

REVIEW

Renal dysfunction in chronic liver disease

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Introduction

Acute kidney injury (AKI), chronic kidney disease, and the evaluation of numerous exogenous and endogenous measures of kidney function and injury continue to be the focus of much research in different patient populations. The key reason behind this effort is the well described independent association that small changes in kidney function are strongly linked with increased mortality, extending to those with chronic liver disease.

The accurate assessment of kidney function and injury is currently affected by the reliance on the measured concentration of serum creatinine, which is significantly affected by the degree of cirrhosis, hyperbilirubinemia, and the nutritional state of the patient. Improved understanding of the pathophysiology of kidney injury and development of more accurate measures of kidney function and injury are necessary to evoke a positive shift in kidney injury diagnosis, treatment, and outcomes. Furthermore, the number of patients with chronic liver disease and chronic kidney disease continues to rise, due to the large numbers of individuals worldwide affected by viral hepatitis, obesity, hypertension, and diabetes. Consequently, preventative health care messages must be louder and further reaching in order to reverse this trend.

Co-existing liver and kidney disease

Chronic liver disease and primary liver cancer account for 1 in 40 (2.5%) deaths worldwide, with hepatitis B the commonest cause in the developing world, followed by alcoholic liver disease and hepatitis C in the Western world [1]. Non-alcoholic steato-hepatitis and non-alcoholic fatty liver disease are increasing causes of chronic liver disease in the general population of Western countries with prevalence rates of 1–5% and 10–24%, respectively [2]. This observation is related to the

increasing incidence of obesity in the Western population and the associated metabolic syndrome, consisting of atherosclerotic coronary vascular disease, hypertension, hyperlipidemia, diabetes, and chronic kidney disease. Metabolic syndrome and non-alcoholic steato-hepatitis/non-alcoholic fatty liver disease are linked by the key feature of insulin resistance. Although initially considered to be a benign disease, non-alcoholic fatty liver disease seems to represent a spectrum of disease with benign hepatic steatosis at one end and steatotic hepatitis at the other. Approximately 30–50% of individuals with steato-hepatitis will develop fibrosis, 15% cirrhosis, and 3% liver failure [2]. Importantly, non-alcoholic fatty liver disease probably accounts for a large proportion of patients diagnosed with cryptogenic cirrhosis and at least 13% of cases of hepatocellular carcinoma [3, 4].

Obesity and metabolic syndrome are also strongly associated with the development of hypertension and diabetes, which affect 70% of the patient population with end-stage renal disease in the USA [5]. There is increasing evidence that obesity itself is an independent risk factor, albeit small, for the progression of chronic kidney disease. Some work has highlighted the association of low-birth weight and reduced nephron mass with an increased risk of obesity and the phenomenon of chronic kidney disease later in life [6]. A small proportion of obese patients will develop obesity-related glomerulosclerosis, a focal segmental glomerulonephropathy associated with proteinuria and progression to end-stage renal disease. Despite numerous obesity-related factors, the overall individual risk for the development of chronic kidney disease in the absence of diabetes and hypertension is low; nevertheless, obesity is likely to contribute increasingly to the burden of chronic disease and end-stage renal disease in the future.

Hepatitis C has long been associated with several glomerulopathies, most notably cryoglobulin- and non-cryoglobulin-associated membranoproliferative glomeru-

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lonephritis. The prevalence of cryoglobulinemia is around 50% [7], although extrarenal manifestations are often absent in the majority of these patients. Viral RNA, proteins and particles have been inconsistently isolated from kidney biopsy specimens, making it difficult to establish whether hepatitis C is causative in other forms of glomerulopathy [7]. In seropositive hepatitis C populations, hepatitis C infection has been reported to be associated with focal segmental glomerulosclerosis, membranous nephropathy with or without nephrotic range proteinuria, IgA nephropathy, and proliferative glomerulonephritides [7].

Hepatitis C has also been associated with an increased risk of albuminuria, progression of diabetic nephropathy, and progression of chronic kidney disease to endstage renal disease [7]. The worldwide prevalence of hepatitis C among patients on hemodialysis is high, ranging from 4–60% [8]. This rate is on the decline, due to stricter adherence to universal infection control measures, with or without isolation, which have been implemented to a greater extent in the USA and in European countries. Risk factors for infection include the length of time of hemodialysis, the number of blood transfusions for renal anemia, and nosocomial transmission [8]. These patients often develop significant chronic liver disease, which adds an additional mortality burden while on hemodialysis. The presence of hepatitis C infection also has a negative effect on patient and renal survival following kidney transplantation [9].

Hepatitis B virus (HBV) is also associated with renal disease, but it is mostly encountered in children from endemic areas. The incidence of HBV-associated renal disease in Europe is low due to the lower prevalence of chronic HBV infection. HBV is associated with a number of renal diseases, including polyarteritis nodosa, membranous and membranoproliferative glomerulonephritis. Most patients have a history of active HBV but are asymptomatic with positive surface antigen and core antibody; in those with membranous nephropathy, e antigen is positive. The pathogenic role of HBV has been demonstrated by the presence of antigen-antibody complexes in kidney biopsy specimens and in particular deposition of HBV e antigen in membranous glomerulonephritis [9, 10].

Autosomal-dominant polycystic kidney disease is associated with polycystic liver disease in up to 75–90% of cases [11]. There are a number of risk factors for liver involvement, including female gender, age, and degree of renal dysfunction [11]. A distinct form of autosomal dominant isolated liver cystic disease was recognized in the mid-1980s. Most patients are asymptomatic, but when symptoms do occur, they are often related to cyst size and number. Symptoms include abdominal pain, nausea, early satiety, breathlessness, ascites, and biliary

obstruction; all can precipitate to result in a significantly malnourished state related to gastric compression. The medical complications seen with autosomal-dominant polycystic kidney disease including intracranial aneurysms, and valvular heart lesion are also encountered in those with cystic liver disease. Therapies involve cyst rupture or sclerosis and liver transplantation if symptoms persist [11].

Familial amyloidosis polyneuropathy is an autosomal dominant disease caused by a point mutation in the gene coding for transthyretin, also called pre-albumin. The amino acid, valine, is replaced by methionine. The mutated protein produced by the liver forms a beta-pleated sheet structure, which accumulates in tissues, particularly nerves and the kidney, resulting in amyloid deposition. Familial amyloidosis polyneuropathy appears in the second decade of life leading to death within 8–13 years. Orthotopic liver transplantation (OLT) represents the best form of treatment, when performed early in the course of the disease, by halting the progression of the peripheral neuropathy and chronic kidney disease. The kidneys are frequently affected and this is recognized by proteinuria and declining kidney function. OLT reduces serum pre-albumin levels but the amount deposited in the kidney remains the same post transplantation. OLT should not be contemplated for patients with severe proteinuria or advanced chronic kidney disease [12].

Serum creatinine concentration for the assessment of kidney function in chronic liver disease

Kidney function is evaluated by assessing the glomerular filtration rate (GFR), which can be determined by measuring the volume of plasma that can be completely cleared of a given substance over a defined unit of time. The ideal marker for GFR determination is often quoted as having the following characteristics: Appears constantly in the plasma, can be freely filtered at the glomerulus, and does not undergo tubular reabsorption, secretion or extra renal elimination [13]. For many years now, the assessment of GFR has relied on the measurement of the concentration of serum creatinine, which is associated with many problems. Creatinine is a product of the metabolism of creatine, which is produced in the liver from three amino acids, methionine, arginine, and glycine, and stored in muscle to be used as a source of energy once phosphorylated. Creatinine does not appear in the plasma at a constant rate; it is secreted in the tubule and can undergo extrarenal elimination, thought to involve creatinase in the gut. Serum creatinine concentration displays an exponential relationship with GFR, rendering it specific, but not a sensitive measure of GFR. The creatinine pool is affected by gender, age, ethnicity, nutritional state, protein intake and importantly liver disease [14].

Table 1. Acute Kidney Injury Network (AKIN) acute kidney injury staging criteria [19]

	Serum creatinine ($\mu\text{mol/l}$)	Urine output (ml/kg/h)
Stage 1	> 26.4 $\mu\text{mol/l}$ > 150–200% change from baseline	< 0.5 for > 6 hours
Stage 2	> 200–300% change from baseline	< 0.5 for > 12 hours
Stage 3	> 300% change from baseline OR > 44 $\mu\text{mol/l}$ change from 354 $\mu\text{mol/l}$	< 0.3 for 24 hours or anuria for 12 hour

In chronic liver disease, the reduction in the serum creatinine pool is due to a 50% decrease in hepatic production of creatine; increases in the volume of distribution due to the accumulation of extracellular fluid, edema, and ascites; malnutrition and loss of muscle mass, which is related to repeated episodes of sepsis and large volume ascites affecting satiety [15]. Ultimately, patients with chronic liver disease have a significantly lower baseline serum creatinine concentration than the general population (35–75 $\mu\text{mol/l}$).

Analytical methods for measuring the serum creatinine concentration have been associated with problems, particularly related to interference from chromatogens, like unconjugated and conjugated bilirubin. The degree of error can be up to 57% [16], but modern auto-analyzers using the endpoint Jaffe method have overcome such interference. Nevertheless, interpreting serum creatinine results in the context of hyperbilirubinemia still requires a degree of caution despite these adjustments. In particular, patients with chronic liver disease display smaller and delayed (up to 48–72 hours) changes in serum creatinine for a given change in GFR, thus impairing the recognition and underestimating the degree of change in GFR [17, 18].

Acute kidney injury network criteria for staging acute kidney injury

In 2005 the Acute Kidney Injury Network (AKIN) was formed, comprising a group of experts in nephrology and critical care who sought to revise the Acute Dialysis Quality Initiative (ADQI) group's original work from the previous year, which resulted in the development of the RIFLE (Risk, Injury, Failure, Loss, End-stage renal disease) criteria. A unifying term for acute renal failure, acute kidney injury (AKI), which encompassed all causes of acute renal failure, was established along with specific defining criteria and a classification based on severity of disease (Table 1) [19]. Patients are assigned to the worse category within the RIFLE criteria, defined by changes in serum creatinine concentration or GFR from baseline or urine output per unit body weight per hour over a defined period of time. The AKIN refined the RIFLE criteria to reflect data demonstrating the finding that small changes in serum creatinine had a significant

impact on patient mortality [19]. The 'Risk' category for AKI was broadened to include changes in serum creatinine up to 26.4 $\mu\text{mol/l}$ within a 48 hour time frame.

The stages of AKI in this revised classification were numbered 1, 2, and 3 rather than being named 'Risk', 'Injury' and 'Failure'. The category of 'Failure' becomes Stage 3 AKI and incorporates anyone commenced on renal replacement therapy regardless of serum creatinine or rate of urine output (Table 1). More subtle changes include the exclusion of urinary tract obstruction and easily reversible causes of transient change in serum creatinine or urine output, such as volume depletion. Importantly, the inappropriate use of estimated GFR in the acute setting was addressed by removing the GFR criteria altogether.

Despite these revisions, there remain problems with both staging systems and these have been the focus of much discussion in the literature. Direct comparison of the two staging systems has been performed and, as expected, AKI is more sensitive than RIFLE, but this difference only affects around 1% of patients [20]. The choice of baseline creatinine for studies has been highlighted to be of critical importance, markedly affecting the incidence of AKI. Several retrospective studies have calculated the baseline serum creatinine by manipulating the Modification of Diet in Renal Disease (MDRD) equation for estimating GFR assuming that patients had an estimated GFR of 75–100 ml/min/1.73 m^2 [21].

It is also evident that slow but persistent changes in serum creatinine over a longer time course than 48 hours can be missed and sometimes impossible to classify. Urine output too is associated with a number of confounding factors, in particular diuretic use, which affects interpretation. Extracorporeal therapies like continuous veno-venous hemofiltration (CVVH), a form of renal replacement therapy used in the critically ill, are often initiated for non-renal reasons, for example, hyperlactatemia or hyperammonemia which are frequently encountered in acute liver failure. More prospective studies with more attention to detail are required to improve the AKI criteria, in particular ensuring that baseline creatinine is measured and not estimated, and providing greater description of the indications for and timing of renal replacement therapy [21].

Despite these limitations, AKI staging does address the phenomenon of the lower baseline serum creatinine seen in patients with chronic liver disease. The broadening of stage 1 is beneficial in the setting of chronic liver disease, because we know that changes in serum creatinine will be smaller and delayed. Urine output, although riddled with numerous confounders, not least diuretic therapy and the difficulties of the un-catheterized patient, can still yield important information if measured accurately on the ward in conjunction with daily weight assessment to provide an assessment of overall fluid balance. Diuretic therapy response varies in patients with decompensated chronic liver disease and has a significant impact on survival outcomes; those that are less responsive tend to experience complications of hyponatremia and AKI with greater frequency [22].

Acute kidney injury pathogenesis

AKI is more than just an isolated ischemic injury. The ischemic insult stimulates an inflammatory response with increased expression of adhesion molecules attracting leukocytes. Intra-luminal debris from tubular cells damaged by ischemia impairs reabsorption of sodium, which polymerizes Tamm-Horsfall proteins forming a gellike substance that occludes the tubule causing increased backpressure and leaking. Endothelial injury affects tonicity of the afferent arteriole, activates the clotting cascade and releases endothelin which causes further vasoconstriction thus compromising the micro-circulation. An injurious reperfusion period can then follow, due to the depletion of ATP, which releases proteases with oxidative substances that further damage the cytoskeleton of the tubules. This pathogenesis perhaps explains the unresponsive nature of this condition when identified late in its clinical course [23].

Patients with chronic liver disease are more susceptible to acute kidney injury

Advanced chronic liver disease is responsible for a significant number of physiological changes that affect the circulation and kidney perfusion. Cirrhosis results in the accumulation of vasodilatory mediators, in particular nitric oxide (NO), which specifically vasodilates the splanchnic circulation reducing the effective circulating blood volume and mean arterial pressure. Hypoperfusion of the kidneys leads to a reduction in the sodium concentration of tubular fluid reaching the distal tubule stimulating the macula densa, to release renin, thus activating the renin-angiotensin-aldosterone (RAA) axis. Glomerular filtration pressure is dependent on afferent and efferent vascular tone. Chronic disease states often seen in association with chronic liver disease, such as atherosclerotic vascular disease, hypertension and chronic kidney disease, affect the responsiveness of the

afferent arteriole, thus shifting the auto regulation curve to the right. Consequently, adjustments in vascular tone of the afferent arteriole are smaller, reducing the ability to increase glomerular perfusion during episodes of hypotension. This, coupled with increased levels of angiotensin II, a product of RAA activation, causes vasoconstriction of blood vessels, in particular the afferent and efferent arteriolar renal vessels. Aldosterone acts on the distal tubule increasing the retention of salt and water. Consequently, there is decreased renal perfusion coupled with avid retention of fluid which increases abdominal ascites accumulation causing abdominal distension and elevation of the intra-abdominal pressure, which further compromises renal perfusion and propagates the vicious cycle.

Furthermore, in advanced chronic liver disease, an intrinsic defect in cardiac performance during exercise has been demonstrated and termed cirrhotic cardiomyopathy [24]. This syndrome encompasses a number of myocardial and electrophysiological changes that occur in cirrhosis and lead to attenuated cardiac function, particularly when exposed to stressful events like sepsis. The features of this condition include: A hyperdynamic myocardium with an increase in baseline cardiac output; attenuated systolic contraction and diastolic relaxation; electrophysiological abnormalities; and unresponsiveness to beta-adrenergic stimulation. Portal hypertension leads to shunting of blood away from the liver, thus reducing portal venous blood flow in the liver. This is thought to affect sodium and water excretion by the kidney via the postulated hepatorenal reflex mechanism whereby the release of adenosine is believed to act as a neurotransmitter stimulating sympathetic nerves supplying the renal vasculature causing vasoconstriction and oliguria. These mechanisms, attempting to maintain the effective circulating blood volume coupled with cirrhotic cardiomyopathy and reduced venous return from raised intra-abdominal pressure, render the circulation helpless in the pursuit of renal perfusion preservation.

Stress events like sepsis, gastrointestinal bleeding, and the use of diuretics, vasodilators or nephrotoxic drugs, which cause renal vasoconstriction, like non-steroidal anti-inflammatory drugs and radiographic contrast agents, can tip this fine balance between circulatory performance and adequacy of renal perfusion resulting in renal ischemia and its associated multi-faceted sequelae. Subsequently, AKI ensues, unless timely interventions targeted at reversing these physiological changes are initiated.

Hepatorenal syndrome

Hepatorenal syndrome was first described in 1939 in patients undergoing biliary surgery [25] and today it remains a clinical entity assigned specific defining criteria. It is divided into two types based on specific

clinical and time course features: Hepatorenal syndrome type 1 is a form of AKI, similar to that encountered in sepsis, which necessitates the exclusion of reversible factors, treatment of hypovolemia, nephrotoxic medications, and a period of resuscitation to assess response to diuretic withdrawal and volume expansion; hepatorenal syndrome type 2 is a form of chronic kidney disease related to diuretic resistant ascites and its management, which typically evolves over months, perhaps displaying features in common with the ischemic nephropathy encountered in severe cardiac failure.

The classifying criteria for defining hepatorenal syndrome are under constant review and scrutiny, in a similar fashion to the AKI and chronic kidney disease classifications. Problems persist with all three classifications largely due to the reliance on serum creatinine concentration. As already discussed, serum creatinine performs poorly as a marker of kidney function in many different cross-sectional patient populations, not least those with chronic liver disease. The subgroup classification of types 1 and 2 hepatorenal syndrome have surprisingly not yet embraced the AKI and chronic kidney disease staging criteria, respectively. The definition of hepatorenal syndrome is centered on the use of an arbitrary level for serum creatinine concentration of 130 $\mu\text{mol/l}$, which does not account for gender, ethnicity, age or for the lower baseline serum creatinine concentrations seen in patients with chronic liver disease. Consequently, patients with chronic liver disease will lose more than 50% of residual renal function before a diagnosis of hepatorenal syndrome can be entertained. Despite the flaws associated with the AKI classification, which are explained below, it seems to have some clear advantages, with at least the recognition that individual baseline creatinine concentration is a much better starting reference point.

Acute kidney injury and chronic liver disease

The incidence of AKI in hospitalized patients with chronic liver disease is around 20% [26]. There are three main causes of AKI in chronic liver disease: Volume-responsive pre-renal failure, volume unresponsive pre-renal failure with tubular dysfunction and acute tubular necrosis (ATN), and hepatorenal syndrome type 1, with prevalence rates of 68%, 33%, and 25% respectively [27]. Of note, these three clinical scenarios should only be considered once acute kidney parenchymal disease and obstructive uropathy have been excluded. This exclusion can be achieved by performing an ultrasound of the kidneys, dipstick urine analysis assessing the presence of hematuria and proteinuria, and appropriate same day serological testing for antibodies against the glomerular basement membrane and for vasculitis if other clinical features suggest such diagnoses are possible. Additionally,

the thorough evaluation and pursuit of occult sepsis is crucial with the early introduction of appropriate broad spectrum antibiotics often proving to be vital. Approximately 20% of patients with decompensated chronic liver disease will have spontaneous bacterial peritonitis [28]. The diagnostic ascitic tap is an invaluable test to rule out this condition, which can be a precipitant of AKI in about 30% of cases. Hypotension in patients with chronic liver disease should prompt meticulous assessment for gastrointestinal bleeding, with variceal hemorrhage an easily treatable cause. Again a detailed search for sepsis and thorough interrogation of the drug chart to stop medications that compromise blood pressure or could in anyway be nephrotoxic is always warranted. Established beneficial treatments include fluid resuscitation, vasopressor analog use, albumin infusions, and the omission of nephrotoxic drugs [29, 30].

Biomarkers of AKI

Traditional blood markers of kidney injury, such as serum creatinine, urea and urine markers, fractional excretion of sodium, and casts on microscopy, are insensitive and non-specific for the diagnosis of AKI. Novel kidney injury biomarkers in both serum and urine have been discovered using genomic and proteomic technology and they are demonstrating superiority in detecting kidney injury before changes in serum creatinine occur. These markers have been assessed primarily after a known specific insult in both adult and pediatric populations, such as cardiopulmonary bypass for cardiac surgery, kidney transplantation, contrast administration, or sepsis and other pathologies encountered in intensive care populations. Subsequently, numerous systematic reviews have been undertaken to assess the validity of these studies. Currently the literature supports the concept of a panel of biomarkers for detecting AKI, including two serum and three urine biomarkers: Serum neutrophil gelatinase lipocalin (sNGAL) and cystatin C, and urinary kidney injury molecule 1 (KIM-1), interleukin-18 (IL-18) and NGAL (uNGAL) [31].

Table 2 illustrates the major studies for each of these biomarkers in the setting of AKI with as many as 31 studies demonstrating broadly similar outcomes [32–35]. However, it is difficult to translate these studies to the wider patient population or indeed specifically to those with chronic liver disease. Many of the 31 studies excluded patients with chronic kidney disease, which affects 30% of patients admitted to intensive care and these patient have an increased risk of AKI [36]. Two large multicenter studies are underway evaluating these biomarkers and our research group at King's College Hospital is evaluating the use of these biomarkers in patients with chronic liver disease. Some work has

Table 2. Summary of studies evaluating the role of novel blood and urine kidney injury biomarkers

Study N [Ref]	Biomarker	Biomarker profile	Precipitants and Confounders	Clinical setting	Cut-off	AKI definition	Sensitivity	Specificity	AUC
Mishra <i>et al.</i> N = 71 [32]	Serum NGAL	25 kDa protein bound to gelatinase from neutrophils. Expressed in low levels in normal tissues, kidney, lung and colon. Increased level with damage to epithelial cells.	Sepsis Ischemia Nephrotoxins CKD UTI and systemic sepsis	Cardiac surgery Children 2 h post cardiac surgery	50 µg/l	> 50 % rise from baseline serum creatinine	0.7	0.94	NR
Herget-Rosenthal <i>et al.</i> N = 85 [33]	Serum cystatin C	13 kDa protein from cysteine protease inhibitor family produced by all nucleated cells. Measure of GFR as freely filtered at proximal tubule. Unaffected by gender, age, ethnicity or muscle mass	Changes in GFR Hypertthyroidism, Corticosteroids	ICU patients, 1 day prior to clinical AKI surgery	> 50% rise from baseline serum creatinine	> 50 % rise	0.82	0.95	0.97
Mishra <i>et al.</i> N = 71 [32]	Urine NGAL	25 kDa protein bound to gelatinase from neutrophils	Ischemia Nephrotoxins UTI CKD Systemic sepsis	Cardiac surgery Children 2 h post-surgery	50 µg/l >	50 % rise	1.0	0.98	0.99
Parikh <i>et al.</i> N = 71 [34]	Urine IL-18	Pro-inflammatory cytokine regulation of T-helper cells. Induced and cleaved in proximal tubule after AKI	Ischemia (Not raised in CKD, UTI or pre-renal AKI)	Cardiac surgery 12 h post-surgery	50 pg/ml	> 50 % rise	0.5	0.94	0.73
Han <i>et al.</i> N = 40 [35]	Urine KIM-1	Type 1 transmembrane protein not detected in normal kidney. Highly expressed in proximal tubule after AKI	Ischemia Nephrotoxins (Not raised in CKD, UTI or pre-renal AKI)	Cardiac surgery 12 h post-surgery	7 ng/mg/ serum creatinine	> 50 % rise	0.74	0.9	

CKD: chronic kidney disease; AKI: acute kidney injury; UTI: urinary tract infection; NGAL: neutrophil gelatinase lipocalin; IL: interleukin; KIM: kidney injury molecule; GFR: glomerular filtration rate; ICU: intensive care unit; AUC: area under the curve; NR: not reported

already demonstrated the usefulness of NGAL post-orthotopic liver transplantation to predict AKI [37]. Whether this will translate to improved kidney injury outcomes remains to be demonstrated, but it is intuitive to believe that an earlier diagnosis would be associated with improved outcomes, much like troponin in patients with acute coronary syndromes.

Kidney Disease Outcome Quality Initiative criteria for staging chronic kidney disease

The definition and classification of chronic kidney disease was established in 2002 by the Kidney Disease Outcome Quality Initiative (KDOQI) group in the USA [38]. There were numerous factors prompting the group to establish clarity for the definition of chronic renal failure, which was already an extensive health care burden. With up to 100,000 new patient cases per year reaching end-stage renal disease, something had to be done to try and detect kidney disease earlier.

The Cockcroft-Gault equation [39] has been widely used to detect renal dysfunction, adjust drug dosing for drugs excreted by the kidneys, and assess the effectiveness of treatments for progressive kidney disease. It has also been used to evaluate patient's health insurance claims and assign them points, which would prioritize them on the waiting list for a kidney transplant, similar to the way in which the model for end-stage liver disease (MELD) is now used for liver transplantation. However, there is established evidence that the degree of chronic kidney disease and not just end-stage renal disease is an important risk factor for cardiovascular disease and AKI [40]. Moreover, new treatments, in particular angiotensin converting enzyme (ACE) inhibitors, have been shown to slow the progression of chronic kidney disease by reducing the damaging effects of the proteinuria and raised intra-glomerular pressure encountered with hypertension [41].

It was recognized that the Cockcroft-Gault equation relied on the serum creatinine concentration, which is notably affected by age, gender, and ethnicity. The MDRD study in 1999 [42] was undertaken to assess patients with established chronic kidney disease and the effect that dietary protein restriction and strict blood pressure control had on preventing the progression of chronic kidney disease. In this study, a baseline period was used to collect demographic data, and to perform timed urine creatinine clearance and I-iothalamate radionuclide GFR measurement on the enrolled patients. The investigators formulated seven equations using a number of combinations including demographic, serum, and urine variables, and incorporating gender, age, ethnicity and serum creatinine. In version 7 of the equation, the additional serum variables of albumin and urea were used in place of the urine variable. This equation

Table 3. Kidney Disease Outcome Quality Initiative (KDOQI) staging criteria for chronic kidney disease [38]

Stage	Estimated GFR (ml/min/1.73 m ²)
1	>90
2	89–60
3A	59–45
3B	44–30
4	29–15
5	<15

provided a validated estimated measure of GFR in patients with chronic kidney disease and from this the staging classification was developed. Importance was leveled at establishing a staging system, because adverse outcomes in chronic kidney disease are linked to the degree of chronic kidney disease and future loss of kidney function. Additionally, chronic kidney disease was understood to be a progressive disease and consequently the staging classification could be adapted to give emphasis to treatment goals to slow progression. The term 'chronic renal failure' was redefined in a similar fashion to 'acute renal failure' and newly termed 'chronic kidney disease'. It was then possible to classify chronic kidney disease into five stages for patients with renal disease and the old classification of mild, moderate, or severe chronic renal failure was abandoned [42].

These five stages have been under review given the epidemiological data demonstrating a significant difference in patient numbers in chronic kidney disease stages 3 and 4 [43]. This difference has been attributed to the significant increase in cardiovascular associated mortality in late chronic kidney disease stage 3 (estimated GFR 30–45 ml/min/1.73 m²). Consequently chronic kidney disease stage 3 is now subdivided into 3A (estimated GFR 59–45 ml/min/1.73 m²) and 3B (estimated GFR 44–30 ml/min/1.73 m²) (Table 3).

There are problems with this staging system, which relate to the original study population and its application to the wider community. An MDRD equation calculation for an estimated GFR above 60 ml/min/1.73 m² has been shown to be inaccurate, underestimating GFR in patients with normal kidney function [43]. The original study population had a mean GFR of 40 ml/min/1.73 m² and included only a few Asian, elderly, and diabetic patients. There are debates about the critical level of estimated GFR for chronic kidney disease in terms of cardiovascular risk, currently deemed to be around 60 ml/min/1.73 m², and the relation of this level to the age and ethnicity of the patient, and the chronicity of the condition. All have a bearing on the implications of labeling patients as having chronic kidney disease and the treatments, if necessary, to address cardiovascular risk and disease progression [26, 44].

Assessment of chronic kidney disease in patients with chronic liver disease

The reliance on serum creatinine concentration is pivotal to the problems with estimated GFR and the gulf between the original MDRD study population and patients with chronic liver disease. This has been highlighted by a meta-analysis that reviewed creatinine clearance and estimated GFR and demonstrated a mean overestimation of 18.7 ml/min/1.73 m² [45]. Timed urine creatinine clearance also performs poorly, significantly overestimating GFR in patients with chronic liver disease, particularly at the lower range of GFR measurements [46]. So why use estimated GFR if it performs so poorly? Despite its drawbacks, it is the most cost-effective method of assessing kidney function in the chronic setting and provides greater clarity on the extent of disease if one considers the overestimation and uses the extended version, which incorporates albumin and urea. Serial measures tend to provide greater information than measures in isolation.

Future directions

Patients with chronic liver disease and chronic kidney disease warrant better evaluation of residual kidney function than is currently offered. Cystatin C has been shown to be a better marker of GFR in patients with chronic liver disease both before and in the immediate period after transplantation [47, 48]. Equations have been developed to give better accuracy to the estimation of GFR using measured cystatin C concentration [48]. However, these equations have been evaluated in small study populations using different gold standard measures of GFR compared to the creatinine based equations. Cystatin C equations have, though, been shown to perform better, with greater accuracy in predicting GFR, in cirrhotic and post-transplant patients using either the Hoek or Larsson equations [47, 48].

uNGAL has also been shown to be significantly elevated in proteinuric patients with membranous nephropathy or membranoproliferative glomerulonephritis with chronic kidney disease when compared to a control group with normal kidney function and no proteinuria [30]. sNGAL has been shown to be significantly elevated in patients with chronic kidney disease or kidney transplant compared to controls [37]. It also appears to increase with chronic kidney disease stage and severity suggesting a role in tracking progression of chronic kidney disease [49]. However, increased sNGAL in the setting of chronic kidney disease is poorly understood; the suggested hypothesis links proteinuria and the apoptotic effect this has on proximal tubular cells. Further evaluation is required, but these biomarkers have shown promise as markers of chronic kidney disease progression.

Ultimately, patients with chronic liver disease and chronic kidney disease need residual kidney function to be

evaluated using gold standard measures of GFR, probably at 3–6 monthly intervals. The evaluation of cystatin C and serum NGAL in the interim period to monitor progression and perhaps detect acute changes could lead to improved outcomes for this group of patients.

Orthotopic liver transplantation

OLT offers the best long-term outcome for patients with advanced liver disease. The method for allocating liver grafts to patients with advanced liver disease relies on scoring systems, like MELD, which helps to predict survival without transplantation. The MELD score incorporates serum creatinine and this carries a high integer weighting which may have a significant impact on the composite score. Consequently, there are two significant problems associated with MELD. First, the prognostication of chronic liver disease itself is somewhat blurred by the emphasis apportioned to kidney dysfunction. Second, the reliance on serum creatinine potentially underestimates prognosis with respect to renal outcomes and overestimates true prognosis with respect to liver outcomes. To address this imbalance, MELD should perhaps incorporate a measure of GFR, either by using a gold standard measure of GFR or cystatin C, to more accurately represent residual kidney function. In recognition of these problems, MELD has been adapted to form the UKELD score, which incorporates the serum sodium concentration, with downward adjustment of the integer weighting for serum creatinine [51]. Consequently, in the UK population, UKELD is a better predictor of survival following listing for liver transplantation [50].

The incidence of chronic kidney disease among liver recipients is high, around 27%, and up to 10% reach end-stage, requiring renal replacement therapy within 10 years [51]. There are a number of independent risk factors in the pre-transplant period that are associated with chronic kidney disease post-transplantation. These include chronic kidney disease stage, age, gender, ethnicity, and the presence of hypertension, diabetes and hepatitis C prior to transplantation [52]. Importantly, chronic kidney disease post-liver transplantation is associated with a four-fold increase in mortality [53]. Strategies have focused on tailoring immunosuppression regimens to improve long-term renal outcome, in particular, reducing the nephrotoxic calcineurin inhibitor burden, which is often possible due to the immunotolerant properties of the liver. The ReSpECT study compared standard tacrolimus dosing and steroids; low-dose tacrolimus plus steroids; and delayed introduction and low-dose tacrolimus plus steroids plus mycophenolate mofetil. The authors demonstrated reduced nephrotoxicity in the delayed, low dose tacrolimus group [54]. Daclizumab, a monoclonal antibody, was used to

provide immunosuppressive cover during the delayed period before the introduction of tacrolimus. The study had a few limitations, however, namely the use of estimated GFR calculated with the Cockcroft-Gault formula, and the fact that a significant number of patients were withdrawn from the high dose group. However, it importantly demonstrated that the tailoring of an immunosuppressive regimen can have a significant impact on nephrotoxicity without detrimental effects on graft function or patient survival [54].

There has also been an increasing trend toward combined liver-kidney transplant if patients have AKI or chronic kidney disease prior to transplantation. However, appropriate allocation of these organs to patients that are most suitable for either OLT alone or combined liver-kidney transplant has created a major dilemma as no single reliable factor has been shown to be predictive of renal recovery or progression of chronic kidney disease after successful OLT.

Pre-emptive kidney transplantation for patients with isolated kidney disease is considered if dialysis is predicted to start within 6 months, which is typically associated with a GFR less than 15 ml/min. Combined liver-kidney transplant is currently indicated for those with combined kidney and liver disease on hemodialysis with viral, polycystic, or primary oxaluria as etiologies. In this scenario, there is a drive to transplant these patients earlier when their liver disease is not so advanced, e.g., Child Pugh score A or B, because of worse outcomes associated with Child Pugh C cirrhosis. Extensive polycystic liver and kidney disease where the mass of cysts exceeds 20 kg causing malnutrition and cachexia is seen as an indication for transplantation, even though liver synthetic function is often well preserved. Primary oxaluria type 1 is an enzymatic defect resulting in renal calculi and extensive extrarenal oxalate deposits. Combined liver-kidney transplant is recommended early in the course of this disease to prevent extra renal manifestations, in a similar way to familial amyloidosis polyneuropathy [55].

End-stage liver and kidney disease is a recognized indication for combined liver-kidney transplant and was first performed in 1983. Retrospective studies have, however, evaluated factors that may help predict the reversibility of kidney dysfunction in patients with end-stage liver disease. There is some evidence that chronic kidney disease (defined as renal dysfunction for more than 12 weeks), pre-transplant serum creatinine > 160 $\mu\text{mol/l}$, and diabetes, are predictors of poor post-transplant kidney function with estimated GFR of less than 20 ml/min/1.73 m² [52]. There is a paucity of research in this field. The implementation and use of improved measures of residual kidney function and the incorporation of these into MELD would help to more precisely prioritize

patients and ensure organ allocation is appropriate for liver, kidney, and combined transplant procedures.

Conclusion

Chronic liver disease is associated with primary and secondary kidney disease and impacts markedly on survival. The evaluation of kidney function and injury relies on the measurement of the concentration of serum creatinine, which is affected by the degree of liver disease and the analytical method employed. The integral role of creatinine concentration in the different classifications of AKI, chronic kidney disease and the survival predictive score, MELD, for chronic liver disease, confers large inaccuracies across this population, but currently offers the most cost-effective measure available. Hepatologists should perhaps use exogenous measures of kidney function and biomarkers, like cystatin C and the cystatin C-based equation for estimated GFR, more frequently, as these have been shown to be superior to creatinine. Improved assessment of the degree of residual kidney function may assist clinical decisions regarding risk of AKI, drug therapy in chronic liver disease, the tailoring of post-liver transplant immunosuppression regimens, and the allocation of organs for combined liver and kidney transplantation. Kidney injury biomarkers need further evaluation in the chronic liver disease population, but they seem likely to continue to perform well. Earlier diagnosis and implementation of currently established beneficial therapies seems to be pivotal in potentially reducing the severity of kidney injury and increasing survival outcomes; whether this will be realized remains to be seen.

Abbreviations

ACE = angiotensin converting enzyme, ADQI = Acute Dialysis Quality Initiative, AKI = acute kidney injury, AKIN = Acute Kidney Injury Network, ATN = acute tubular necrosis, AUC = area under the curve, CKD = chronic kidney disease, CVVH = continuous veno-venous hemofiltration, GFR = glomerular filtration rate, HBV = hepatitis B virus, ICU = intensive care unit, IL = interleukin, KIM-1 = urinary kidney injury molecule-1, KDOQI = Kidney Disease Outcome Quality Initiative, MDRD = Modification of Diet in Renal Disease, MELD = model for end stage liver disease, NGAL = neutrophil gelatinase lipocalin, NO = nitric oxide, OLT = orthotopic liver transplantation, RAA = renin-angiotensin-aldosterone, RIFLE = Risk, Injury, Failure, Loss, End-stage renal disease, sNGAL = serum neutrophil gelatinase lipocalin, UTI: urinary tract infection.

Competing interests

The authors declare that they have no competing interests.

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