# The kidney at risk in liver transplantation recipients: Review of the literature

## KIDNEY PROBLEMS IN LIVER TRANSPLANTATION

Renal complications are an important issue after liver transplantation. Many patients with ESLD awaiting a liver transplant have renal impairment and they are at risk for short- and long-term renal problems afterwards. AKI is frequently observed in the early postoperative phase and is the result of several donor, recipient and surgical risk factors. A significant proportion of the recipients will be in need of peri-operative RRT and not all of them have a full recovery of kidney function and will develop CKD, and in some cases ESRD, requiring long-term RRT or kidney transplantation. Considering the growing pre-transplant renal problems due to the 'sickest-first' allocation policy in many countries and the increased use of marginal grafts in liver transplantation, the rate of renal complications is likely to increase. In this chapter we will discuss the renal problems in patients with ESLD and risk factors for development of AKI and CKD after liver transplantation.

### Renal failure in cirrhosis

Patients with ESLD will frequently present with AKI due to ascites with subsequent volume depletion or episodes of spontaneous bacterial peritonitis. On the other hand, some have a slower decrease in kidney function over the years of developing decompensated cirrhosis. The majority of kidney function in ESLD is thought to be functional (rather than damage) and related to hemodynamic disbalances (1). The portal hypertension in cirrhosis causes primary arterial vasodilatation in the splanchnic circulation, leading to a reduction in the systemic vascular resistance. Increased cardiac output can compensate for this reduction initially, but in advanced stages of cirrhosis the systemic vascular resistance will be so much reduced the cardiac compensation is not sufficient (**Figure 1**). This will lead to hypovolemia and subsequent activation of vasoconstrictor systems will keep up the arterial blood pressure, but will impair the kidneys, leading to more ascites and renal vasoconstriction and hypoperfusion (2). There are four types of renal failure in ESLD: (I) the hepatorenal syndrome (HRS), (II) hypovolemia-induced renal failure, (III) parenchymal renal disease and (IV) drug-induced renal failure (1). HRS is the far most common form and can be divided into HRS-type 1 or HRS-AKI and HRS-type-2. HRS-type 1 classically presents like AKI within several days which usually responds well to medical therapy with vasoconstrictors (i.e. terlipressin), and is often related to a precipitating factor, such as spontaneous bacterial peritonitis, gastrointestinal haemorrhage or acute-on-chronic liver failure (3). HRS-type 2 has a more gradual decrease in kidney function (>two weeks) and often severe ascites, resistant to diuretic therapies (4). The MELD-score was developed in 2000 to predict mortality in patients undergoing transjugular

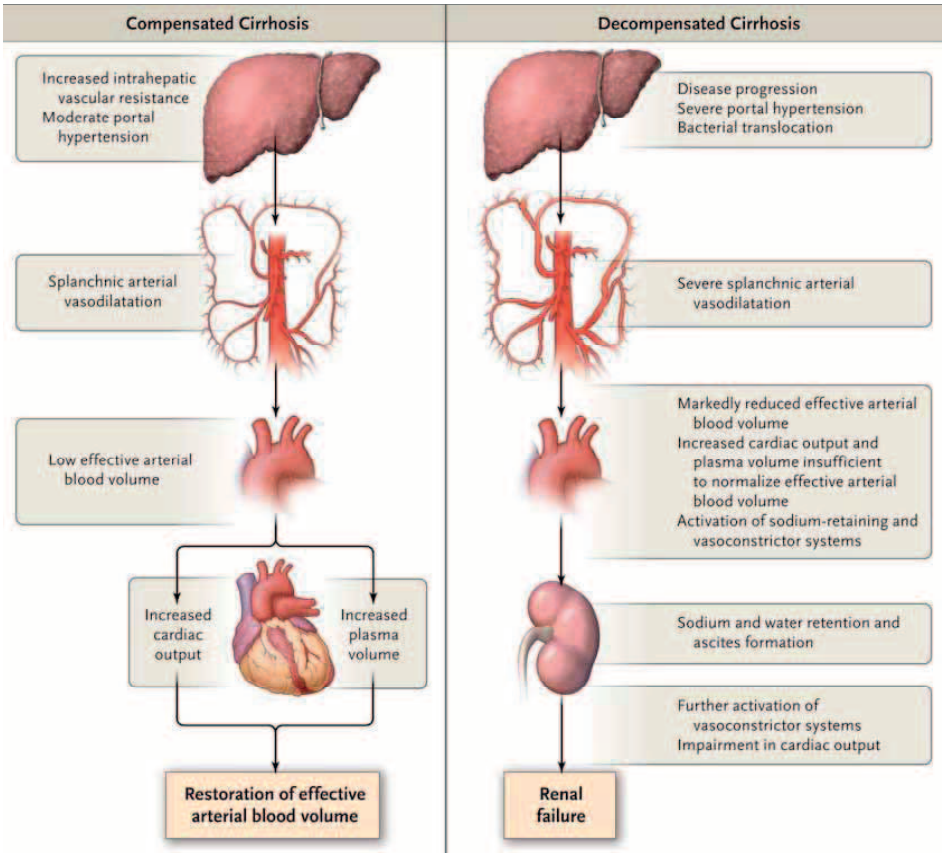


**Figure 1** – Pathogenesis of circulatory abnormalities and renal failure in cirrhosis.
From Ginès et al, New Eng J Med, 2009 (1).

intrahepatic portosystemic shunt for refractory ascites and soon this prediction model was implemented in the US and many European countries to allocate grafts for liver transplantation (5–7). The MELD-score consists of three pillars: coagulopathy (INR), impaired bilirubin metabolism (serum bilirubin), and renal dysfunction (serum creatinine). A patient gets additional points, when he or she is in need of regular RRT, acknowledging the importance and predictive value of renal dysfunction in patients on the liver transplant waiting list. As a result, patients undergoing a liver transplant have more frequently severe renal dysfunction over the last years, increasing the risk for renal problems after the liver transplantation (8–10).

### Acute kidney injury after liver transplantation

Several centres have reported their experience with AKI after liver transplantation, with incidence rates ranging from 24% to 85% (11–24). This wide variance is partly

**Table 1** – Criteria based on serum creatinine levels to classify AKI after liver transplantation.

| Criteria | Stages | Year |
|---|---|---|
| RIFLE (25) | § Risk: increased creatinine x 1.5 **OR** decreased GFR >25% from baseline<br>§ Injury: increased creatinine x 2.0 **OR** decreased GFR >50%<br>§ Failure: increased creatinine x 3.0 **OR** decreased GFR >75% **OR** creatinine level ≥354 µmol/L with an acute rise of ≥ 44.2 µmol/L<br>§ Loss: complete loss of renal function for >4 weeks (renal replacement therapy)<br>§ End stage renal disease: no recovery of kidney function | 2004 |
| AKIN (26) | § Stage 1: increased creatinine x 1.5 **OR** ≥26.4 µmol/L from baseline (within 48h)<br>§ Stage 2: increased creatinine x 2.0<br>§ Stage 3: increased creatinine x 3.0 **OR** creatinine level ≥354 µmol/L with an acute rise of ≥ 44.2 µmol/L **OR** requiring renal replacement therapy | 2007 |
| KDIGO (27) | § Stage 1: increased creatinine x 1.5 (within 7 days) **OR** ≥26.4 µmol/L (within 48h) from baseline<br>§ Stage 2: increased creatinine x 2.0<br>§ Stage 3: increased creatinine x 3.0 **OR** creatinine level ≥354 µmol/L with an acute rise of ≥ 44.2 µmol/L **OR** requiring renal replacement therapy | 2012 |

the result of the criteria used to classify AKI. **Table 1** gives an overview of the criteria used for AKI over the last years. Officially, AKI is defined by either an increase in serum creatinine levels or decrease or loss of urine output. However, since serum creatinine levels are most widely available and more accurately measured than urine output in the daily practice, almost all studies only use the creatinine levels to define AKI after liver transplantation. The Kidney Disease Improving Global Outcomes (KDIGO)-criteria are considered as the most up-to-date and is used in most of the recent literature.

*Risk factors for acute kidney injury*

Postoperative AKI is the result of the combination of donor, graft, recipient and surgical risk factors. Furthermore, the early use of nephrotoxic immunosuppression after the liver transplant increases the risk for AKI (15,17,22,28). The peri-operative practice in liver transplantation is very diverse worldwide and the numerous studies evaluating factors associated with AKI identified different risk factors. The literature (US National Library of Medicine - PubMed online database) since 2000 was screened for factors associated with development of AKI (acute kidney injury or acute renal failure) after liver transplantation. An overview of independent risk factors (using multivariable regression analysis) that were identified in *at least two* single-centre experiences were included, which is shown in **Table 2**. The preoperative MELD-score was identified by most previous studies, other recipient factors included the serum creatinine, a raised BMI and history of DM. The use of DCD grafts and a longer recipient WIT during the transplant have an impact on AKI development as well.

Table 2 – Factors associated with development of AKI after liver transplantation

| | Risk factor | References |
|---|---|---|
| ***Donor / Graft*** | § Use of a DCD graft | Leithead 2012 (29), Doyle 2015 (30) |
| | § Duration of recipient warm ischemia time | Leithead 2014 (21), Barreto 2015 (14), Park 2015 (15), Zongyi 2017 (28) |
| ***Recipient*** | § Preoperative serum creatinine | Gallardo 2004 (11), Sanchez 2004 (31), O'Riordan 2007 (12), Wadei 2016 (32), Zongyi 2017 (28) |
| | § Raised BMI | Iglesias 2010 (17), Park 2015 (15), Hilmi 2015 (33) |
| | § Non-Caucasian race | Contreras 2002 (34), Iglesias 2010 (17) |
| | § Diabetes mellitus | Utsumi 2013 (22), Hilmi 2015 (33) |
| | § Viral hepatitis | Barreto 2015 (14), Wadei 2016 (32) |
| | § APACHE-II-score | Gallardo 2004 (11), Zhu 2010 (35) |
| | § MELD-score | Sanchez 2004 (31), Zhu 2010 (35), Klaus 2011 (36), Utsumi 2013 (22), Romano 2013 (23), Kim 2014 (37), Park 2015 (15) |
| | § Child-Pugh-score | Iglesias 2010 (17), Fonseca-Neto 2011 (20), Hilmi 2015 (33) |
| | § Blood urea nitrogen | Contreras 2002 (34), Sanchez 2004 (31) |
| | § Hypoalbuminemia | Chen 2011 (19), Park 2015 (15), Cabezuelo (38) |
| ***Surgical*** | § Operation time | Park 2015 (15), Wadei 2016 (32) |
| | § Blood loss | Utsumi 2013 (22), Hilmi 2015 (33), Park 2015 (15), Zongyi 2017 (28) |
| | § Red blood cell transfusion | Contreras 2002 (34), Gallardo 2004 (11), Chen 2011 (19), Park 2015 (15), Wadei 2016 (32) |
| | § Inotrope/vasopressor requirement | Sanchez 2004 (31), Chen 2011 (19) |
| | § Postreperfusion syndrome | Fonseca-Neto 2011 (20), Park 2015 (15) |
| ***Post-operative*** | § Calcineurin inhibitor (overexposure) | Iglesias 2010 (17), Utsumi 2013 (22), Park 2015 (15), Zongyi 2017 (28) |
| | § Transaminase peak | Contreras 2002 (34), Leithead 2014 (21), Rahman 2017 (39), Jochmans 2017 (40) |
| | § Prolonged dopamine use | Cabezuelo (38), Zongyi 2017 (28) |

Furthermore, blood loss with subsequent transfusion requirements and the use of vasopressors were identified by multiple centres. As expected, overexposure to calcineurin inhibitors was associated with AKI.

*Graft quality and acute kidney injury*

The Birmingham group showed a simultaneous increase in incidence of AKI after liver transplantation with the evolving use of marginal grafts, and especially with DCD grafts (21,29). In both studies, the postoperative release of transaminases was an independent factor associated with AKI, representing the severity of hepatic IRI as the link between graft quality and development of AKI. Interestingly, in a subgroup

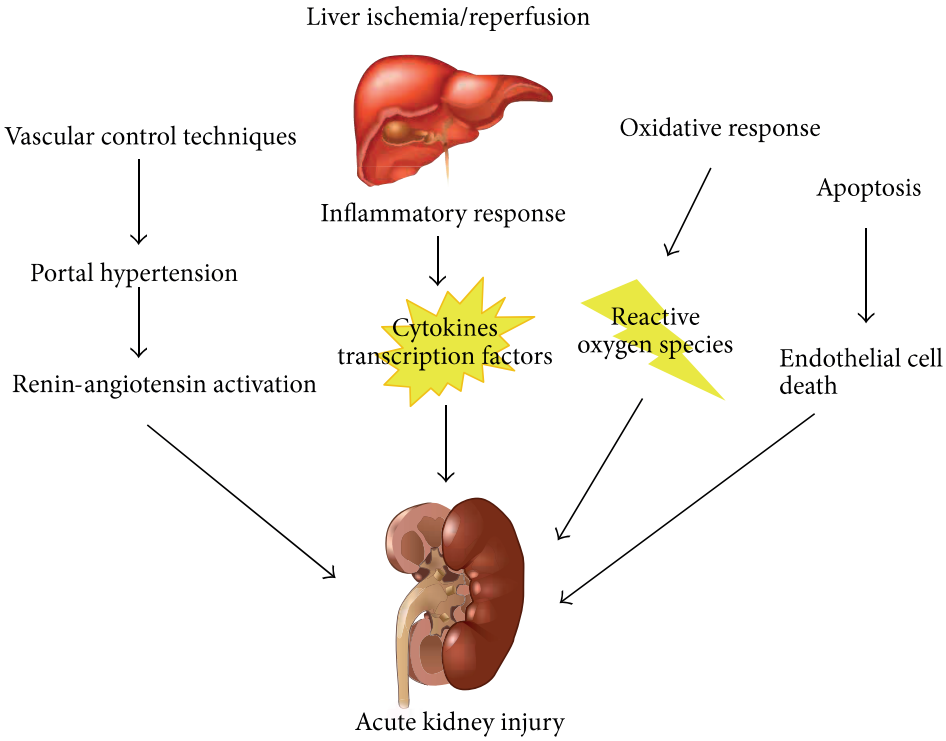


**Figure 2** – overview of the mechanism causing AKI after hepatic ischemia/reperfusion injury
From Nastos *et al*, Oxidative Medicine and Cellular Longevity, 2014 (49).

analysis of DBD grafts, these peak transaminase levels were also higher in recipients with post-transplant AKI (41). Several factors impact on graft quality. Grafts from older donors, steatotic graft and DCD grafts are known to be more susceptible to hepatic IRI, as are grafts who experience longer cold and warm ischemia times (42–47). It is known that hepatic IRI induces a systemic inflammatory response similar as seen in sepsis (48). The subsequent release of pro-inflammatory cytokines and reactive oxygen species causes renal injury (**Figure 2**) (49). Although the pathogenesis between hepatic IRI and development of AKI is not fully understood yet, there is evidence that the release of these cytokines (including TNF-α) leads to dysregulation of endothelial adhesion molecules and renal endothelial cell apoptosis, which promotes leukocyte recruitment in the interstitial space, causing renal injury (50–52). The reactive oxygen species released by activated neutrophils cause direct renal damage and recruitment of leukocytes like monocytes and macrophages further aggravate the oxidative injury in the kidney (53).

*Acute kidney injury biomarkers*

Over the last years, several serum and urine biomarkers for the prediction for AKI after liver transplantation have been identified. The most common cause of AKI in this setting is acute tubular necrosis. Therefore, markers of acute tubular injury, including kidney injury molecule-1 (KIM-1), neutrophil gelatinase-associated lipocalin (NGAL), and interleukin-18 (IL-18) are the main subject of interest (54). In a recent study evaluating the relationship between postreperfusion gene expression, serum mediator and development of postoperative AKI revealed that a combination of endothelin-1 (ET-1) and IL-18 expression was highly predictive for AKI (55).

*Acute kidney injury in relation to other outcomes after liver transplantation*

Development of AKI after liver transplantation does not stand on its own. Due to the intense relation with hepatic IRI, recipients developing (severe) AKI are also likely to experience other complications, including infections and the need for a reoperation in the first days after liver transplantation with an prolonged admission in intensive care and in the hospital (11,19,34,39). Postoperative AKI in general is related with increased use of hospital resources and costs and previous studies have also linked AKI to an increased risk for graft loss (19,28,56,57). Furthermore, there is a clear relation between AKI and recipient mortality on the short and long-term, especially in recipients that require RRT in the early postoperative phase (12,14,34–36). Although most recipients recover from the direct renal damage in the following months after liver transplantation, Ojo *et al* already reported in 2003, that postoperative AKI requiring RRT is a risk factors for development of CKD, which was later confirmed by several single-centre experiences (29,32,33,58).

## Development of chronic kidney disease after liver transplantation

In the US nationwide study from Ojo and colleagues including 69.321 recipients of non-renal organs, the 5-year cumulative incidence of severe CKD (eGFR <30 ml/min/1.73 $m^2$) was 18% for liver transplantation recipients (58). This is relatively high, compared to recipients of heart (11%) and lung (16%) transplants, even though liver transplant recipients require less nephrotoxic immunosuppression. Other studies reported observed overall CKD (eGFR <30 ml/min/1.73 $m^2$) in 39% up to 78% of the recipients (16,33,59,60). Severe CKD and ESRD incidence rates reached from 6% to 18% and 1% to 12%, respectively (16,32,33,60–63). **Figure 3** shows the course of renal function over 25 years after liver transplantation in a US large cohort with more than 1.000 recipients (60). This study (and several others) has shown that recipients who develop CKD after liver transplantation have an increased mortality-risk, especially when the eGFR drops <30 ml/min/1.73 $m^2$ (58,64,65).

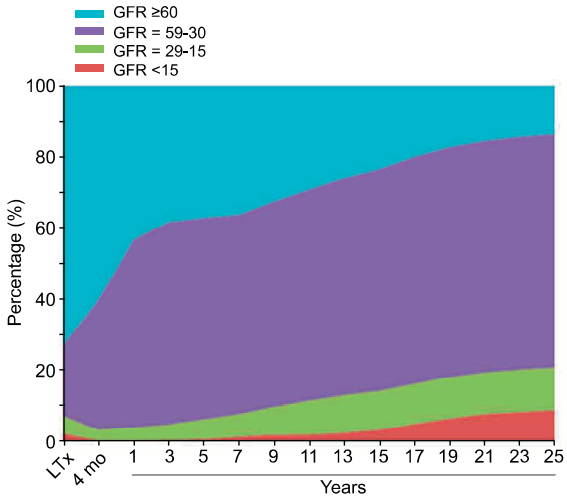


**Figure 3** – Course of renal function after liver transplantation
From Allen et al, Journal of Hepatology, 2014 (60).

*Risk factors for CKD*

Similar to AKI after liver transplantation, CKD has a multifactorial origin. Sharma *et al* introduced the three-hit model with risk factors contributing to the development of post-transplant CKD (**Figure 4**) (66). The first hit is the combination of pre-transplant renal impairment due to HRS, glomerulonephritis, comorbidities such

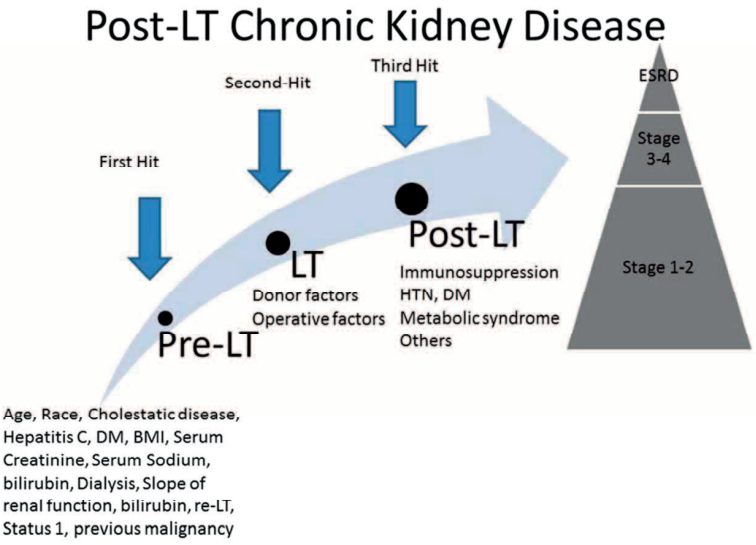


**Figure 4** – the three-hit model of risk factors for development of CKD after liver transplantation
From Sharma et al, Advances in Chronic Kidney Disease, 2015 (66).

as hypertension and DM, and additional acute tubular necrosis due to episodes of sepsis (1,58,59,67–70). The second hit happens peri-operatively: blood loss and hypotensive episodes during the transplant procedure and postoperative complications such as infections, bleeding and biliary complications further impact on kidney function. As described above, the use of marginal grafts increase the severity of hepatic IRI with subsequent AKI, potentially increasing the risk for renal impairment on the long-term. The third hit is the result of immunosuppression that not only has direct nephrotoxic consequences, but long-term use of calcineurin inhibitors and steroids also increase the risk for post-transplant metabolic syndrome. This syndrome and its individual components DM and hypertension have a further negative impact on kidney function (66,71,72).

*Recovery of renal function after liver transplantation*

Up to one fourth of the recipients with AKI require RRT in the first weeks after liver transplantation (12,21,37,73). This group is a mix of those who have with pre-transplant renal failure, those who have a difficult transplant procedure and/or postoperative complications. Recovery of renal function ranges from 70% to 98%, which mostly depends on the duration of RRT prior to liver transplantation (62,64,69,74–76). Other risk factors for non-recovery of kidney function include recipient age, MELD-score and pre-existing DM (69,74–76). In a study with 155 patients requiring post-transplant RRT the average duration until recovery was 33 days and after one year 83% was not dialysis dependent anymore (74). It should be noted that in most countries there is a thorough and careful selection of patients who are likely to not recover from their renal failure and they are offered a simultaneous liver and kidney transplant (68,77).

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