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TOPIC HIGHLIGHT

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Difficulties in diagnosing acute kidney injury post liver transplantation using serum creatinine based diagnostic criteria

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Abstract

Renal function in patients with advanced cirrhosis is an important prognostic factor for survival both prior to and following liver transplantation. The importance of renal function is reflected by the introduction of the model for end stage liver disease (MELD) score, which includes serum creatinine. The MELD score has been shown to predict the short term risk of death for transplant wait listed patients and is currently used by many countries to allocate liver transplants on the basis of severity of underlying illness. Changes in serum creatinine are also used to stage acute kidney injury. However prior to liver transplantation the serum creatinine typically over estimates underlying renal function, particularly when a colorimetric Jaffe based assay is used, and paradoxically then under estimates renal function post liver transplantation, particularly when immunophyllins are started early as part of transplant immunosuppression. As acute kidney injury is defined by changes in serum creatinine, this potentially leads to over estimation of the incidence and severity of acute kidney injury in the immediate post-operative period.

Key words: Serum creatinine; Acute kidney injury; Liver transplantation

Core tip: Acute kidney injury is defined and severity graded based on changes in serum creatinine. Increasing concentrations of bilirubin interefere with laboratory determination of creatinine and reduce creatinine estimations. Post transplantation serum creatinine increases due to a combination of fall bilirubin and the loading doses of calcineurin inhibitor immunosupressants. This combination leads to an over estimation of the lesser grades of acute kidney injury post liver transplantation.

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WHY IS PERI-OPERATIVE RENAL DYSFUNCTION IMPORTANT IN LIVER TRANSPLANT RECIPIENTS?

Renal dysfunction is strongly associated with increased risk of mortality in patients with advanced chronic liver disease both awaiting liver transplantation (LT) and also peri-operatively[1-4]. Indeed renal function as determined by estimation of the serum creatinine concentration has been included in the model for end stage liver disease (MELD) score, which predicts the likelihood of death within 3 mo for patients wait listed for liver transplanta-

Table 1 Definitions of acute kidney injury using changes in serum creatinine between the Risk Injury Failure EndStage[7], Akute Kidney Injury Network[8] and Kidney Disease Improving Global Outcomes[9] criteria

Criteria	RIFLE[7]	AKIN[8]	KDIGO[9]
Date of release	2004	2007	2012
Time interval	Diagnosis and Staging: Within 1-7 d and sustained more than 24 h	Diagnosis: Within 48 h Staging: 1 wk	Diagnosis: 50% increase within 7 d or ⩾ 0.3 mg/dL (26.5 μmol/L) within 48 h
Stage 1 or R	Increased SCr 1.5-1.9 times baseline	Increased SCr 1.5-1.9 times baseline or ⩾ 0.3 mg/dL (⩾ 26.5 μmol/L) increase	Increased SCr 1.5-1.9 times baseline (7 d) or ⩾ 0.3 mg/dL (⩾ 26.5 μmol/L) increase (48 h)
Stage 2 or I	Increased SCr 2.0-2.9 times baseline	Increased SCr 2.0-2.9 times baseline	Increased SCr 2.0-2.9 times baseline
Stage 3 or F	Increased SCr 3.0 times baseline, or Increase in SCr ⩾ 4.0 mg/dL (350 μmol/L) with an acute rise of ⩾ 0.5 mg/dL (44 μmol/L)	Increased SCr 3.0 times baseline, or Increase in SCr ⩾ 4.0 mg/dL (350 μmol/L) with an acute rise of ⩾ 0.5 mg/dL (44 μmol/L)	Increased SCr 3.0 times baseline, or Increase in SCr ⩾ 4.0 mg/dL (350 μmol/L)

SCr: Serum creatinine; RIFLE: Risk Injury Failure EndStage; AKIN: Akute Kidney Injury Network; KDIGO: Kidney Disease Improving Global Outcomes.

tion and is used by several countries to preferentially allocate organs to those with more severe disease[2]. Serum creatinine is also part of the United Kingdom End Stage Liver Disease (UKELD) score which similarly predicts 12 mo waiting list mortality[5]. As such accurate assessment of renal function is important, particularly for patients with underlying chronic kdney disease, for example, patients with non-alcoholic steatohepatitis (NASH), due to coexisting diabetic, hypertensive micro or macrovascular renal disease[4,6]. Hence these patients then develop more renal dysfunction after LT, which is associated with increased mortality.

CURRENT DEFINITIONS OF ACUTE KIDNEY INJURY

In order to standardize the definition of acute renal failure, now termed acute kidney injury (AKI), the risk injury failure loss of function and end stage renal failure (RIFLE) guideline criteria were developed[7]. These were subsequently revised by both the acute kidney injury network (AKIN)[8] and more recently by the kidney disease improving global outcomes (KDIGO) group[9] (Table 1). Although all three classifications define stages of severity of AKI by both urine ouput and serum creatinine concentration, in practice most studies have retrospectively used changes in serum creatinine to determine both the incidence and severity of AKI in peri-operative LT transplant recipients. Although these AKI classification systems report increasing mortality with increasing AKI severity, in keeping with other patient groups[10], the question arises as to whether they accurately detect acute kidney injury. In theory the diagnosis of AKI based on these classifications should be relatively straight forward as to whether patients post LT have a 50%, 200%, 300% increase in serum creatinine or an absolute rise above a critical threshold to make the diagnosis of AKI and award an AKI classification (Table 1) Whereas the major hurdle in general medical or surgical practice is determining the "true" baseline serum creatinine measurement upon which to evaluate subsequent changes, all LT patients will have a pre-operative measurement, and initial daily post-operative serum creatinine estimations. So it would appear a simple matter of cataloguing changes in serum creatinine post-operatively to determine the incidence and severity of AKI post LT.

However serum creatinine estimations typically over estimate "true" renal function pre-operatively[11], and then under estimate renal function post-operatively so potentially increasing the reported incidence of AKI.

WHY DOES SERUM CREATININE OVER ESTIMATE RENAL FUNCTION PRE-OPERATIVELY?

Creatinine is non-enzymatically converted from creatine in muscle. Creatinine is predominantly synthesized in the liver. As such patients with chronic liver disease awaiting LT typically have reduced creatine synthesis due to the combination of reduced dietary protein intake and chronic liver disease. The conversion of creatine through to creatinine depends upon both muscle mass and muscle turnover. Patients wait listed for LT are at increased risk of sarcopenia (muscle wasting) and typically take less exercise than healthy controls, so have a lowered conversion of creatine to creatinine[12]. In addition as creatinine is measured as a concentration, then as many patients with chronic liver disease have oedema, with ascites this results in a larger volume of distribution of creatinine in the body and a lower serum creatinine concentration[13]. Serum creatinine may also be affected by the concomitant prescription of drugs, such as calcitriol which affect the renal tubular secretion of creatinine[14].

Serum creatinine estimations tend to overestimate glomerular filtration rate (GFR) in patients with chronic liver disease, as the most commonly used laboratory method is a colorimetric assay which is subject to interference by chromogens, including bilirubin (both conjugated and unconjugated). As such these chromogens lower the measurement of creatinine, so making serum creatinine an even less precise surrogate of GFR in jaundiced patients. There have been several attempts to improve the accuracy of the Jaffe assay in an attempt to reduce interference from chromogens, such as bilirubin, glucose, uric acid, ketoacids, pyruvate, and some antibiot-

Table 2 Cohort of 329 adult patients transplanted for advanced cirrhosis

	RIFLE[7]	AKIN[8]	KDIGO[9]
Stage 1 or R	53	93	97
Stage 2 or I	28	28	28
Stage 3 or R	8	8	8
Stage 3 initiation of RRT	17	17	17

Changes in renal as assessed bt RIFLE, AKIN and KDIGO criteria for acute kidney injury for changes in serum creatinine. RIFLE: Risk Injury Failure EndStage; AKIN: Akute Kidney Injury Network; KDIGO: Kidney Disease Improving Global Outcomes; RRT: Renal replacement therapy.

ics[15]. These include acid blanking and absorption techniques with Fuller's earth or Lloyd's reagent, and delayed rate reactions. Initially these were laborious and time consuming so unsuitable for routine use. However the newer generations of chemical pathology laboratory multichannel analyzers now often routinely incorporate modified delayed rate or blank correction creatinine assays. Another modification, the kinetic alkaline picrate method produces a differential rate of colour change between creatinine and non-creatinine chromogens. Enzymatic methods to determine serum creatinine, using creatininases and creatininase hydrolases have been shown to be more reliable and less affected by chromogens[16], but are generally much more expensive and as such has not been widely introduced into routine clinical practice. To put this into clinical perspective[17] the interference that occurs with serum bilirubin concentrations > 62 μmol/L (3.68 mg/dL), result in significant differences in reported serum creatinine values between different methods (modified Jaffe, compensated kinetic Jaffe, enzymatic and standard Jaffe), resulting in significantly different MELD scores. If differences in MELD score are only 1-2 points, then this would have little clinical consequence, but differences of 3 or 4 points which are seen with bilirubin concentrations between 100 μmol/L (5.85 mg/dL) and 200 μmol/L (11.6 mg/dL) are clinically relevant. At even higher serum bilirubin concentrations (> 23.4 mg/dL), *i.e.*, those with the highest priority for LT. then this interference can result in differences in up to 7 MELD points As such the method used to estimate serum creatinine used in MELD scoring should be taken into account, as some patients inadvertently will be discriminated against with respect to others, in terms of priority for LT , when allocation is based on MELD score.

A further problem associated with accuracy and precision of serum creatinine measurements is a lack of universal standard for creatinine. For example in the United Kingdom there were 34 variations of the standard Jaffe reaction used by United Kingdom National Health Service (NHS) clinical chemistry laboratories. To standardize assays, all NHS laboratories were sent isotope dilution mass spectroscopy (IDMS) standards to develop their own correction factors for their creatinine assays. However IDMS standards do not allow for interfering chromogens and as such marked differences remain in serum creatinine estimations between UK NHS laboratories serving liver transplant centres[17,18].

Perhaps not surprisingly because of these multiple limitations of serum creatinine in estimating renal function in patients with advanced chronic liver disease a meta-analysis proposed that GFR estimation by inulin clearance was the only way for accurate assessment of renal function[19], but unfortunately inulin clearance remains impractical for routine clinical use.

WHY DOES SERUM CREATININE UNDER ESTIMATE RENAL FUNCTION POST-OPERATIVELY?

Although creatinine excretion is predominantly by glomerular filtration, there is an additional amount of creatinine secreted by the renal tubule. As such drugs which cause a reversible reduction in glomerular filtration can lead to an increase in serum creatinine, without necessarily causing renal damage. In the post-operative LT patient these would include non-steroidal anti-inflammatories given for post-operative analgesia, and on-going prescription of pre-operative antihypertensive medications, not just angiotensin converting enzyme inhibitors, angiotensin receptor blockers and renin inhibitors. However the drugs most likely to reduce GFR in the immediate post-operative period are the immunophyllins, particularly tacrolimus. In addition to reducing GFR, immunophyllins also reduce renal tubular creatinine secretion by inhibiting cyclooxygenase 2 in the renal medulla so causing renal tubular ischaemia[20].

Hence serum creatinine tends to overestimate renal function prior to LT, and then under estimate renal function post operatively. Thus when using the current definitions of acute kidney injury based on changes in serum creatinine there is a tendency to overestimate both the incidence and severity of acute kidney injury post LT (Figure 1, Table 2). This is most marked for lesser degrees of acute kidney injury, and most noticeable between the RIFLE and other scoring systems (Table 2), due to the differences in definitions with RIFLE requiring a 50% increase compared to AKIN and KDIGO which only require an absolute increase of 0.3 mg/dL. So that switching from a high to a low serum bilirubin post transplantation and starting immunophyllin immunosuppression may be sufficient to cause a minor increase in measured serum creatinine to be classified as acute kidney injury stage 1 by AKIN and KDIGO, but less than the 50% increase required by RIFLE.

Altering peri-operative immunosuppression protocols to delay or avoid the initial use of immunophyllins may help to reduce kidney injury, by using monoclonal antibodies, such as simulect and CAMPath-1, particularly in those with NASH and other patients with pre-existing chronic kidney disease. Lower targets for tacrolimus trough doses have also recently been shown to improve graft survival and reduce both acute and chronic renal impairment[21,22]. Thus, risk modification is needed to optimize renal function in the pre, peri and postoperative

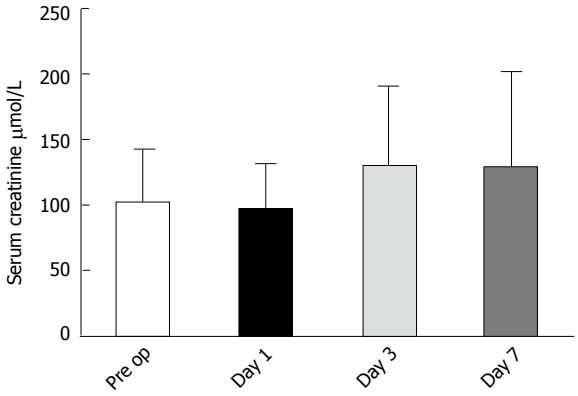

Figure 1 Cohort of 329 adult patients undergoing liver transplantation at the Royal Free Hospital. Serum creatinine measured using an enzymatic method shows a significant increase between the pre-operative and 1st post-operative day and the 3rd and 7th post-operative days respectively. Only 2.4% developed acute kidney injury stage 3 on serum creatinine criteria alone, suggesting that the most probable cause for the significant increase was due to changes in serum creatinine measurement due to a reduction in bilirubin and other chromagens, and the use of immunophyllins as immunosuppressive agents.

management of LT candidates: which may prevent or delay post-LT end stage renal disease[22].

WHAT ARE THE ALTERNATIVES TO MEASURING SERUM CREATININE?

Exogenous markers which are only cleared by the kidney are the most accurate methods for determining renal function. Inulin clearance remains the gold standard for measurement of renal function but cost and technical difficulties limit its use for routine practice[19]. Other direct methods of measuring GFR include exogenous radiolabelled substances (^{51}Cr-ethylene diamine tetra acetic acid (EDTA), ^{99m}Tc-diethylenetriamine pentaacetate (DPTA) and ^{51}I-iothlamate) or non-radioactive agents (iohexol or iothalamate)[23]. However these methods have typically not been extensively validated in patients with cirrhosis and ascites. As such the British Nuclear Medicine Society Guidelines stated that liver failure, ascites, oedema and low clearance status may produce inaccurate clearance values[24]. Following injection there will be an initial redistribution from plasma into the ascites, and then a later re-equilibration from the ascites back into the plasma. As such ascites has been reported with increased clearances of 16-20 mL/min based on compartmental models[24]. To overcome these difficulties delayed sampling has been used to improve the calculation of the decay slope and time zero[25]. These isotope and radiocontrast techniques correct measurements of glomerular filtration for body surface area, which is calculated using equations based on height and weight. The presence of ascites and changes in body composition[26-28], with loss of muscle and fat mass change the normal relationship between calculated body surface area and muscle mass, and so add errors to the determination of GFR. Ideally these methods can be used for pre-operative assement of renal function, which can then be used to stratify patients for risk of acute kidney injury post LT and individualise immunosuppression policies. However there use in the immediate post LT period is unclear when renal function is changing.

ESTIMATION OF CREATININE CLEARANCE BY URINE COLLECTIONS

Creatinine clearance, using 24 h urine or shorter timed collections was the traditional method for assessing renal function. However, creatinine clearance underestimates GFR in children and when the serum creatinine levels are high the relative proportion of creatinine secreted by the renal tubules is greater[29] (Table 3). In healthy adults, creatinine clearance typically overestimates "true" GFR based on inulin clearance. Limitations are associated not only with the use of serum creatinine, measurements but also tubular creatinine secretion, which increases with underlying chronic kidney disease, proteinuria, drugs and also extra-renal elimination of creatinine by micro-organisms in the gastro-intestinal tract[14]. Pre-operatively , there may be up to 25% variation in GFR estimation based on creatinine clearance[29], due to incomplete urine collections, timing errors, errors in urine volume measurement, variations in tubular excretion or re-absorption of creatinine, serum creatinine dilution due to increased fluid retention and other unpredictable factors. Due to these multiple errors, there is no evidence that creatinine clearance is superior to serum creatinine in determining renal function in cirrhosis.

MATHEMATICAL ESTIMATIONS OF GLOMERULAR FILTRATION RATE

To overcome some of the limitations of 24 h urine collection, a number of different mathematical formulae have been developed, which incorporate serum creatinine to provide an estimate of GFR (eGFR). However these formulae were developed from a stable chronic kidney disease population, and not for patients with chronic liver disease, or for patients with changing renal function in the post-operative LT period. Although these formulae are increasingly being used in the intensive care setting they have not been validated. Currently used formulae include the Cockcroft-Gault (C-G)[30] and Modification of Diet in Renal Disease (MDRD)[31] formulae. The C-G formula requires serum creatinine, weight, gender and age whereas the MDRD formula incorporates serum creatinine, ethnicity, gender and age (MDRD-4), or creatinine, ethnicity, gender, age, albumin and urea (MDRD-6). Thus, in contrast to C-G formula, a body weight variable (which is difficult to assess as lean body mass in ascitic and malnourished patients) is not needed, and the MDRD equations use ethnicity, gender and age and then adjusts for 1.73 m^2 body surface area (without any assessment of height or weight). In cirrhosis, although there is discrepancy when compared to ^{125}I-iothalamate[32], the MDRD-6 equation is considered a more accurate for-

Table 3 Comparison of the established methods for assessing renal function in clinical practice

	Advantages	Disadvantages
Serum marker		
Creatinine	Widely available	Influenced by several factors unrelated to renal function, including dehydration and volume expansion, dietary protein, muscle mass, physical activity and thyroid hormones renal tubular secretion affected by chronic kidney disease, proteinuria and drugs not an early biomarker of acute kidney injury
Clearance of exogenous marker	"Gold standard"	Absence of standardization of the laboratory methods for jaundiced patients technical difficulties and expense make impractical for routine clinical practice stable renal function Less reliable in patients with oedema, ascites, pleural effusions and sarcopenia
Creatinine Clearance f (24 h urine collection)	? more accurate compared to Cr	Inconvenient for outpatientsoverestimates GFR in proteinuria chronic kidney disease influenced by muscle metabolism and diet, inflammatory disease and malnutrition Unexplained variation due to incomplete urine collection and errors in urine volume measurement overestimation of GFR in patients with cirrhosis
Mathematical formulae based on Cr	Easier method compared to 24 h urine collection	Not validated for patients with changing renal function (acute kidney injury, muscle wasting disorders) Does not overcome the limitations in serum creatinine
C-G formula	Requires only gender, age, body weight	Difficult to determine body weight in patients with ascites and post LT
MDRD formula	Body weight is not needed ethnicity, gender and age are taken into account	Has not been validated in patients with chronic liver disease 6-variables formula: needs albumin, urea Only validated in stable chronic kidney disease patients

GFR: Glomerular filtration rate; Cr: Serum creatinine; C-G: Cockcroft-Gault; MDRD: Modification of Diet in Renal Disease; CKD: Chronic kidney disease; LT: Liver transplantation.

mula, compared to C-G, possibly because it incorporates urea and albumin, which are abnormal in cirrhotics and it excludes body weight, a variable which may be difficult to determine in malnourished patients with ascites[28]. However the MDRD-4 formula is the formula reported by most laboratories, as it was equally accurate as the original six-variable formula in screening for patients with chronic stable kidney disease. In cirrhosis, C-G and both MDRD formulae typically overestimate true GFR, particularly in those patients below 50 years old or those with ascites[33]. Due to inaccuracies of the MDRD-4 equation in determining renal function in patients with an eGFR > 60 mL/min, a new creatinine-based equation known as the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, using the same variables with MDRD-4 formula, has been proposed, but its superiority in patients with cirrhosis has not been validated[34]. Nevertheless, the use of such formulae does not overcome the limitations in serum creatinine measurement. It has been recommended that creatinine results used for calculating eGFR should be traceable to an IDMS reference method[34], but the IDMS standards do not correct for the effects of chromogens. To overcome the problem that these formulae were derived from cohorts without liver disease new formulae for patients with cirrhosis have been proposed including adding the Child Turcot Pugh (CTP) score and ascites into the formula[35]. These newer formulae have been reported to show better agreement with "true" GFR, compared to the MDRD formulae, but require further external validation before they can be introduced into clinical practice.

ALTERNATIVES TO CREATINNE

Serum cystatin C

Serum cystatin C is an extracellular inhibitor of cysteine proteases[36]. It was originally thought that cystatin C was uniformly produced and secreted by all nucleated cells, but actually has a greater diurnal variation than serum creatinine. Cystatin C is freely filtered by the renal glomeruli and then taken up and catabolized in the proximal tubules. It was initially considered a more sensitive indicator of renal function compared to creatinine[37], in several disease groups including cirrhosis[38,39]. Consequently several Cystatin C based GFR equations, were derived[40,41]. More recently cystatin C has been recognized to be affected by numerous factors including inflammation[42] body composition, proteinuria, cardiovascular risk factors[43,44] infection, thyroid dysfunction, underlying malignancy, smoking and a number of drugs; including corticosteroids, cotrimoxazole, angiotensin converting enzyme inhibitors, and calcineurin inhibitors. Cystatin C has been reported to increase with severity of chronic liver disease[45] as it correlates with bilirubin, INR and CTP stage, and negatively with serum albumin and peripheral platelet count[46]. As cirrhosis evolves the increasing cystatin C values may be related to increased production, secondary to inflammation, or decreased clearance due to reduced renal function. The original cystatin C equations were all derived from non-liver disease populations[47,48]. Recentstudies have evaluated cystatin C GFR formulas in patients with cirrhosis[35]. One reported that although cystatin C formulas were more accurate than the creatinine formulas[49]. GFR estimations were significantly different

to inulin clearance. In the second study serum cystatin C formulas not only significantly overestimated renal clearance compared with ^{51}Cr-EDTA but did not provide any advantage over serum creatinine formulas[35], and serum cystatin C values were significantly affected by the presence of ascites. Although a third study reported cystatin C to more accurately represent renal function than serum creatinine[50]. There has recently been standardisation of serum cystatin C assays and more studies are required to try and develop specific GFR formulae for cystatin C in patients with cirrhosis. However as cystatin C is increased by inflammatory states, changes in cystatin C performs no better than serum creatinine in determing acute kidney injury in the immediate post operative lT period.

NEUTROPHIL GELATINASE ASSOCIATED LIPOCALIN

Acute kidney injury is a potentially life threatening complication in patients with cirrhosis. Neutrophil Gelatinase associated Lipocalin (NGAL) has been recently introduced as an early marker of tubular dysfunction in acute kidney injury. Several studies have reported that NGAL increases in urine and plasma shortly after injury to renal tubular cells and it can be used to aid the differential diagnosis between acute tubular necrosis and volume responsive causes of acute kidney injury in patients with chronic liver disease. Urinary and serum NGAL not only reflect renal tubular injury but are also markers of the host systemic inflammatory response, as NGAL is part of the innate immune response designed to restrict iron availability to invading micro-organisms. After initial promising reports of the superiority of NGAL to other acute kidney injury biomarkers including creatinine[51] more recent reports have failed to substantiate the earlier studies, especially when studies include patients with pre-existing chronic kidney disease.

NGAL has been evaluated in patients with cirrhosis[52]. Patients with kidney dysfunction irrespective of aetiology had greater serum NGAL levels compared to those without kidney dysfunction irrespective of the presence of ascites. Urinary NGAL levels were also increased significantly in patients with cirrhosis and acute tubular necrosis (median values 417, range 239-2242 μg/g creatinine) compared to those with other causes of acute impairment of kidney function, for example hepatorenal syndrome (not associated with active infections), pre-renal azotemia secondary to volume depletion, and chronic kidney disease. However, plasma levels of NGAL were not helpful in the differential diagnosis of kidney dysfunction, in particular reversibility of acute kidney injury. Urinary NGAL levels were found to be significantly increased with urinary tract infections, whereas plasma NGAL was not different in patients with and without bacterial sepsis. As such, NGAL did not aid the differential diagnosis between acute tubular necrosis and hepatorenal syndrome precipitated by infection, as NGAL levels increased in both groups. Thus, larger multicentre trials are awaited to determine whether urinary NGAL, and newer markers of acute kidney injury, such as kidney injury molecule 1 (KIM-1) and urinary IL-18 excretion have a role in diagnosing acute kidney injury in patients with chronic liver disease. Similarly studies in patients following LT have reported that NGAL rises in patients who develop acute kidney injury[53]. Although n serum NGAL may rise earlier than creatinine post LT, this may simply reflect the severity of the ischaemia-reperfusion injury and the initial dilutional effect of intra-operative fluid administration on serum creatinine. Additional studies are warranted to determine whether there is a clinical role for these newer biomarkers in the diagnosis of acute kidney injury following LT.

CONCLUSION

Renal dysfunction increases the risk for mortality in patients with chronic liver disease both prior to and post liver transplantation. Changes in serum creatinine are now used to define acute kidney injury. As such, although small changes in serum creatinine are linked to adverse outcomes, changes in serum creatinine concentration can be influenced by changes in hydration status[54], and in particular for the patient with cirrhosis a falling serum bilirubin post liver transplant can lead to an apparent increase in serum creatinine, simply due to loss of interference with the colorimetric assay, and secondly due to changes in intra-renal perfusion associated with immunphyllins, without necessarily implying acute kidney injury. As serum creatinine is likely to remain the routine clinical marker of kidney function, additional biomarkers are required to help differentiate between assay interference and reversible changes in renal function on one hand and acute kidney injury on the other.

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