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ACUTE KIDNEY INJURY AFTER LIVER TRANSPLANTATION

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Abstract

Liver transplantation is the only curative treatment for terminal liver failure. Advances in immunosuppressive therapy and improvements in surgical techniques have improved patient survival in the post-transplant period. At the same time, however, the incidence of late complications is increasing, which has been contributed to by the broadening of the indication criteria in liver allocation. The most common complications include chronic kidney disease, the aetiology of which is multifactorial with a predominance of calcineurin inhibitor toxicity in the post-transplant period. The prevalence ranges from 30% to 90% depending on the definition used and the methodology used to measure renal function. Early detection of risk factors and early intervention lead to a significant improvement in the quality of life of recipients in the post-transplant period.

Key words: chronic kidney disease, immunosuppression, liver transplantation

List of abbreviations

ACEi	angiotensin converting enzyme inhibitors
AKI	acute kidney injury
BMI	body mass index
CKD	chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CNI	calcineurin inhibitors
DM	diabetes mellitus
eGFR	estimated glomerular filtration rate
FENa	fractionated excretion of sodium
GRAIL	GFR Assessment In Liver disease
HbA1c	glycated haemoglobin
HCC	hepatocellular carcinoma
HRS-AKI	hepatorenal syndrome - acute kidney injury
ICA	International Club of Ascites
KDIGO	Kidney Disease Improving Global Outcomes
LT	liver transplantation
MELD	Model for End – Stage Liver Disease
mTOR	mammalian target of rapamycin
NAFLD	nonalcoholic fatty liver disease
NASH	nonalcoholic steatohepatitis
NGAL	neutrophil gelatinase-associated lipocain
PTDM	post-transplant diabetes mellitus

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RAAS	renin – angiotensin – aldosterone system
RRT	renal replacement therapy (method replacing kidney function)
sCr	serum creatinine
SGLT2i	sodium-glucose transporter inhibitor

INTRODUCTION

Liver transplantation (LT) is so far the only definitive treatment for patients with acute hepatic injury, liver cirrhosis, and hepatocellular carcinoma, with a 5-year survival rate of 75% (1, 2). With the increasing success rate of liver transplantation, the incidence of late complications, including malignancy, cardiovascular disease, infections, metabolic complications, and chronic kidney disease (CKD), is also increasing. The prevalence of renal failure after LT has an increasing trend, due to a change in liver allocation based on the MELD (Model for End-Stage Liver Disease) score, which favours LT candidates with impaired renal function (4). The use of a graft from a marginal donor is associated with more severe ischemia-reperfusion liver injury, which more often leads to renal insufficiency. Renal dysfunction after LT can be divided into acute kidney injury (AKI) and chronic kidney disease. The aetiology of AKI and CKD is multifactorial and is associated with donor, recipient, surgical procedure, and posttransplant immunosuppression **(3).** The aim of this review is to present the causes of renal injury after liver transplantation, focusing on diagnosis and prevention.

Aetiology of acute kidney injury after liver transplantation

The International Consensus Conference and the International Club of Ascites (ICA) have defined AKI in patients after liver transplantation based on the Kidney Disease Improving Global Outcomes (KDIGO) definition, with a modification for patients with hepatic cirrhosis and exclusion of diuresis from the criteria (Table 1). Patients with cirrhosis are often oliguric with preserved glomerular filtration rate and, on the other hand, may have increased diuresis as a result of diuretic therapy. Another change to the KDIGO criteria in patients with cirrhosis is that the serum creatinine (sCr) value for the last 3 months prior to admission is taken as the baseline value, unless a value from the previous 7 days is available. The etiopathogenesis of AKI after liver transplantation is multifactorial (Table 2) (4).

Table 1 Stages of AKI according to KDIGO 2012

Stage	sCr (μmol/l)	Diuresis
1 2	1.5 – 1.9 times the baseline value *or* increase by 26.5 μmol/l in 48 hours	<0.5ml/kg/hour for 6 – 12 hours
3	2.0 – 2.9 times the baseline value	<0.5ml/kg/hour for ≥ 12 hours
	3.0 times the baseline value *or* increase by ≥ 353.6 μmol/l *or* initiation of renal function replacement	< 0.3ml/kg/hour for ≥ 24 hours *or* anuria

sCr – seru
m creatinine, AKI – acute kidney injury

Table 2 AKI risk factors after liver transplantation

Pre-transplant	Perioperative	Post-transplant
AKI	Hypotension	CNI
CKD	Postreperfusion syndrome	Nephrotoxic drugs
Obesity	Blood loss	Diuretics
Hypertension	Number of transfusions	Infections
Diabetes	Oliguria	
Hepatitis B, C		
HCC		
Alcoholic liver disease		
Donor age > 60 years		
BMI ≥ 30 years		
Cold ischemia time		
Warm ischemia time		
Marginal donor		
Infections		

AKI – acute kidney injury, BMI – body mass index, CKD – chronic kidney disease, CNI – calcineurin inhibitor, HCC – hepatocellular carcinoma

Recipients with a high MELD score have an increased risk of developing hepatorenal syndrome – AKI (HRS – AKI) in the post-transplant period. It is defined by changes in sCr and/or diuresis and other diagnostic criteria (Table 3). It is a functional and progressive renal failure whose pathomechanism is based on systemic vasodilatation caused by hemodynamic changes in hepatopathy and/or translocation of bacteria from the intestine. Splanchnic vasodilatation leads to activation of the sympathetic nervous system, the renin-angiotensin aldosterone system (RAAS), and arginine-vasopressin release. The named mechanisms cause extreme renal vasoconstriction with renal hypoperfusion and sodium and water retention. HRS-AKI develops in 27–53% of hospitalized patients with cirrhosis, with a mortality rate of 36–100% reported in the literature due to the timeliness of initiation of treatment (5, 6, 7).

Perioperative hypotension and hemodynamic instability are major risk factors for renal hypoperfusion. The proximal tubule cells represent the most sensitive structure because of their energy requirements (8). The main cause of hemodynamic instability is the postreperfusion syndrome, as a consequence of vena portae unclamping with subsequent restoration of circulation to the donor liver. During reperfusion, proinflammatory cytokines (interleukin 6, tumour necrosis factor α) are released into the circulation with the development of an inflammatory response. The unwanted postreperfusion syndrome can be eliminated by a

Table 3 Diagnostic criteria of HRS-AKI according to ICA

Cirrhosis, acute liver failure, acute liver failure in the field of its chronic disease
26.5 μmol/l increase in sCr over 48 hours or ≥ 50% increase from baseline and/or diuresis < 0.5 ml/kg/hr for ≥ 6 hours
Absence of a decrease in sCr after 2-day discontinuation of diuretics and albumin volume expansion, the recommended dose of albumin is 1 g/kg body weight, maximum 100g
Absence of shock
Exclusion of recent administration of nephrotoxic drugs
Exclusion of parenchymal kidney damage Absence of proteinuria 500 mg/day, microhaematuria 50 erythrocytes in the field of view, normal sonographic findings
Suspected renal vasoconstriction at FENa < 0.2% (values < 0.1% indicate high risk)

sCr – serum creatinine, FENa – fractionated excretion of sodium, HRS-AKI – hepatorenal syndrome-acute kidney injury

surgical technique sparing the inferior vena cava (piggyback technique), where flow through the inferior vena cava is preserved with maintenance of cardiac output (9, 10). Perioperative blood loss due to portal hypertension with collateral vasculature also leads to renal hypoperfusion. Subsequent transfusion of erymass with nephrotoxic free hemoglobin and iron contributes to tubular damage. A 2017 study by De Haan and colleagues points to glycemic variability as a risk factor for perioperative AKI, although the etiopathogenesis is not fully elucidated (11, 12). However, neither perioperative fluid resuscitation nor sparing surgical technique has been shown to be beneficial in preventing AKI after LT (10, 13).

Calcineurin inhibitors (CNIs) as part of standard triple combination immunosuppression (calcineurin inhibitor, mycophenolate mofetil, corticosteroids) are classified as nephrotoxic drugs where toxicity correlates with the dose administered. The cause of early nephrotoxicity, which is mostly functional, is vasoconstriction of the vas afferens with a decrease in renal perfusion with subsequent activation of the RAAS. A decrease in vasodilator production and an increase in vasoconstrictor substrates results in a decrease in glomerular filtration rate and an increase in creatinemia, while renal structure is preserved. For this reason, regular monitoring of serum CNI concentration with dose adjustment is necessary (14, 15, 16). It is also important to avoid drugs that increase the nephrotoxicity of CNI, such as: antifungals, aminoglycosides, nonsteroidal antiphlogistic drugs, and contrast agents (17).

Aetiology of chronic kidney disease after liver transplantation

CKD is defined by the KDIGO as structural and functional renal impairment of at least 3 months duration and has an impact on the patient's health status (58). Based on estimated glomerular filtration rate (eGFR) and albuminuria, there are 5 stages of CKD (Table 4). The incidence of CKD after liver transplantation is significantly higher than after lung and heart transplantation (18). The risk factors for the development of CKD after liver transplantation are almost identical in the pre-transplant and post-transplant periods. They can be divided into non-modifiable recipient factors (female sex for increased susceptibility to CNI, older age, and donor factors) and modifiable factors (19, 20).

Table 4 Stages of CKD according to KDIGO

		Albuminuria (mg/g)		
GFR categories	eGFR (ml/min/1.73 m^2)	A1	A2	A3
		<30	30-299	≥300
G1	≥ 90			
G2	60 – 89			
G3a	45 – 59			
G3b	30 – 44			
G4	15 – 29			
G5	< 15			

eGFR – estimated glomerular filtration rate, CKD – chronic kidney disease, KDIGO – Kidney Disease Improving Global Outcomes

Arterial hypertension is a well-known risk factor for CKD and cardiovascular disease with a prevalence of 70% after liver transplantation. In addition to steroids, which increase systemic vascular resistance by their mineralocorticoid action, other immunosuppressive agents contribute to the development of secondary arterial hypertension. In addition to increasing systemic vascular resistance with a subsequent activation of the RAAS, CNIs decrease nitric oxide and prostaglandin production while increasing endothelin and thromboxane release. Many studies have reported a higher incidence of arterial hypertension with cyclosporine compared with tacrolimus (21).

Diabetes mellitus (DM) type I, type II, and post-transplant DM (PTDM) is a significant risk factor for graft and patient survival. The incidence ranges from 2.5%-25% with a risk period of development during the first 6 months after LT due to reduced physical activity and immunosuppression. Corticosteroids increase hepatic gluconeogenesis and also induce peripheral insulin resistance along with decreasing insulin production. Tacrolimus, compared with cyclosporine, is associated with a higher incidence of PTDM because of its toxicity to pancreatic β-cells (22, 23).

These risk factors, together with obesity, are part of the metabolic syndrome, which has become a worldwide epidemic. Approximately 30% of patients meet criteria for obesity before LT, with a significant percentage increase after LT (40.3% after 5 years) (24, 25). In the post-transplant period, in addition to the well-known risk factors (lack of physical activity, lifestyle, genetic predisposition), it is immunosuppression that contributes to the development of metabolic syndrome and its associated diseases. Studies have shown an increased incidence of hyperlipidaemia and hypertriacylglycerolaemia with the use of cyclosporine compared with tacrolimus, and also the combination of mTOR (mammalian target of rapamycin) inhibitors with cyclosporine contributes to hyperlipidaemia (26). The metabolic syndrome also results in the development of nonalcoholic steatohepatitis (NASH) and nonalcoholic fatty liver disease (NAFLD), the severity of which is directly correlated with the risk of CKD (27, 28). The pathogenetic correlation between NASH and CKD is based on the proinflammatory state of the body, whereby the hepatoprotein fetuin-A is produced at an increased rate, which reduces the release of the protective molecule adiponectin from adipocytes. Elevated levels of adiponectin induce a procoagulant state. Chronic systemic inflammation with oxidative stress, dyslipidemia, and decreased adiponectin levels lead to renal endothelial dysfunction and progression of CKD (29, 30).

Among all solid organ transplant recipients, post-LT patients have the second highest incidence of CKD, including an end-stage renal failure, despite the use of the lowest doses of calcineurin inhibitors compared with heart and lung transplant recipients (31, 32). This is chronic nephrotoxicity in which irreversible structural renal damage occurs. Aetiologically, it is an obliterative afferent arteriolopathy with interstitial fibrosis and tubular atrophy. However, there is a significant interindividual variability in the development of CNI-induced nephropathy, with a 4-fold higher risk of developing it in patients with the ACE D/D genotype compared with other polymorphisms (16, 33).

Diagnosis of AKI and CKD after liver transplantation

Currently, serum creatinine is used as a marker of AKI in clinical practice. Creatinemia is dependent on age, sex, amount of muscle mass, hydration status and distribution volume, or bilirubinemia. Another biomarker is cystatin, which has the main advantage of being independent of the aforementioned factors; however, the determination of serum cystatin concentration is one of the more costly examinations (34, 35). Over the past decades, attention has been focused on the investigation of markers of acute tubular injury, with NGAL (neutrophil gelatinase-associated lipocaine) achieving the most attention. However, even this biomarker can be largely modified by infection and inflammation; therefore, the detection of a specific marker of AKI/CKD remains a major challenge (36, 3).

In practice, the decline in renal function in chronic kidney disease is determined by calculating eGFR from serum creatinine/cystatin values using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI-Cr) or CKD-EPI-Cys equations. The modified creatinemia value leads to an overestimation of renal function, so an equation for patients with liver disease was developed in 2017. GRAIL (GFR Assessment in Liver Disease) includes ethnicity, sex, age, creatinine, urea, and albumin levels (38, 39).

Renal biopsy is not performed as a protocol after LT due to the risk of bleeding but is fully indicated in cases of unexplained decline in renal function, development of proteinuria, and persistent positive urinary sediment. The histopathological findings are dominated by the finding of calcineurin inhibitor toxicity in 15% to 50% of cases, with further evidence of diabetic nephropathy and thrombotic microangiopathy (40, 41).

Treatment of AKI and CKD after liver transplantation

Treatment of HRS-AKI is based on the administration of vasopressors (terlipressin) and albumin. The initial dose of terlipressin 1 mg administered every 4–6 hours can be increased to a dose of 2 mg every 4 hours after 3 days with a decrease in creatinemia < 25%. In the absence of response, terlipressin should be withdrawn from therapy after 14 days. Only 50% of patients achieve a complete response to vasopressor therapy. Renal replacement therapy (RRT) represents a second-line treatment for HRS-AKI, especially in patients who are unable to maintain a negative or balanced fluid balance despite forced diuresis. Other indication criteria for initiation of RRT are identical to the general population: hyperkalaemia, uraemia, refractory acidosis. Because of greater cardiovascular stability and slower correction of even severe hyponatremia, continuous elimination methodologies are preferred over intermittent ones (42, 43, 44, 45).

The treatment of CKD after liver transplantation is mainly aimed at preventing the occurrence and influencing the risk factors after transplantation. Cardiovascular complications are a frequent cause of death in patients after LT. The target blood pressure in the presence of proteinuria is <130/80 mmHg, without proteinuria <140/90 mmHg. Among antihypertensive medications, dihydropyridine calcium channel blockers are the first-choice agents in the post-transplant period because of their CNI blocking vasoconstrictor effect (34). Conversely, prescription of ACEi (angiotensin-converting enzyme inhibitors) and angiotensin receptor blockers should be avoided, given the reduced serum renin activity and the possibility of progression of hyperkalemia in the early posttransplant period. On the other hand, these drugs are the drugs of choice in patients with DM, proteinuria, and CKD in the late post-transplant period (46).

Compensation of DM with achievement of HbA1c (glycated haemoglobin) < 7% is also crucial after LT. In the case of higher doses of corticosteroids, the use of insulin is safer and more effective. Studies show that the inclusion of sodium-glucose transporter inhibitors (SGLT2i) in the treatment leads to weight loss and improved glycaemic control even in patients after LT (46, 47). Hypolipidemics are not contraindicated in post-LT patients; however, in the context of interaction with cytochrome P-450, administration of pravastatin and fluvastatin is safer in patients treated with CNI (48). The nephrotoxicity of CNIs largely contributes to renal dysfunction in both the short- and long-term after LT. The greatest challenge is to minimize the administered CNI dose without affecting the graft function. In the period up to 1 month after LT, short-term induction therapy with monoclonal or polyclonal antibodies with a delayed administration of CNI is an option.

Another option is to version CNI to mTOR inhibitors, but these impair wound healing and cause proteinuria and are therefore not suitable for patients with diabetes mellitus (46, 49).

Pharmacological management must also be supplemented by general dietary measures. Reduction of salt intake (<2 g/day) and regular physical activity (>30 min/day) together with a low-protein diet (<0.8 g/kg/day) contribute to an improved control of arterial hypertension and proteinuria (48).

CONCLUSION

Acute kidney injury and chronic kidney disease after liver transplantation is a common and serious problem that adversely affects morbidity and mortality of patients. Their aetiology is multifactorial and includes factors before, during, and after transplantation. The prevalence increased after the introduction of the MELD score in organ allocation in 2002 with the aim of reducing the mortality of patients on the waiting list. Early diagnosis is paramount, but most conventional methods of estimating GFR have limitations and there is currently no accurate non-invasive marker ready for use in clinical practice. Given that CNI toxicity is an important cause of renal dysfunction after LT, strategies to minimize their use, such as induction therapy followed by the reduction of CNI levels, are still the best options to preserve renal function. Identification of potentially reversible causes of CKD and effective prevention and personalized care aimed at modifying risk factors for CKD may further improve post-transplant survival and quality of life for patients.

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