C is an endogenous inhibitor of cysteine proteinases, specifically cathepsin H, B, L and Calpains [16]. Cystatin C is produced in nucleated cells and is not bound to plasma proteins [37], hence freely filtered by the glomerulus and subsequently reabsorbed and degraded in the proximal tubules of the kidney and their appearance in the urine depends on the severity of AKI [38]. Cystatin C and albumin are both reabsorbed by megalin-facilitated endocytosis in the proximal tubule; hence albuminuria may inhibit reabsorption and increase urinary excretion of Cystatin C [17–20]. The blood concentration of Cystatin C depends on individual's GFR and the link between Cystatin C and GFR is evident even in ranges where serum creatinine cannot detect changes, GFR 60–90 ml/min [21]. Urine Cystatin C appears earlier and is a more sensitive marker in AKI. Use of Cystatin C as a biomarker in renal pathology is constantly evolving and it is unclear if the value of Cystatin C is generalizable to all forms of AKI [22].

Microalbumin is an inexpensive diagnostic tool in identifying the progression of renal diseases. Microalbumin detects urinary albumin below the threshold level by urinary dipstick (30–300 mg/l) [16, 22, 23]. Gene expressing albumin is increased in AKI and is more of a sensitive marker than previously thought [23]. Microalbumin as a marker fails to specify the site of injury and does not have the ability to separate CKD from AKI as albumin degrades with storage [24].

N-Acetyl-beta-d glucosaminidase (NAG) originates from lysosomes of the cells lining the proximal convoluted tube and can be measured using coulometry assay, hence is a sensitive marker for proximal tubule injury with loss of lysosome integrity. Critically ill patients awaiting liver transplant with elevated NAG levels have shown poor outcome. Urinary NAG is inhibited by urea and tends to degrade most appreciably over time compared with other biomarkers even when stored at extremely low temperature [25].

NGAL is a novel 25-kDa protein associated with gelatinase from human neutrophil [26]. NGAL is intensively upregulated in the condition of sepsis, suggesting that the release of NGAL into the urinary system is a major response of the kidney to systemic infection [27]. Clinical studies have shown that urinary and plasma NGAL are powerful and independent predictors of AKI when compared to serum creatinine [28].

IL-18 is expressed in human peripheral blood mononuclear cells, murine splenic macrophages and non-immune cells [29]. IL-18 levels in kidney double following AKI [30].

A recent study suggests two novel biomarkers—insulin-like growth factor binding protein 7 and tissue inhibitor of Metalloproteinases 2 which are sensitive in the early detection of acute kidney injury [15], but lack supporting data to standardise its efficacy.

11.3 Pathophysiology of Renal Dysfunction in Liver Impairments

Patients with liver pathology develop portal hypertension with splanchnic vasodilatation and pooling of blood secondary to increased resistance to portal flow [31]. Pooling of blood leads to decrease in circulatory blood volume in patients with cirrhosis [32]. Increase in cardiac output maintains sufficient renal perfusion, however with decompensation of the liver in cirrhosis and an increase in severity of portal hypertension, the compensatory increase in cardiac output is

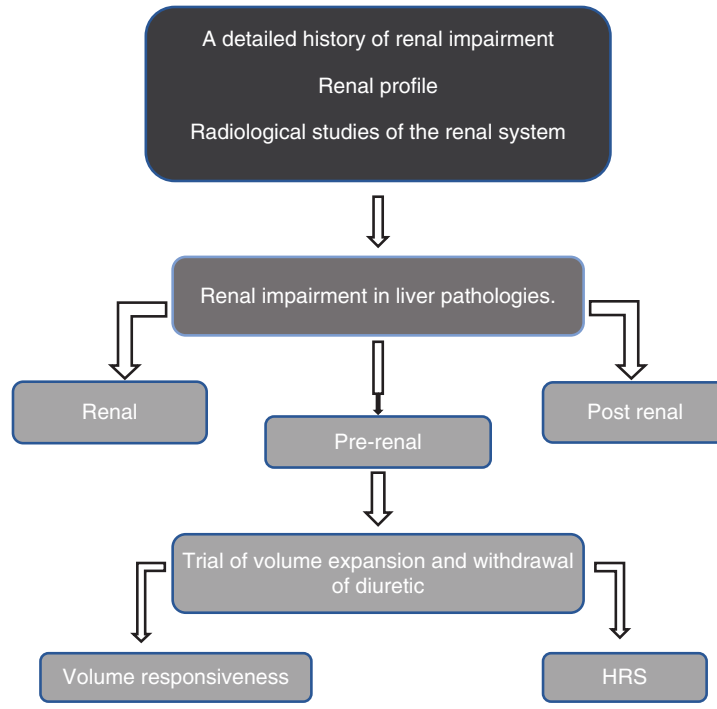
inadequate to maintain circulatory blood volume and adequate renal perfusion [32], and this causes activation of the renin-angiotensin-aldosterone system, resulting in sodium and water retention and extra-splanchnic vasoconstriction [33], causing ascites and explains the signs of adult kidney injury in liver pathologies.

11.4 Evaluating Criteria

Serum creatinine level is a variable in calculating the model for end-stage liver disease score, a recognised predictor of the three-month mortality risk and a method for allocating liver transplants [34, 35]; however, patients with compromised liver pathology show lower baseline serum creatinine as a result of liver dysfunction, drug-induced tubular secretion of creatinine, decreased conversion of creatine to creatinine as a consequence of reduced skeletal muscle mass from malnutrition and underestimation of serum creatinine in pre-existing hyperbilirubinemia in a laboratory setting [36, 37]. As mentioned earlier, Biomarker Cystatin C is the best alternative method for estimating the glomerular filtration rate (GFR), and it has proven accurate in patients with liver pathologies as it is independent of hepatic function [14, 38].

Renal impairment in liver pathologies is usually hypovolemia-induced prenatal acute kidney injury, acute tubular necrosis and hepatorenal syndrome (HRS), with HRS being most fatal [37]. Hence a simplified algorithm in diagnosing renal impairments in patients with liver pathology can be adopted (Flow Chart 11.1) [37].

Prerenal impairment accounts for 68% of acute kidney impairment in patients with liver pathologies [31] due to underlying circulatory disturbances. Pathophysiological changes in the kidney are mild in prerenal impairment but severe in HRS due to neurohormonal activation [39]. The two main causes for prerenal impairment can be differentiated by the response to volume expansion - A) hypovolemia induced impairment responds whereas - B) HRS is insensitive to volume expansion [40]. The hypovolemia induced prerenal impairment results from excessive fluid loss due to diarrhoea, sodium and water restriction, gastrointestinal haemorrhage, large-volume



Flow Chart 11.1 Algorithm in diagnosing renal impairment in liver pathologies [37]

paracentesis and excessive diuretic therapy [41]. Measures should be taken to reduce and prevent intravascular volume depletion; and hence the risk of prerenal impairment which includes attaining fluid balance, judicious use of diuretics, avoidance of Reno toxic drugs, avoidance of lactose therapy and administration of intravenous albumin [42] Albumin is superior and safer to saline for volume expansion; the recommended dose of intravenous albumin is 1gm/kg of body weight/day up to a maximum of 100gm per day [39, 41, 42]. The incidence of renal impairment was 10% when albumin was added to antibiotic compared to renal impairment with antibiotic therapy alone which was 33% [7]; further, the 3-month mortality rate was lower with Albumin and Antibiotic combination compared to Antibiotic alone [32]. Albumin is suggested in patients with serum creatinine >88.4micro mol/l or bilirubin >68.4 micro mol/l and is not necessary for patients who do not meet this criterion [43]. The American Association for the Study of Liver Diseases suggests that patients with SBP who have serum creatinine >1 mg/dl, blood urea >30 mg/dl or total bilirubin >4 mg/dl should receive 1.5 g/kg of body weight within 6 hours of detection and 1gm/kg of body weight on day 3, and the European Association for the Study of the Liver recommends that the patient should be covered up with broad-spectrum antibiotics along with albumin [1, 37, 42].

Renal impairments due to acute tubular necrosis account for 41.7% to 44.4% of cases with liver pathologies [37, 43]. Hypovolemia-induced prerenal impairment may progress into renal impairment leading to severe ischemic acute tubular necrosis [37]. In acute tubular necrosis, reabsorption of sodium is hampered leading to increased concentration of sodium in urine (>40 mEq/L) and low urine osmolality (<35 mOsm/kg) [43] and vice versa in patients with HRS. This differentiation can be challenging in patients with liver pathologies on diuretic therapy which can hamper the results. Casts are seen both in acute tubular necrosis and HRS but epithelial casts are characteristic of acute tubular necrosis [44]. Renal biopsy is confirmatory for histological diagnosis in unresolved cases [45] but carries the risk of internal bleeding due to coagulopathy and thrombocytopenia; hence it is rarely sought after in these instances [31].

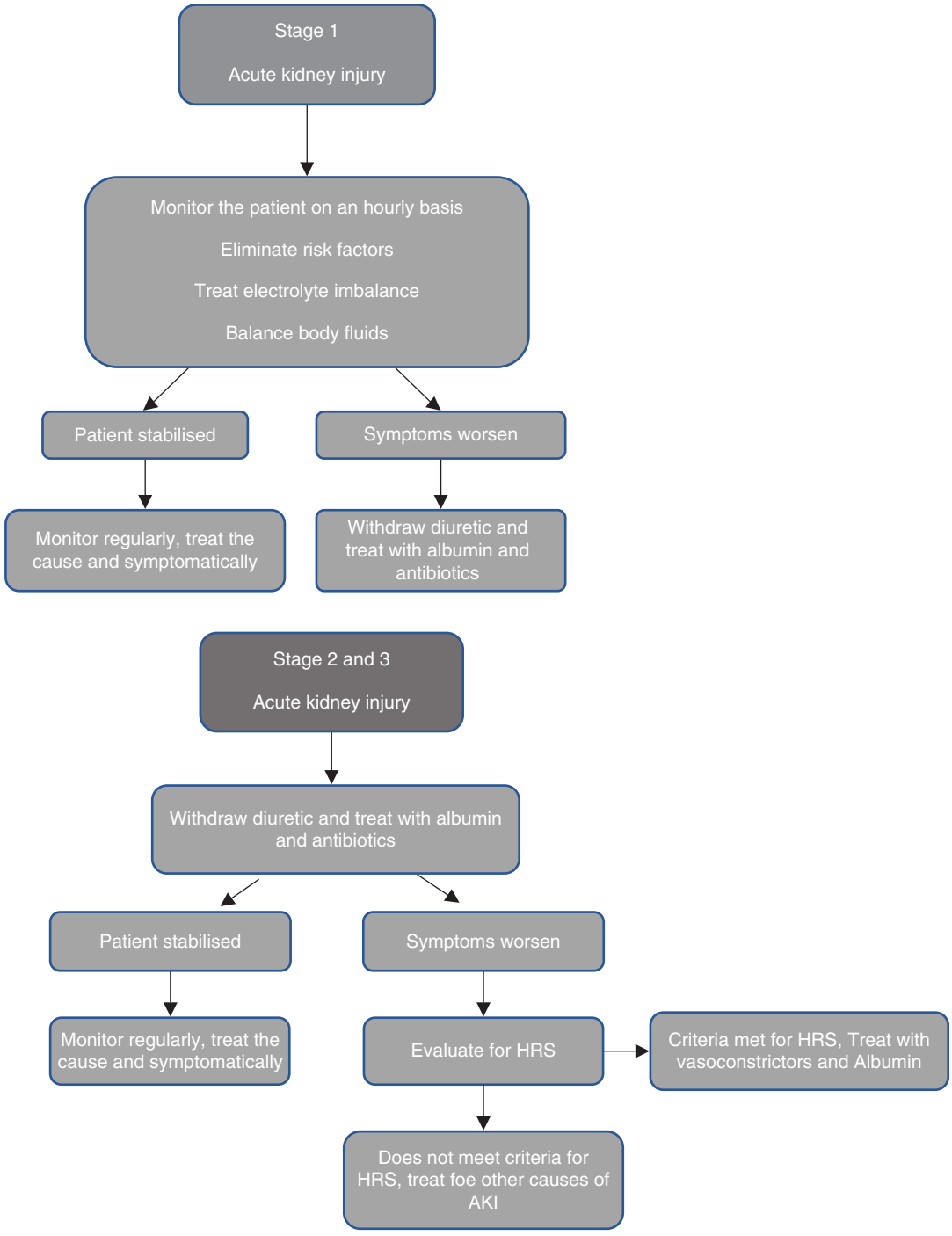
Post-renal impairment due to urinary tract obstruction is uncommon and accounts for <1% of acute kidney injury in patients with liver pathology [46]. Imaging studies are most effective in differentiating hydronephrosis from pre- to post-renal causes.

11.5 Management

As per observations made by renowned authors, we would like to propose a working party algorithm in the management of renal issues in liver pathologies (Flow Chart 11.2).

Liver transplant is the ideal treatment for patients suffering from HRS with short-term survival rate. Systemic vasoconstrictor therapy with terlipressin and noradrenaline have proven beneficial in patients awaiting a liver transplant. MARS (molecular adsorbent recirculation system) and TIPS (Transjugular intrahepatic portosystemic shunt) improve renal function during the waiting period [1]. Additionally, the surgical and the anaesthetic team is advised to take measures to reduce blood loss and avoid unnecessary transfusion. Intraoperative hypotension should be avoided as it carries a risk of postoperative acute kidney injury. Normovolemia is of utmost importance [6]. Maintenance of higher blood pressure is required in hypertensive patients. Fluids in excess should not be administered to treat oliguria and administration of low chloride solution has shown beneficial effects [1, 3, 5].

Prognosis of transplant surgeries depends on the duration of renal failure before the surgery and appears to be a negative predictor of post-transplant renal function [47]. A retrospective study of patients undergoing liver transplant in regard to aetiology of renal dysfunction showed acute tubular necrosis as a cause of acute kidney injury with worst survival at 1 and 5 years after liver transplant compared to patients with hepatorenal syndrome [48]. Patients with hepatorenal syndrome recover their renal function after liver transplantation while patients with acute tubular



Flow Chart 11.2 Algorithm for the management of renal issues in liver pathologies [14]

necrosis (intrarenal causes) do not recover their renal functions post-liver transplant and would need simultaneous liver and kidney (SLK) transplant [31, 48]. Biomarkers such as NGAL, KIM-1, IL-18, ET-1 and FABP-2 have shown promise in making an early diagnosis of acute kidney injury and predicting reversal of acute kidney injury. Studies show that biomarkers have been successful in distinguishing acute tubular necrosis from prerenal aetiology of acute kidney injury [49]. The data on the use of biomarkers among patients with liver pathologies and receiving a liver transplant is limited. Conventional parameters such as serum creatinine, GFR and urine output along with biomarkers would be ideal for evaluation in patients with liver pathologies to avoid complications in all the phases of treatment.

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