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**Acute kidney injury and post-reperfusion syndrome in liver transplantation**

Umbro I *et al*. AKI and PRS in liver transplantation

Ilaria Umbro, Francesca Tinti, Irene Scalera, Felicity Evison, Bridget Gunson, Adnan Sharif, James Ferguson, Paolo Muiesan, Anna Paola Mitterhofer

**Ilaria Umbro**, **Francesca Tinti**, **Anna Paola Mitterhofer**, Department of Clinical Medicine, Nephrology and Dialysis B, Sapienza University of Rome, 00185 Rome, Italy

**Ilaria Umbro**, **Francesca Tinti**, **Irene Scalera**, **James Ferguson**, **Paolo Muiesan**, The Liver Unit, Queen Elizabeth Hospital Birmingham, Birmingham B15 2TH, United Kingdom

**Felicity Evison**, Department of Health Informatics, University Hospitals Birmingham NHS Foundation Trust, Birmingham B15 2TH, United Kingdom

**Bridget Gunson**, National Institute for Health Research Birmingham Liver Biomedical Research Unit, the Liver Unit, Queen Elizabeth Hospital Birmingham, Birmingham B15 2TH, United Kingdom

**Adnan Sharif**, Department of Nephrology and Transplantation, Queen Elizabeth Hospital Birmingham, Birmingham B15 2TH, United Kingdom

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**Correspondence to: Anna Paola Mitterhofer, MD, PhD, FEBTM, Associate Professor,** Department of Clinical Medicine, Nephrology and Dialysis B, Sapienza University of Rome, Viale dell’Università 37, 00185 Rome, Italy. annapaola.mitter@uniroma1.it

**Telephone:** +39-6 -49972089

**Fax:** +39-6 -49972089

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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 sever 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 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. Post-reperfusion syndrome 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 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 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 (Table 1).

**ACUTE KIDNEY INJURY POST-LIVER TRANSPLANTATION**

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-days 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, serum bilirubin and INR); it was validated by the Organ Procurement and Transplantation Network (OPTN) 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 serum creatinine (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-month 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 (ACLF) 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, ≥ 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 (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 (FFA), hormones, tumor necrosis factor-alpha, interleukin (IL)-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, macrovescicular 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 incuding 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 of > 50% within 7 d or an increase in sCr of ≥ 26.4 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 membrano-prolipherative GN, but also with vasculitis, such as polyarteritis nodosa[70]. Hepatitis C virus-related cirrhosis is associated primarily with membrano-prolipherative 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]. Alcoholiccirrhosis 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-month 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 CO, 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 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[85]. 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 mean arterial pressure 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**

***Post-reperfusion syndrome***

Post-reperfusion syndrome is an intra-operative complication that characterizes specific intra-operative 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.

circulatory death (DCD) 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 BP < 50 mmHg) or hypoxia (02 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 ischaemia reperfusion injury (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 liver transplantation, the only consistent predictor of renal outcomes was peak peri-operative aspartate aminotransferase (AST), 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 with 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 in several studies associated with PRS[6,13,17,21,22] and 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. in their retrospective study, where they report a double incidence of PRS in DCD compared to DBD (25.7% *vs* 12.2%, respectively)[104]. 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 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.

**REFERENCES**

1 **Ojo AO**, Held PJ, Port FK, Wolfe RA, Leichtman AB, Young EW, Arndorfer J, Christensen L, Merion RM. Chronic renal failure after transplantation of a nonrenal organ. *N Engl J Med* 2003; **349**: 931-940 [PMID: 12954741 DOI: 10.1056/NEJMoa021744]

2 **Allen AM**, Kim WR, Therneau TM, Larson JJ, Heimbach JK, Rule AD. Chronic kidney disease and associated mortality after liver transplantation--a time-dependent analysis using measured glomerular filtration rate. *J Hepatol* 2014; **61**: 286-292 [PMID: 24713190 DOI: 10.1016/j.jhep.2014.03.034]

3 **Chawla LS**, Eggers PW, Star RA, Kimmel PL. Acute kidney injury and chronic kidney disease as interconnected syndromes. *N Engl J Med* 2014; **371**: 58-66 [PMID: 24988558 DOI: 10.1056/NEJMra1214243]

4 **Cabezuelo JB**, Ramírez P, Ríos A, Acosta F, Torres D, Sansano T, Pons JA, Bru M, Montoya M, Bueno FS, Robles R, Parrilla P. Risk factors of acute renal failure after liver transplantation. *Kidney Int* 2006; **69**: 1073-1080 [PMID: 16528257 DOI: 10.1038/sj.ki.5000216]

5 **O'Riordan A**, Wong V, McQuillan R, McCormick PA, Hegarty JE, Watson AJ. Acute renal disease, as defined by the RIFLE criteria, post-liver transplantation. *Am J Transplant* 2007; **7**: 168-176 [PMID: 17109735 DOI: 10.1111/j.1600-6143.2006.01602.x]

6 **Guitard J**, Cointault O, Kamar N, Muscari F, Lavayssière L, Suc B, Ribes D, Esposito L, Barange K, Durand D, Rostaing L. Acute renal failure following liver transplantation with induction therapy. *Clin Nephrol* 2006; **65**: 103-112 [PMID: 16509459]

7 **Siniscalchi A**, Gamberini L, Laici C, Bardi T, Ercolani G, Lorenzini L, Faenza S. Post reperfusion syndrome during liver transplantation: From pathophysiology to therapy and preventive strategies. *World J Gastroenterol* 2016; **22**: 1551-1569 [PMID: 26819522 DOI: 10.3748/wjg.v22.i4.1551]

8 **Wong F**, Nadim MK, Kellum JA, Salerno F, Bellomo R, Gerbes A, Angeli P, Moreau R, Davenport A, Jalan R, Ronco C, Genyk Y, Arroyo V. Working Party proposal for a revised classification system of renal dysfunction in patients with cirrhosis. *Gut* 2011; **60**: 702-709 [PMID: 21325171 DOI: 10.1136/gut.2010.236133]

9 **Lima EQ**, Zanetta DM, Castro I, Massarollo PC, Mies S, Machado MM, Yu L. Risk factors for development of acute renal failure after liver transplantation. *Ren Fail* 2003; **25**: 553-560 [PMID: 12911159]

10 **Contreras G**, Garces G, Quartin AA, Cely C, LaGatta MA, Barreto GA, Roth D, Gomez E. An epidemiologic study of early renal replacement therapy after orthotopic liver transplantation. *J Am Soc Nephrol* 2002; **13**: 228-233 [PMID: 11752042]

11 **Tinti F**, Umbro I, Meçule A, Rossi M, Merli M, Nofroni I, Corradini SG, Poli L, Pugliese F, Ruberto F, Berloco PB, Mitterhofer AP. RIFLE criteria and hepatic function in the assessment of acute renal failure in liver transplantation. *Transplant Proc* 2010; **42**: 1233-1236 [PMID: 20534269 DOI: 10.1016/j.transproceed.2010.03.128]

12 **Fabrizi F**, Dixit V, Martin P, Messa P. Chronic kidney disease after liver transplantation: Recent evidence. *Int J Artif Organs* 2010; **33**: 803-811 [PMID: 21140356]

13 **Wilkinson A**, Pham PT. Kidney dysfunction in the recipients of liver transplants. *Liver Transpl* 2005; : S47-S51 [PMID: 16237714 DOI: 10.1002/lt.20618]

14 **Cholongitas E**, Senzolo M, Patch D, Shaw S, O'Beirne J, Burroughs AK. Cirrhotics admitted to intensive care unit: the impact of acute renal failure on mortality. *Eur J Gastroenterol Hepatol* 2009; **21**: 744-750 [PMID: 20160527 DOI: 10.1097/MEG.0b013e328308bb9c]

15 **Velidedeoglu E**, Bloom RD, Crawford MD, Desai NM, Campos L, Abt PL, Markmann JW, Mange KC, Olthoff KM, Shaked A, Markmann JF. Early kidney dysfunction post liver transplantation predicts late chronic kidney disease. *Transplantation* 2004; **77**: 553-556 [PMID: 15084934]

16 **Bucaloiu ID**, Kirchner HL, Norfolk ER, Hartle JE, Perkins RM. Increased risk of death and de novo chronic kidney disease following reversible acute kidney injury. *Kidney Int* 2012; **81**: 477-485 [PMID: 22157656 DOI: 10.1038/ki.2011.405]

17 **Lebrón Gallardo M**, Herrera Gutierrez ME, Seller Pérez G, Curiel Balsera E, Fernández Ortega JF, Quesada García G. Risk factors for renal dysfunction in the postoperative course of liver transplant. *Liver Transpl* 2004; **10**: 1379-1385 [PMID: 15497160 DOI: 10.1002/lt.20215]

18 **Chuang FR**, Lin CC, Wang PH, Cheng YF, Hsu KT, Chen YS, Lee CH, Chen CL. Acute renal failure after cadaveric related liver transplantation. *Transplant Proc* 2004; **36**: 2328-2330 [PMID: 15561239 DOI: 10.1016/j.transproceed.2004.07.002]

19 **Planinsic RM**, Lebowitz JJ. Renal failure in end-stage liver disease and liver transplantation. *Int Anesthesiol Clin* 2006; **44**: 35-49 [PMID: 16832205 DOI: 10.1097/01.aia.0000210807.24298.f7]

20 **Bellomo R**, Kellum JA, Ronco C. Defining and classifying acute renal failure: from advocacy to consensus and validation of the RIFLE criteria. *Intensive Care Med* 2007; **33**: 409-413 [PMID: 17165018 DOI: 10.1007/s00134-006-0478-x]

21 **Ronco C**, Levin A, Warnock DG, Mehta R, Kellum JA, Shah S, Molitoris BA. Improving outcomes from acute kidney injury (AKI): Report on an initiative. *Int J Artif Organs* 2007; **30**: 373-376 [PMID: 17551899]

22 **Malinchoc M**, Kamath PS, Gordon FD, Peine CJ, Rank J, ter Borg PC. A model to predict poor survival in patients undergoing transjugular intrahepatic portosystemic shunts. *Hepatology* 2000; **31**: 864-871 [PMID: 10733541 DOI: 10.1053/he.2000.5852]

23 **Kamath PS**, Wiesner RH, Malinchoc M, Kremers W, Therneau TM, Kosberg CL, D'Amico G, Dickson ER, Kim WR. A model to predict survival in patients with end-stage liver disease. *Hepatology* 2001; **33**: 464-470 [PMID: 11172350 DOI: 10.1053/jhep.2001.22172]

24 **Wiesner RH**, McDiarmid SV, Kamath PS, Edwards EB, Malinchoc M, Kremers WK, Krom RA, Kim WR. MELD and PELD: application of survival models to liver allocation. *Liver Transpl* 2001; **7**: 567-580 [PMID: 11460223 DOI: 10.1053/jlts.2001.25879]

25 **Umbro I**, Tinti F, Mordenti M, Rossi M, Ianni S, Pugliese F, Ruberto F, Ginanni Corradini S, Nofroni I, Poli L, Berloco PB, Mitterhofer AP. Model for end-stage liver disease score versus simplified acute physiology score criteria in acute renal failure after liver transplantation. *Transplant Proc* 2011; **43**: 1139-1141 [PMID: 21620072 DOI: 10.1016/j.transproceed.2011.02.045]

26 **Saab S**, Wang V, Ibrahim AB, Durazo F, Han S, Farmer DG, Yersiz H, Morrisey M, Goldstein LI, Ghobrial RM, Busuttil RW. MELD score predicts 1-year patient survival post-orthotopic liver transplantation. *Liver Transpl* 2003; **9**: 473-476 [PMID: 12740789 DOI: 10.1053/jlts.2003.50090]

27 **Nair S**, Verma S, Thuluvath PJ. Pretransplant renal function predicts survival in patients undergoing orthotopic liver transplantation. *Hepatology* 2002; **35**: 1179-1185 [PMID: 11981768 DOI: 10.1053/jhep.2002.33160]

28 **Cholongitas E**, Marelli L, Kerry A, Goodier DW, Nair D, Thomas M, Patch D, Burroughs AK. Female liver transplant recipients with the same GFR as male recipients have lower MELD scores--a systematic bias. *Am J Transplant* 2007; **7**: 685-692 [PMID: 17217437 DOI: 10.1111/j.1600-6143.2007.01666.x]

29 **Schrier RW**, Arroyo V, Bernardi M, Epstein M, Henriksen JH, Rodés J. Peripheral arterial vasodilation hypothesis: a proposal for the initiation of renal sodium and water retention in cirrhosis. *Hepatology* 1988; **8**: 1151-1157 [PMID: 2971015]

30 **Jalan R**, Williams R. Acute-on-chronic liver failure: pathophysiological basis of therapeutic options. *Blood Purif* 2002; **20**: 252-261 [PMID: 11867872 DOI: 47017]

31 **Moreau R**, Jalan R, Gines P, Pavesi M, Angeli P, Cordoba J, Durand F, Gustot T, Saliba F, Domenicali M, Gerbes A, Wendon J, Alessandria C, Laleman W, Zeuzem S, Trebicka J, Bernardi M, Arroyo V. Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. *Gastroenterology* 2013; **144**: 1426-137, 1426-137, [PMID: 23474284 DOI: 10.1053/j.gastro.2013.02.042]

32 **de Alwis NM**, Day CP. Non-alcoholic fatty liver disease: the mist gradually clears. *J Hepatol* 2008; **48** Suppl 1: S104-S112 [PMID: 18304679 DOI: 10.1016/j.jhep.2008.01.009]

33 **Marchesini G**, Moscatiello S, Di Domizio S, Forlani G. Obesity-associated liver disease. *J Clin Endocrinol Metab* 2008; **93**: S74-S80 [PMID: 18987273 DOI: 10.1210/jc.2008-1399]

34 **Vuppalanchi R**, Chalasani N. Nonalcoholic fatty liver disease and nonalcoholic steatohepatitis: Selected practical issues in their evaluation and management. *Hepatology* 2009; **49**: 306-317 [PMID: 19065650 DOI: 10.1002/hep.22603]

35 **Targher G**, Chonchol M, Zoppini G, Abaterusso C, Bonora E. Risk of chronic kidney disease in patients with non-alcoholic fatty liver disease: is there a link? *J Hepatol* 2011; **54**: 1020-1029 [PMID: 21145850 DOI: 10.1016/j.jhep.2010.11.007]

36 **Targher G**, Day CP, Bonora E. Risk of cardiovascular disease in patients with nonalcoholic fatty liver disease. *N Engl J Med* 2010; **363**: 1341-1350 [PMID: 20879883 DOI: 10.1056/NEJMra0912063]

37 **Targher G**, Bertolini L, Padovani R, Rodella S, Tessari R, Zenari L, Day C, Arcaro G. Prevalence of nonalcoholic fatty liver disease and its association with cardiovascular disease among type 2 diabetic patients. *Diabetes Care* 2007; **30**: 1212-1218 [PMID: 17277038 DOI: 10.2337/dc06-2247]

38 **Targher G**, Chonchol M, Miele L, Zoppini G, Pichiri I, Muggeo M. Nonalcoholic fatty liver disease as a contributor to hypercoagulation and thrombophilia in the metabolic syndrome. *Semin Thromb Hemost* 2009; **35**: 277-287 [PMID: 19452403 DOI: 10.1055/s-0029-1222606]

39 **Targher G**, Zoppini G, Moghetti P, Day CP. Disorders of coagulation and hemostasis in abdominal obesity: emerging role of fatty liver. *Semin Thromb Hemost* 2010; **36**: 41-48 [PMID: 20391295 DOI: 10.1055/s-0030-1248723]

40 **Vlagopoulos PT**, Sarnak MJ. Traditional and nontraditional cardiovascular risk factors in chronic kidney disease. *Med Clin North Am* 2005; **89**: 587-611 [PMID: 15755469 DOI: 10.1016/j.mcna.2004.11.003]

41 **Weiner DE**, Tighiouart H, Elsayed EF, Griffith JL, Salem DN, Levey AS, Sarnak MJ. The relationship between nontraditional risk factors and outcomes in individuals with stage 3 to 4 CKD. *Am J Kidney Dis* 2008; **51**: 212-223 [PMID: 18215699 DOI: 10.1053/j.ajkd.2007.10.035]

42 **Kendrick J**, Chonchol MB. Nontraditional risk factors for cardiovascular disease in patients with chronic kidney disease. *Nat Clin Pract Nephrol* 2008; **4**: 672-681 [PMID: 18825155 DOI: 10.1038/ncpneph0954]

43 **Kronenberg F**. Emerging risk factors and markers of chronic kidney disease progression. *Nat Rev Nephrol* 2009; **5**: 677-689 [PMID: 19935815 DOI: 10.1038/nrneph.2009.173]

44 **Badman MK**, Flier JS. The adipocyte as an active participant in energy balance and metabolism. *Gastroenterology* 2007; **132**: 2103-2115 [PMID: 17498506 DOI: 10.1053/j.gastro.2007.03.058]

45 **Shoelson SE**, Herrero L, Naaz A. Obesity, inflammation, and insulin resistance. *Gastroenterology* 2007; **132**: 2169-2180 [PMID: 17498510 DOI: 10.1053/j.gastro.2007.03.059]

46 **Massy ZA**, Stenvinkel P, Drueke TB. The role of oxidative stress in chronic kidney disease. *Semin Dial* 2009; **22**: 405-408 [PMID: 19708991 DOI: 10.1111/j.1525-139X.2009.00590.x]

47 **Vlassara H**, Torreggiani M, Post JB, Zheng F, Uribarri J, Striker GE. Role of oxidants/inflammation in declining renal function in chronic kidney disease and normal aging. *Kidney Int Suppl* 2009; **(2009)**: S3-11 [PMID: 19946325 DOI: 10.1038/ki.2009.401]

48 **Carrero JJ**, Park SH, Axelsson J, Lindholm B, Stenvinkel P. Cytokines, atherogenesis, and hypercatabolism in chronic kidney disease: a dreadful triad. *Semin Dial* 2009; **22**: 381-386 [PMID: 19708986 DOI: 10.1111/j.1525-139X.2009.00585.x]

49 **Matsuzawa Y**, Funahashi T, Kihara S, Shimomura I. Adiponectin and metabolic syndrome. *Arterioscler Thromb Vasc Biol* 2004; **24**: 29-33 [PMID: 14551151 DOI: 10.1161/01.ATV.0000099786.99623.EF]

50 **Chung IS**, Kim HY, Shin YH, Ko JS, Gwak MS, Sim WS, Kim GS, Lee SK. Incidence and predictors of post-reperfusion syndrome in living donor liver transplantation. *Clin Transplant* 2012; **26**: 539-543 [PMID: 22168355 DOI: 10.1111/j.1399-0012.2011.01568.x]

51 **Orlando R**, Floreani M, Padrini R, Palatini P. Evaluation of measured and calculated creatinine clearances as glomerular filtration markers in different stages of liver cirrhosis. *Clin Nephrol* 1999; **51**: 341-347 [PMID: 10404694]

52 **Rognant N**, Bacchetta J, Dubourg L, Ahmed SN, Radenne S, Dumortier J, Hadj-Aïssa A. What is the best alternative to inulin clearance to estimate GFR in patients with decompensated alcoholic cirrhosis? *Nephrol Dial Transplant* 2010; **25**: 3569-3575 [PMID: 20466685 DOI: 10.1093/ndt/gfq248]

53 **Fleming JS**, Nunan TO. The new BNMS guidelines for measurement of glomerular filtration rate. *Nucl Med Commun* 2004; **25**: 755-757 [PMID: 15266168]

54 **Proulx NL**, Akbari A, Garg AX, Rostom A, Jaffey J, Clark HD. Measured creatinine clearance from timed urine collections substantially overestimates glomerular filtration rate in patients with liver cirrhosis: a systematic review and individual patient meta-analysis. *Nephrol Dial Transplant* 2005; **20**: 1617-1622 [PMID: 15855207 DOI: 10.1093/ndt/gfh839]

55 **Newman DJ**. Cystatin C. *Ann Clin Biochem* 2002; **39**: 89-104 [PMID: 11928770]

56 **Woitas RP**, Stoffel-Wagner B, Flommersfeld S, Poege U, Schiedermaier P, Klehr HU, Spengler U, Bidlingmaier F, Sauerbruch T. Correlation of serum concentrations of cystatin C and creatinine to inulin clearance in liver cirrhosis. *Clin Chem* 2000; **46**: 712-715 [PMID: 10794756]

57 **Orlando R**, Mussap M, Plebani M, Piccoli P, De Martin S, Floreani M, Padrini R, Palatini P. Diagnostic value of plasma cystatin C as a glomerular filtration marker in decompensated liver cirrhosis. *Clin Chem* 2002; **48**: 850-858 [PMID: 12029000]

58 **Xirouchakis E**, Marelli L, Cholongitas E, Manousou P, Calvaruso V, Pleguezuelo M, Guerrini GP, Maimone S, Kerry A, Hajjawi M, Nair D, Thomas M, Patch D, Burroughs AK. Comparison of cystatin C and creatinine-based glomerular filtration rate formulas with 51Cr-EDTA clearance in patients with cirrhosis. *Clin J Am Soc Nephrol* 2011; **6**: 84-92 [PMID: 20829419 DOI: 10.2215/CJN.03400410]

59 **Pöge U**, Gerhardt T, Stoffel-Wagner B, Klehr HU, Sauerbruch T, Woitas RP. Calculation of glomerular filtration rate based on cystatin C in cirrhotic patients. *Nephrol Dial Transplant* 2006; **21**: 660-664 [PMID: 16326735 DOI: 10.1093/ndt/gfi305]

60 Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO Clinical Practice Guideline for Acute Kidney Injury. *Kidney Int Suppl* 2012; **2**: 1–138

61 **Ginès P**, Schrier RW. Renal failure in cirrhosis. *N Engl J Med* 2009; **361**: 1279-1290 [PMID: 19776409 DOI: 10.1056/NEJMra0809139]

62 **Sakaguchi H**, Dachs S, Grishman E, Paronetto F, Salomon M, Churg J. Hepatic glomerulosclerosis. an electron microscopic study of renal biopsies in liver diseases. *Lab Invest* 1965; **14**: 533-545 [PMID: 14286387]

63 **Axelsen RA**, Crawford DH, Endre ZH, Lynch SV, Balderson GA, Strong RW, Fleming SJ. Renal glomerular lesions in unselected patients with cirrhosis undergoing orthotopic liver transplantation. *Pathology* 1995; **27**: 237-246 [PMID: 8532390]

64 **Berger J**, Yaneva H, Nabarra B. Glomerular changes in patients with cirrhosis of the liver. *Adv Nephrol Necker Hosp* 1977; **7**: 3-14 [PMID: 96677]

65 **Crawford DH**, Endre ZH, Axelsen RA, Lynch SV, Balderson GA, Strong RW, Kerlin P, Powell LW, Fleming SJ. Universal occurrence of glomerular abnormalities in patients receiving liver transplants. *Am J Kidney Dis* 1992; **19**: 339-344 [PMID: 1562023]

66 **Sam R**, Leehey DJ, Picken MM, Borge MA, Yetter EM, Ing TS, Van Thiel DH. Transjugular renal biopsy in patients with liver disease. *Am J Kidney Dis* 2001; **37**: 1144-1151 [PMID: 11382682]

67 **Poggio ED**, Batty DS, Flechner SM. Evaluation of renal function in transplantation. *Transplantation* 2007; **84**: 131-136 [PMID: 17667802 DOI: 10.1097/01.tp.0000269108.59275.dc]

68 **Garcia-Tsao G**, Parikh CR, Viola A. Acute kidney injury in cirrhosis. *Hepatology* 2008; **48**: 2064-2077 [PMID: 19003880 DOI: 10.1002/hep.22605]

69 **Stratta P**, Canavese C, Quaglia M, Balzola F, Bobbio M, Busca A, Franchello A, Libertucci D, Mazzucco G. Posttransplantation chronic renal damage in nonrenal transplant recipients. *Kidney Int* 2005; **68**: 1453-1463 [PMID: 16164622 DOI: 10.1111/j.1523-1755.2005.00558.x]

70 **Lai KN**, Li PK, Lui SF, Au TC, Tam JS, Tong KL, Lai FM. Membranous nephropathy related to hepatitis B virus in adults. *N Engl J Med* 1991; **324**: 1457-1463 [PMID: 2023605 DOI: 10.1056/NEJM199105233242103]

71 **Johnson RJ**, Gretch DR, Yamabe H, Hart J, Bacchi CE, Hartwell P, Couser WG, Corey L, Wener MH, Alpers CE. Membranoproliferative glomerulonephritis associated with hepatitis C virus infection. *N Engl J Med* 1993; **328**: 465-470 [PMID: 7678440 DOI: 10.1056/NEJM199302183280703]

72 **Markowitz GS**, Cheng JT, Colvin RB, Trebbin WM, D'Agati VD. Hepatitis C viral infection is associated with fibrillary glomerulonephritis and immunotactoid glomerulopathy. *J Am Soc Nephrol* 1998; **9**: 2244-2252 [PMID: 9848778]

73 **Soma J**, Saito T, Taguma Y, Chiba S, Sato H, Sugimura K, Ogawa S, Ito S. High prevalence and adverse effect of hepatitis C virus infection in type II diabetic-related nephropathy. *J Am Soc Nephrol* 2000; **11**: 690-699 [PMID: 10752528]

74 **Mulder AH**, Horst G, Haagsma EB, Limburg PC, Kleibeuker JH, Kallenberg CG. Prevalence and characterization of neutrophil cytoplasmic antibodies in autoimmune liver diseases. *Hepatology* 1993; **17**: 411-417 [PMID: 8444414]

75 **Min JK**, Park KS, Yu WJ, Lee YS, Park SM, Park SH, Cho CS, Kim HY. Systemic mononuclear inflammatory vasculopathy associated with Sjögren's syndrome in a patient with primary biliary cirrhosis. *Korean J Intern Med* 2000; **15**: 89-92 [PMID: 10714099]

76 **Baliga P**, Merion RM, Turcotte JG, Ham JM, Henley KS, Lucey MR, Schork A, Shyr Y, Campbell DA. Preoperative risk factor assessment in liver transplantation. *Surgery* 1992; **112**: 704-10; discussion 710-1 [PMID: 1411941]

77 **Gonwa TA**, McBride MA, Anderson K, Mai ML, Wadei H, Ahsan N. Continued influence of preoperative renal function on outcome of orthotopic liver transplant (OLTX) in the US: where will MELD lead us? *Am J Transplant* 2006; **6**: 2651-2659 [PMID: 16939515 DOI: 10.1111/j.1600-6143.2006.01526.x]

78 **Cárdenas A**, Ginès P, Uriz J, Bessa X, Salmerón JM, Mas A, Ortega R, Calahorra B, De Las Heras D, Bosch J, Arroyo V, Rodés J. Renal failure after upper gastrointestinal bleeding in cirrhosis: incidence, clinical course, predictive factors, and short-term prognosis. *Hepatology* 2001; **34**: 671-676 [PMID: 11584362 DOI: 10.1053/jhep.2001.27830]

79 **Fraley DS**, Burr R, Bernardini J, Angus D, Kramer DJ, Johnson JP. Impact of acute renal failure on mortality in end-stage liver disease with or without transplantation. *Kidney Int* 1998; **54**: 518-524 [PMID: 9690218 DOI: 10.1046/j.1523-1755.1998.00004.x]

80 **Campbell MS**, Kotlyar DS, Brensinger CM, Lewis JD, Shetty K, Bloom RD, Markmann JF, Olthoff KM, Shaked A, Reddy KR. Renal function after orthotopic liver transplantation is predicted by duration of pretransplantation creatinine elevation. *Liver Transpl* 2005; **11**: 1048-1055 [PMID: 16123966 DOI: 10.1002/lt.20445]

81 **Hilmi I**, Horton CN, Planinsic RM, Sakai T, Nicolau-Raducu R, Damian D, Gligor S, Marcos A. The impact of postreperfusion syndrome on short-term patient and liver allograft outcome in patients undergoing orthotopic liver transplantation. *Liver Transpl* 2008; **14**: 504-508 [PMID: 18383079 DOI: 10.1002/lt.21381]

82 **Siniscalchi A**, Dante A, Spedicato S, Riganello L, Zanoni A, Cimatti M, Pierucci E, Bernardi E, Miklosova Z, Moretti C, Faenza S. Hyperdynamic circulation in acute liver failure: reperfusion syndrome and outcome following liver transplantation. *Transplant Proc* 2010; **42**: 1197-1199 [PMID: 20534260 DOI: 10.1016/j.transproceed.2010.03.097]

83 **Henriksen JH**, Møller S. Cardiac and systemic haemodynamic complications of liver cirrhosis. *Scand Cardiovasc J* 2009; **43**: 218-225 [PMID: 19145534 DOI: 10.1080/14017430802691528]

84 **Gelman S**. Hemodynamic support in patients with liver disease. *Transplant Proc* 1991; **23**: 1899-1901 [PMID: 2063423]

85 **Garutti Martinez I**, Olmedilla L, Perez-Peña JM, Zaballos M, Sanz J, Vigil MD, Navia J. Response to clamping of the inferior vena cava as a factor for predicting postreperfusion syndrome during liver transplantation. *Anesth Analg* 1997; **84**: 254-259 [PMID: 9024011]

86 **Kim YK**, Lee K, Hwang GS, Cohen RJ. Sympathetic withdrawal is associated with hypotension after hepatic reperfusion. *Clin Auton Res* 2013; **23**: 123-131 [PMID: 23467970 DOI: 10.1007/s10286-013-0191-0]

87 **Battarbee HD**, Farrar GE, Spears RP. Pressor responses in conscious rats with chronic portal venous hypertension. *Am J Physiol* 1989; **257**: G773-G781 [PMID: 2574540]

88 **Laragh JH**, Cannon PJ, Bentzel CJ, Sicinski AM, Meltzer JI. Angiotensin ii, norepinephrine, and renal transport of electrolytes and water in normal man and in cirrhosis with asciteS. *J Clin Invest* 1963; **42**: 1179-1192 [PMID: 16695909 DOI: 10.1172/JCI104803]

89 **Kiel JW**, Pitts V, Benoit JN, Granger DN, Shepherd AP. Reduced vascular sensitivity to norepinephrine in portal-hypertensive rats. *Am J Physiol* 1985; **248**: G192-G195 [PMID: 3970200]

90 **Xu ZD**, Xu HT, Yuan HB, Zhang H, Ji RH, Zou Z, Fu ZR, Shi XY. Postreperfusion syndrome during orthotopic liver transplantation: a single-center experience. *Hepatobiliary Pancreat Dis Int* 2012; **11**: 34-39 [PMID: 22251468]

91 **Bernard F**, Denault A, Babin D, Goyer C, Couture P, Couturier A, Buithieu J. Diastolic dysfunction is predictive of difficult weaning from cardiopulmonary bypass. *Anesth Analg* 2001; **92**: 291-298 [PMID: 11159219]

92 **Pine JK**, Aldouri A, Young AL, Davies MH, Attia M, Toogood GJ, Pollard SG, Lodge JP, Prasad KR. Liver transplantation following donation after cardiac death: an analysis using matched pairs. *Liver Transpl* 2009; **15**: 1072-1082 [PMID: 19718634 DOI: 10.1002/lt.21853]

93 **de Vera ME**, Lopez-Solis R, Dvorchik I, Campos S, Morris W, Demetris AJ, Fontes P, Marsh JW. Liver transplantation using donation after cardiac death donors: long-term follow-up from a single center. *Am J Transplant* 2009; **9**: 773-781 [PMID: 19344466 DOI: 10.1111/j.1600-6143.2009.02560.x]

94 **Jay C**, Ladner D, Wang E, Lyuksemburg V, Kang R, Chang Y, Feinglass J, Holl JL, Abecassis M, Skaro AI. A comprehensive risk assessment of mortality following donation after cardiac death liver transplant - an analysis of the national registry. *J Hepatol* 2011; **55**: 808-813 [PMID: 21338639 DOI: 10.1016/j.jhep.2011.01.040]

95 **Ruebner RL**, Reese PP, Abt PL. Donation after cardiac death liver transplantation is associated with increased risk of end-stage renal disease. *Transpl Int* 2014; **27**: 1263-1271 [PMID: 25070497 DOI: 10.1111/tri.12409]

96 **Doyle MB**, Collins K, Vachharajani N, Lowell JA, Shenoy S, Nalbantoglu I, Byrnes K, Garonzik-Wang J, Wellen J, Lin Y, Chapman WC. Outcomes Using Grafts from Donors after Cardiac Death. *J Am Coll Surg* 2015; **221**: 142-152 [PMID: 26095563 DOI: 10.1016/j.jamcollsurg.2015.03.053]

97 **Abu-Amara M**, Yang SY, Tapuria N, Fuller B, Davidson B, Seifalian A. Liver ischemia/reperfusion injury: processes in inflammatory networks--a review. *Liver Transpl* 2010; **16**: 1016-1032 [PMID: 20818739 DOI: 10.1002/lt.22117]

98 **Muiesan P**, Girlanda R, Jassem W, Melendez HV, O'Grady J, Bowles M, Rela M, Heaton N. Single-center experience with liver transplantation from controlled non-heartbeating donors: a viable source of grafts. *Ann Surg* 2005; **242**: 732-738 [PMID: 16244548]

99 **Leithead JA**, Tariciotti L, Gunson B, Holt A, Isaac J, Mirza DF, Bramhall S, Ferguson JW, Muiesan P. Donation after cardiac death liver transplant recipients have an increased frequency of acute kidney injury. *Am J Transplant* 2012; **12**: 965-975 [PMID: 22226302 DOI: 10.1111/j.1600-6143.2011.03894.x]

100 **Schrier RW**, Wang W. Acute renal failure and sepsis. *N Engl J Med* 2004; **351**: 159-169 [PMID: 15247356 DOI: 10.1056/NEJMra032401]

101 **Bonegio R**, Lieberthal W. Role of apoptosis in the pathogenesis of acute renal failure. *Curr Opin Nephrol Hypertens* 2002; **11**: 301-308 [PMID: 11981260]

102 **Bonventre JV**, Weinberg JM. Recent advances in the pathophysiology of ischemic acute renal failure. *J Am Soc Nephrol* 2003; **14**: 2199-2210 [PMID: 12874476]

103 **Park SW**, Kim M, Brown KM, D'Agati VD, Lee HT. Paneth cell-derived interleukin-17A causes multiorgan dysfunction after hepatic ischemia and reperfusion injury. *Hepatology* 2011; **53**: 1662-1675 [PMID: 21360570 DOI: 10.1002/hep.24253]

104 **Pan X**, Apinyachon W, Xia W, Hong JC, Busuttil RW, Steadman RH, Xia VW. Perioperative complications in liver transplantation using donation after cardiac death grafts: a propensity-matched study. *Liver Transpl* 2014; **20**: 823-830 [PMID: 24711100 DOI: 10.1002/lt.23888]

105 **Fukazawa K**, Yamada Y, Gologorsky E, Arheart KL, Pretto EA. Hemodynamic recovery following postreperfusion syndrome in liver transplantation. *J Cardiothorac Vasc Anesth* 2014; **28**: 994-1002 [PMID: 25107717 DOI: 10.1053/j.jvca.2014.02.017]

106 **Khosravi MB**, Sattari H, Ghaffaripour S, Lahssaee M, Salahi H, Sahmeddini MA, Bahador A, Nikeghbalian S, Parsa S, Shokrizadeh S, Malek-Hosseini SA. Post-reperfusion Syndrome and Outcome Variables after Orthotopic Liver Transplantation. *Int J Organ Transplant Med* 2010; **1**: 115-120 [PMID: 25013576]

107 **Paugam-Burtz C**, Kavafyan J, Merckx P, Dahmani S, Sommacale D, Ramsay M, Belghiti J, Mantz J. Postreperfusion syndrome during liver transplantation for cirrhosis: outcome and predictors. *Liver Transpl* 2009; **15**: 522-529 [PMID: 19399736 DOI: 10.1002/lt.21730]

108 **Bukowicka B**, Akar RA, Olszewska A, Smoter P, Krawczyk M. The occurrence of postreperfusion syndrome in orthotopic liver transplantation and its significance in terms of complications and short-term survival. *Ann Transplant* 2011; **16**: 26-30 [PMID: 21716182]

109 **Figueras J**, Llado L, Ramos E, Jaurrieta E, Rafecas A, Fabregat J, Torras J, Sabate A, Dalmau A. Temporary portocaval shunt during liver transplantation with vena cava preservation. Results of a prospective randomized study. *Liver Transpl* 2001; **7**: 904-911 [PMID: 11679990 DOI: 10.1053/jlts.2001.27870]

110 **Belghiti J**, Noun R, Sauvanet A. Temporary portocaval anastomosis with preservation of caval flow during orthotopic liver transplantation. *Am J Surg* 1995; **169**: 277-279 [PMID: 7840394 DOI: 10.1016/S0002-9610(99)80151-2]

111 **Agopian VG**, Dhillon A, Baber J, Kaldas FM, Zarrinpar A, Farmer DG, Petrowsky H, Xia V, Honda H, Gornbein J, Hiatt JR, Busuttil RW. Liver transplantation in recipients receiving renal replacement therapy: outcomes analysis and the role of intraoperative hemodialysis. *Am J Transplant* 2014; **14**: 1638-1647 [PMID: 24854341 DOI: 10.1111/ajt.12759]

112 **Leithead JA**, Rajoriya N, Gunson BK, Muiesan P, Ferguson JW. The evolving use of higher risk grafts is associated with an increased incidence of acute kidney injury after liver transplantation. *J Hepatol* 2014; **60**: 1180-1186 [PMID: 24631601 DOI: 10.1016/j.jhep.2014.02.019]

113 **Elaffandi AH**, Bonney GK, Gunson B, Scalera I, Mergental H, Isaac JR, Bramhall SR, Mirza DF, Perera MT, Muiesan P. Increasing the donor pool: consideration of prehospital cardiac arrest in controlled donation after circulatory death for liver transplantation. *Liver Transpl* 2014; **20**: 63-71 [PMID: 24142867 DOI: 10.1002/lt.23772]

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

|  |  |  |  |
| --- | --- | --- | --- |
| **Study** | **Journal and Year** | **Outcome** | **Diagnosis** |
| Doyle *et al*[96] | J Am Coll Surg 2015 | AKI | RRT |
| Ruebner *et al*[95] | Transpl Int 2014 | End stage renal disease |  |
| Leithead *et al*[112] | J Hepatol 2014 | AKI | KDIGO criteria |
| Elaffandi  *et al*[113] | Liver Transpl 2014 | Prehospital cardiac arrest |  |
| Leithead  *et al*[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.