

Acute kidney injury and post-reperfusion syndrome in liver transplantation

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Abstract

In the past decades liver transplantation (LT) has become the treatment of choice for patients with end stage liver disease (ESLD). The chronic shortage of cadaveric organs for transplantation led to the utilization of a greater number of marginal donors such as older donors or donors after circulatory death (DCD). The improved survival of transplanted patients has increased the frequency of long-term complications, in particular chronic kidney disease (CKD). Acute kidney injury (AKI) post-LT has been recently recognized as an important risk factor for the occurrence of de

novo CKD in the long-term outcome. The onset of AKI post-LT is multifactorial, with pre-LT risk factors involved, including higher Model for End-stage Liver Disease score, more severe ESLD and pre-existing renal dysfunction, either with intra-operative conditions, in particular ischaemia reperfusion injury responsible for post-reperfusion syndrome (PRS) that can influence recipient's morbidity and mortality. Post-reperfusion syndrome-induced AKI is an important complication post-LT that characterizes kidney involvement caused by PRS with mechanisms not clearly understood and implication on graft and patient survival. Since pre-LT risk factors may influence intra-operative events responsible for PRS-induced AKI, we aim to consider all the relevant aspects involved in PRS-induced AKI in the setting of LT and to identify all studies that better clarified the specific mechanisms linking PRS and AKI. A PubMed search was conducted using the terms liver transplantation AND acute kidney injury; liver transplantation AND post-reperfusion syndrome; acute kidney injury AND post-reperfusion syndrome; acute kidney injury AND DCD AND liver transplantation. Five hundred seventy four articles were retrieved on PubMed search. Results were limited to title/abstract of English-language articles published between 2000 and 2015. Twenty-three studies were identified that specifically evaluated incidence, risk factors and outcome for patients developing PRS-induced AKI in liver transplantation. In order to identify intra-operative risk factors/mechanisms specifically involved in PRS-induced AKI, avoiding confounding factors, we have limited our study to "acute kidney injury AND DCD AND liver transplantation". Accordingly, three out of five studies were selected for our purpose.

Key words: Liver transplantation; Acute kidney injury; Post-reperfusion syndrome; Donation after circulatory death; Chronic kidney disease

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Core tip: Post-reperfusion syndrome (PRS)-induced acute kidney injury (AKI) has been recognized as an important complication occurring after liver transplantation (LT) that characterizes kidney involvement caused by PRS with mechanisms not clearly understood and implication on graft and patient survival. Since pre-LT risk factors may influence intra-operative events responsible for post-reperfusion syndrome-induced AKI (PRS-induced AKI), we aim to consider all the relevant aspects involved in PRS-induced AKI in the setting of LT and to identify all studies that better clarified the specific mechanisms linking PRS and AKI, in particular in LT recipients from donation after circulatory death.

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INTRODUCTION

Liver transplantation (LT) is the treatment of choice for patients with end stage liver disease (ESLD). Ongoing progress in organ preservation, surgical and anaesthetic techniques and immunosuppression has improved outcomes with 1-year survival > 85% and 5-year survival > 75%. The chronic shortage of cadaveric organs for transplantation led to the utilization of a greater number of marginal donors such as older donors or donors deceased after circulatory death (DCD). The improved survival of transplanted patients has increased the frequency of long-term complications, in particular chronic kidney disease (CKD). The incidence of CKD at 10 years after LT can be as high as 28%^[1] leading to 4-fold increase in mortality^[1,2].

Acute kidney injury (AKI) post-LT has been recently recognized as an important risk factor for the occurrence of *de novo* CKD in the long-term follow up after LT^[3].

Risk factors for AKI may be related to pre-LT conditions, such as severe ESLD, higher model for end-stage liver disease (MELD) score and pre-existing renal dysfunction, either to intra-operative conditions, in particular ischaemia reperfusion injury (IRI)^[4-6]. The latter is responsible for the post-reperfusion syndrome (PRS), which is an intra-operative complication, whose definition is still under debate, that may influence morbidity and mortality of recipients. PRS involves intra-operative events such as reduction of mean arterial pressure (MAP), presence of haemodynamic arrhythmias, need for inotropic drugs during transplantation^[7]. This condition promotes multi-organ damage, with particular kidney involvement through systemic inflammatory and haemodynamic mechanisms in addition to a direct damage with tubular cell death. Post-reperfusion syndrome-induced AKI (PRS-induced AKI) is an important complication post-LT that characterizes kidney involvement caused by PRS with mechanisms not clearly understood and implication on graft and patient survival.

Furthermore, after LT period, graft dysfunction, reoperation, bacterial infection, sepsis and acute CNIs toxicity may be associated to renal dysfunction^[8-12].

Since pre-LT risk factors may influence intra-operative events responsible for PRS-induced AKI, we aim to consider all the relevant aspects involved in PRS-induced AKI in the setting of LT and to identify all studies that find out the specific mechanisms linking PRS and AKI.

LITERATURE SEARCH

A PubMed search was conducted using the terms

Table 1 Summary of studies evaluating acute kidney injury in donors after circulatory death liver transplant recipients

Study	Journal and Year	Outcome	Diagnosis
Doyle <i>et al</i> ^[96]	J Am Coll Surg 2015	AKI	RRT
Ruebner <i>et al</i> ^[95]	Transpl Int 2014	End stage renal disease	
Leithead <i>et al</i> ^[112]	J Hepatol 2014	AKI	KDIGO criteria
Elaffandi <i>et al</i> ^[113]	Liver Transpl 2014	Prehospital cardiac arrest	
Leithead <i>et al</i> ^[99]	Am J Transplant 2012	AKI	RIFLE classification

AKI: Acute kidney injury; RRT: Renal replacement therapy; KDIGO: Kidney disease improving global outcomes; RIFLE: Risk, injury, failure, loss of kidney function, and end-stage kidney disease.

liver transplantation AND acute kidney injury; liver transplantation AND post-reperfusion syndrome; acute kidney injury AND post-reperfusion syndrome; acute kidney injury AND DCD AND liver transplantation. Five hundred seventy four articles were retrieved on PubMed search. Results were limited to title/abstract articles published in English between 2000 and 2015; studies on children, case reports, editorials and review articles were not considered. We have identified twenty-three papers that specifically evaluated incidence, risk factors and outcome for patients developing PRS-induced AKI in LT.

In order to identify intra-operative risk factors/mechanisms specifically involved in PRS-induced AKI, avoiding confounding factors, we have limited our study to "acute kidney injury AND DCD AND liver transplantation". Accordingly, three out of five studies were selected for our purpose (Table 1).

ACUTE KIDNEY INJURY POST-LT

Acute kidney injury is a significant complication after LT. It is reported to be associated to an increased mortality^[13,14] and to the development of CKD after LT^[15]. Recently, reversible AKI has been recognised as an important risk factor for *de novo* CKD in the non-transplant setting, suggesting important implications also for the surveillance in patients without pre-existing and clinically evident kidney disease^[16].

The incidence of post-operative AKI in the setting of LT ranges between 12% and 80%, depending on the definition adopted^[17,18], with a 30-d mortality of up to 50% in case of renal dysfunction at transplantation and as high as 90% if renal replacement therapy (RRT) is required^[4,19].

Different criteria have been used to diagnose and classify AKI. A recent new definition of AKI has been proposed on the basis of the universal consensus of KDIGO criteria, which are an evolution of RIFLE and AKIN criteria^[20,21].

Moreover, since all risk factors for AKI in the setting of LT are intertwined between the pre-LT and the intra-

operative period, we should consider all risk factors in order to evaluate the PRS-induced AKI.

PRE-TRANSPLANT RISK FACTORS FOR POST-LT PRS-INDUCED AKI

MELD

MELD score was created to predict poor survival in patients with liver cirrhosis and portal hypertension complications, undergoing elective transjugular intrahepatic porto-systemic shunts placement^[22]. The formula for calculation of MELD includes only 3 objective parameters [serum creatinine (sCr), serum bilirubin and INR]; it was validated by the Organ Procurement and Transplantation Network in 2002 as an accurate predictor of poor survival in patients with various stages of liver disease, as well as in patients of different geographic origin^[23]. The main use of MELD score is regarded to liver graft allocation, identifying those patients in greater immediate need for LT^[24], and in predicting outcome and survival post-LT^[25,26]. Pre-operative sCr was identified as an independent predictor of post-transplant mortality before the introduction of MELD score^[27].

Other factors affect sCr, such as gender. It is reported that women are disadvantaged in MELD era possibly due to the inclusion of sCr. Women are less likely than men to receive a LT and have greater 3-mo mortality, probably due to low sCr and MELD compared to men. However within most MELD strata, women had more deranged serum bilirubin and INR^[28].

End stage liver disease

In advanced cirrhosis, the systemic vascular resistance is particularly decreased, and any additional increase in cardiac output can no longer compensate, leading to under filling of arterial circulation^[29]. In this scenario, systemic arterial pressure and effective arterial blood volume are maintained through the activation of vasoconstrictor systems, including renin-angiotensin-aldosterone system (RAAS), sympathetic nervous system, and, later, non-osmotic hyper-secretion of antidiuretic hormone. This leads to sodium and solute-free water retention and renal failure due to intra-renal vasoconstriction and hypoperfusion^[29].

Recently, a new specific form, named acute-on-chronic liver failure has been recognised to be associated to high risk for short-term mortality in advanced ESLD. This syndrome is defined as an acute decompensation of cirrhosis (development of ascites, bacterial infections, gastrointestinal hemorrhage and/or encephalopathy) associated to organ failure (liver, kidney, coagulation, circulation, respiration, brain) and high short-term mortality, $\geq 15\%$ within a period of 28 d^[30]. The type of organ failure is obviously a risk factor for mortality and it is $> 15\%$ in patients with kidney failure compared to $< 15\%$ for single non-kidney organ failures^[31].

The aetiology of ESLD in some cases seems to be involved in the occurrence of AKI. Non-alcoholic steatohepatitis (NASH), now regarded as the hepatic manifestation of the metabolic syndrome^[32-34], was found to be more frequently associated with post-LT AKI compared to other liver diseases leading to ESLD. This association is not surprising, since the increasing prevalence of NASH and non-alcoholic fatty liver disease (NAFLD) contributes to hyperlipidaemia and diabetes.

Clear evidences suggest the existence of a link between NAFLD/NASH and renal impairment. Different mechanisms have been hypothesized, involving multiple pro-inflammatory substances that originate in the steatotic and inflamed liver or through the contribution of systemic insulin resistance and atherogenic dyslipidemia^[35].

Patients with NAFLD have significantly low levels of adiponectin, higher levels of hemostatic and inflammatory factors, oxidative stress and endothelial dysfunction biomarkers^[34,36-39]. Similarly, patients with renal disease showed reduced adiponectin levels, as well as increased levels of oxidative stress and systemic inflammation biomarkers, hypofibrinolysis and hypercoagulation^[40-43]. The supposed mechanisms that link NAFLD and renal disease may begin from the inflamed and expanded visceral adipose tissue that releases multiple molecules, such as free fatty acids, hormones, tumor necrosis factor- α , interleukin-6, and other pro-inflammatory cytokines, that seem to be implicated in the insulin resistance and kidney damage^[44,45]. In this context, the liver is both source of several mediators and target of these systemic abnormalities, amplifying kidney damage. Even though the mechanisms by which oxidative stress and chronic inflammation can damage kidney are not completely described, some studies on animal models showed that cytokine imbalance may have a role in the pathogenesis of kidney involvement through the activation of different pro-inflammatory pathways, up-regulation of adhesion molecules, induction of oxidative stress and endothelial dysfunction, as well as reduction of adiponectin expression^[43,46-49]. As a result, patients with NAFLD should be considered at increased risk for the occurrence of pre-transplant renal disease^[35]. Furthermore, macrovesicular steatosis was described as a risk factor for PRS by Chung *et al.*^[50].

Evaluation of renal function

The evaluation of renal function in patients with ESLD waiting for LT remains a challenge. Serum creatinine may be influenced by several factors including age, race, gender, body weight, medications, diet and laboratory techniques. In the context of cirrhosis, sCr can be affected by reduced hepatic production of creatine (> 40%), protein malnutrition, decreased muscle mass, oedema and increased tubular secretion of creatinine^[51]. As a result, low levels of sCr are the

result of an underestimation of glomerular filtration rate (GFR). Therefore, the evaluation of sCr modifications from baseline is the best way to assess renal function in patients with ESLD^[8].

Since the multiple limitations of sCr as a measure of renal function in these patients, alternative methods were proposed such as GFR estimation by inulin clearance^[52]. This is the gold standard for renal function assessment but its routinely use is limited due to high cost and technical difficulties^[52]. Other direct methods are characterized by the use of exogenous radiolabelled substances or non-radioactive agents^[53]. Nevertheless they have not been widely confirmed in patients with ESLD. Furthermore, creatinine clearance is not better than sCr in evaluating renal function in patients with cirrhosis due to several variables including potential errors in collection and measurement of urine, variations in re-absorption or excretion of creatinine and sCr dilution caused by fluid retention^[54].

Serum cystatin C is freely filtered by glomeruli and then re-absorbed and catabolized by proximal tubules^[55]. For this reason, it is recognised as a sensitive indicator of renal function in liver cirrhosis^[56,57], significantly different from inulin or exogenous radiolabelled substances^[58,59]. However, further studies are needed to develop specific cystatin C-based GFR estimation formulas in patients with ESLD.

Nevertheless, sCr remains the clinical marker of kidney function for routinely practice, and changes in sCr are currently used specifically to define AKI.

Therefore, in order to standardize its definition, the classification of AKI was recently revised by KDIGO group including all causes of acute renal dysfunction as indicated by an increase in sCr to 1.5-1.9 times from baseline within 7 d or an increase in sCr by ≥ 26.5 mmol/L (≥ 0.3 mg/dL) in < 48 h, allowing patients with less severe degrees of renal dysfunction to receive treatment^[60].

Pre-existing renal disease

Kidney failure among patients with ESLD is closely related to liver disease severity. This is due to circulatory disturbances characterized by reduced systemic vascular resistance secondary to splanchnic arterial vasodilatation due to portal hypertension^[29,61].

Hepatic and renal disorders are frequently associated as a result of a number of systemic conditions that concurrently affect liver and kidney. Furthermore, renal dysfunction is also a common complication of primary liver disorders with renal histological changes mainly of glomerular type, named hepatic glomerulosclerosis. It was initially described predominantly in patients with advanced liver cirrhosis and recently in HCV-related cirrhosis^[62,63]. This is characterised by mesangial expansion, thickening of capillary walls, a mild increase in size and number of endothelial and epithelial cells, and deposits of immunoglobulins and electron-dense material in the mesangium and capillary walls^[63,64],

as demonstrated in renal biopsies performed at the time of LT^[63,65]. Recently, trans-jugular renal biopsies performed in cirrhotic patients with clotting problems showed an incidence > 70% of glomerular lesions with a prevalence of IgA deposition^[66].

In advanced cirrhosis, renal dysfunction results mainly from renal hypoperfusion due to intravascular volume depletion secondary to diuretic use, lactulose-induced diarrhoea, gastrointestinal bleeding, infections, use of nephrotoxic agents such as nonsteroidal anti-inflammatory drugs, contrast agents, and aminoglycosides. Intense renal vasoconstriction, as seen during hepatorenal syndrome, can in turn lead to renal tubular necrosis. The histological changes are very similar to those reported for chronic nephrotoxicity from calcineurin inhibitors and differential diagnosis may be difficult^[61,67-69].

Hepatitis B virus-related cirrhosis is associated with membranous glomerulonephritis (GN) and membranoproliferative GN, but also with vasculitis, such as polyarteritis nodosa^[70]. Hepatitis C virus-related cirrhosis is associated primarily with membranoproliferative GN and cryoglobulinaemia, but also with fibrillary GN^[71,72]. In addition, the occurrence of type 2 diabetes mellitus in HCV-infected patients is associated with earlier loss of renal function compared with uninfected patients^[73]. Alcoholic cirrhosis is linked mainly with IgA nephropathy^[74]. Primary sclerosing cholangitis and primary biliary cirrhosis are associated with anti-neutrophil cytoplasmic autoantibody-positive vasculitis and membranous nephropathy^[74,75].

A few primary diseases can affect both liver and kidney, including polycystic disease, primary oxaluria, alpha1-antitrypsin deficiency and Wilson's disease. A secondary involvement of the kidney may result such as in diabetic nephropathy.

In literature it is increasingly reported a close association between renal failure and severe liver dysfunction in patients with ESLD^[76-79]. In the setting of LT the interval of pre-transplant renal dysfunction is predictive of 6- and 12-mo sCr post-transplant^[80].

MELD score, ESLD, pre-existing Renal Disease and PRS-induced AKI

Recipient characteristics including older recipient age^[81], higher MELD score, sCr levels^[82], bilirubin and higher pre-operative heart rate^[50] seem to have a role in the development of PRS. This may reflect the occurrence of haemodynamic and cardiovascular complications that characterise patients with cirrhosis^[83]. These patients develop splanchnic arteriolar vasodilatation, leading to reductions of systemic vascular resistance, central volume, and arterial filling. The activation of RAAS and sympathetic nervous system, and the release of vasopressin all contribute to maintain the arterial blood pressure, thus inducing a hyperdynamic circulatory state^[83]. The progression of cirrhosis leads to more pronounced splanchnic vasodilatation with failure of the hyperdynamic compensation, lower

systemic vascular resistance index, higher cardiac output, and decreased arterial blood pressure^[83,84]. The state of advanced cirrhosis is in line with the higher MELD score and the more pronounced haemodynamic changes with the occurrence of renal dysfunction.

The loss of integrity of the vasoconstrictive response during graft reperfusion is also believed to be, at least partially, responsible for the development PRS^[85,86].

In an experimental model of rats with portal hypertension the pressor response generated by the sympathetic system was found to be impaired^[87]. Similarly, the peripheral vascular response to angiotensin II and noradrenaline is attenuated in patients with liver cirrhosis^[88,89]. Garutti Martinez *et al.*^[85] reported a lower increase in vascular muscle tone reflected by an increased systemic vascular resistance index in patients experiencing PRS, suggesting a reduced vascular adaptability in these patients. A significant reduction in sympathetic tone has also been reported in patients who developed PRS^[86]. Although altered cardiovascular autonomic control may not clarify the reason for the occurrence of graft reperfusion-related hypotension during LT, the assessment of autonomic indices may be helpful in predicting PRS occurrence and may help anaesthesiologist management in preventive treatment with vasoconstrictors before any substantial decrease in MAP in the first minutes after reperfusion.

Left ventricular diastolic dysfunction was found to be a risk factor for the development of PRS in a Chinese population of liver transplanted patients by Xu *et al.*^[90]. Diastolic dysfunction has been entitled as cause of perioperative haemodynamic instability and an adverse outcome following cardiac surgery^[91] and may contribute to the development of PRS by inducing haemodynamic instability during LT.

SPECIFIC INTRA-OPERATIVE RISK FACTORS FOR POST-LT PRS-INDUCED AKI

PRS

PRS is an intra-operative complication that characterizes specific surgical phases related to instability at reperfusion involving cardiovascular and metabolic alterations, together with a PRS-induced AKI, that can influence recipient's morbidity and mortality. Pathophysiology of PRS has not been clarified yet; several mechanisms have been hypothesized, considering factors related to recipient or donor characteristics, graft quality and intra-operative factors.

Donors deceased after circulatory death characterized by prolonged ischaemic phase of the graft compared to traditional brain death donors. Although LT from DCD donors demonstrates satisfactory long-term outcomes, these are burdened by a higher degree of delayed graft function compared to donation after brain death (DBD) and a higher frequency of AKI as well as CKD^[92-95], despite similar pre-LT renal

function^[96]. In this setting, the damage sustained by the graft during cold preservation following recovery from the donor and during subsequent warm at implantation into the recipient^[97] is intensified by the period of warm ischaemia in the donor. The functional donor warm ischemic time (dWIT) is defined as the interval between hypotension (Systolic Blood Pressure < 50 mmHg) or hypoxia (O₂ saturations < 70%) and cold perfusion of the aorta^[98]. Functional dWIT adds complementary injury to cold ischaemia. Elevation of serum aminotransferase enzymes is the first clinical evidence of IRI of the graft, which can lead up to clinical liver dysfunction and progressive graft failure. In a study by Leithead *et al*^[99] on AKI in DCD LT, the only consistent predictor of renal outcomes was peak peri-operative aspartate aminotransferase, which represents a surrogate marker of hepatic IRI. The hepatic IRI is known to evoke a systemic inflammatory response, which can cause distant organ dysfunction and AKI through haemodynamic mechanisms and direct tubular cell death, associated to PRS^[23,100-103]. Therefore, graft injury, by driving a systemic inflammatory response, may be a contributing factor of PRS-induced AKI.

Furthermore, in the same single-centre case-controlled study it has been shown for the first time that LT from DCD donors was associated with higher incidence of AKI and RRT, evaluated by RIFLE criteria, compared to propensity score-matched DBD recipients, despite a significant (53.4% vs 31.8%, $P = 0.004$) better renal function in DCD vs DBD^[99].

Donor and graft characteristics

Cold ischaemia time (CIT) and graft steatosis have been reported to be associated with PRS in several studies^[6,13,17,21,22]. The increased CIT is likely to increase the IRI which is associated with release of increased amounts of pro-inflammatory mediators, generation of free radicals, neutrophil sequestration and activation^[50]. Steatotic livers tolerate less the IRI and it is conceivable that the higher percentage of steatosis is linked to a higher degree of damage. The release of vasoactive substances, including reactive oxygen species^[32], pro-inflammatory chemokines and cytokines^[33], from the transplanted liver is also considered as a possible mechanism of PRS.

An important link between IRI and PRS is similarly accounted by Pan *et al*^[104] in their retrospective study, where they report a double incidence of PRS in DCD compared to DBD (25.7% vs 12.2%, respectively). These authors also suggest that the severe IRI experienced by DCD grafts during the additional warm ischaemia occurring before organ procurement may play a role in the development of PRS.

Donor age and donor risk index (DRI) are also reported being associated with the development of PRS^[105] and with greater haemodynamic instability and delayed intra-operative haemodynamic recovery.

A role for poor tolerance of ischemia-reperfusion phenomenon or age-related steatotic parenchymal changes (senescence) has been advocated^[105].

Intra-operative factors

Intra-operative events additionally play a role in transfusion requirements^[50,81,106]. These are associated to the severity of liver disease, characterized by anaemia and coagulation abnormalities. Intra-operative blood loss thereby increases, requiring transfusion of blood products, which itself is linked to fibrinolysis associated with severe PRS^[81,106].

The use of piggy-back technique and porto-caval shunt seems to reduce the occurrence of PRS^[107,108]. The piggy-back technique is proven to provide better haemodynamic stability and the severity of PRS has been associated to the surgical technique utilised. Currently, piggy-back technique is widely used making difficult to clearly ascertain the role of operation technique as a risk factor^[108].

Otherwise the preservation of caval flow does not prevent hypotension during graft reperfusion^[109]. The creation of a temporary portocaval shunt in patients with cirrhosis during the anhepatic phase, reducing splanchnic congestion, in theory limits splanchnic ischaemia and the subsequent release of toxic mediators at reperfusion^[110]. This hypothesis may in part account for the protective effect of a portocaval shunt toward the incidence of intra-operative PRS^[107].

The need for emergent and unplanned intra-operative RRT (IORRT) during LT is associated with a greater incidence of PRS compared to both patients not receiving IORRT and patients receiving planned IORRT^[111]. IORRT become part of a complex multifactorial cause of reduced patients short-term survival. A role has been advocated for planned IORRT to correct metabolic derangements due to electrolyte and acid/base disturbances occurring in patients with pre-transplant renal failure^[111].

CONCLUSION

Although advances in medical and surgical techniques have been done to improve survival among LT recipients, mortality rates related to post-LT renal complications remain a concern. The onset of AKI post-LT is multifactorial, with pre-LT risk factors involved, including higher MELD score, ESLD and pre-existing renal dysfunction, either with intra-operative conditions such as IRI and PRS. Recently, PRS-induced AKI is considered an important complication post-LT that characterizes kidney involvement caused by PRS with mechanisms not clearly understood and implication on graft and patient survival. Pre-LT risk factors for AKI and PRS are closely intertwined and the impact of PRS-induced AKI on the onset of long-term CKD is very important. Furthermore, a strong influence of donor quality has also been described on the development of CKD post-LT^[95]. Receiving a liver from DCD or with

higher DRI increase the risk of end-stage renal disease by 40%, despite favourable recipient characteristics, supporting the current knowledge that donor quality is associated with short and long-term outcomes, renal injury in particular^[95]. The better understanding of predisposing factors for post-LT AKI may give the possibility to improve methods to prevent or ameliorate injury. Therefore, this new understanding may possibly help researchers to develop further studies in order to better clarify PRS and PRS-induced AKI, in particular in DCD recipients.

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