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NEW TRENDS IN THE STUDY OF POST-TRANSPLANT ACUTE KIDNEY INJURY AFTER LIVER TRANSPLANTATION

I.M. Iljinsky, O.M. Tsirulnikova

Shumakov National Medical Research Center of Transplantology and Artificial Organs, Moscow, Russian Federation

Acute kidney injury (AKI) after liver transplantation (LT) is a pressing issue and remains the focus of many researchers. The etiology of AKI is multifactorial, but the main one is ischemia-reperfusion injury to the liver transplant. Numerous preoperative, intraoperative and postoperative risk factors contribute to the development of AKI. The use of standard classifications, such as AKIN, RIFLE and KDIGO, has improved post-transplant AKI diagnosis. However, determination of creatinine levels in the blood enables AKI diagnosis only in the later stages of this syndrome. Therefore, studies are currently underway to find ways of early diagnosis of AKI using biomarkers. Transition to a molecular level not only improves accuracy but also facilitates early diagnosis of AKI. Currently, the diagnostic capabilities of neutrophil gelatinase-associated lipocalin (NGAL) are the most investigated. To date, there are no known measures of preventing post-transplant AKI. Moreover, treatment of this condition cannot be considered satisfactory. Even a mild post-transplant AKI can be fatal. In severe AKI, where renal replacement therapy is used, there is a risk of death in the intensive care unit. More than half of AKI patients develop chronic kidney disease requiring chronic hemodialysis.

Keywords: acute kidney injury, liver transplantation, risk factors, predictors, biomarkers.

INTRODUCTION

Acute kidney injury (AKI) following liver transplantation remains a pressing issue in modern medicine. It concerns both severe therapeutic and surgical patients. Patients with cardiovascular disease and sepsis have a particularly high risk of developing AKI. About 40% of patients with acute decompensated heart failure have AKI. With increased incidence of heart failure, AKI prevalence is predicted to rise [1, 2]. Sepsis is the most common cause of AKI in critically ill patients. Differences in patient characteristics, pathophysiology and outcomes distinguish septic AKI as a separate clinical entity from non-septic AKI [3]. About 40% of patients who underwent surgical interventions develop AKI after cardiac (18.7%), general (13.2%), and thoracic (12.0%) surgeries [1, 2, 4, 5].

The AKI problem has not spared the transplantology sector. After transplantation of non-kidney solid organs, most patients develop acute reduction in renal function [1, 2]. Moreover, some patients develop end-stage renal disease requiring renal replacement therapy (RRT). Many patients also develop CKD. AKI incidence varies depending on the organ to be transplanted. AKI after transplantation of non-kidney solid organs leads to longer hospital stay, higher cost of treatment, increased risk of death, and more common *de novo* CKD [6, 7]. AKI is a common and severe complication developing after liver transplantation (LT) [8–12]. It is more often common for livers retrieved from asystolic donors. It usually develops in the early stages following a LT – from six hours to the end of the first day after reperfusion [13]. Late onset of AKI is observed in fewer patients [14]. Post-LT AKI develops not only from deceased donor LT, but also from living donor LT [15–17]. After living donor LT, 6.3% of patients (34/538) required postoperative RRT [15]. This complication is less common after LT (29%) than after abdominal surgery (47%). However, the number of cases requiring RRT is higher after LT than after abdominal surgery (71% and 53% of patients respectively) [1, 2].

INCIDENCE OF ACUTE KIDNEY INJURY

Since the Model for End-Stage Liver Disease (MELD), which uses serum creatinine levels to predict survival for liver disease, was introduced in 2002, incidence of kidney dysfunction among potential liver recipients has increased significantly. This has led to increased incidence of simultaneous liver-kidney transplantation. A decision to conduct simultaneous liver-kidney transplant surgery is difficult and must be strictly balanced. The severity and duration of pre-LT renal dysfunction, hepatitis C, diabetes, and other risk factors for kidney disease are associated with higher risk of post-transplant renal failure. However, there are currently no clinical findings that would accurately predict renal recovery after LT [18].

Incidence of post-LT AKI ranges from 17% to 94% [7]. According to E.A.J. Hoste et al. [19], AKI prevalence ranges from 1% to 66%. Table 1 shows information on

Corresponding author: Iljinsky Igor Mihajlovich. Address: 1, Shchukinskaya str., Moscow, 123182, Russian Federation. Tel. (999) 877-60-95. E-mail: iiljinsky@mail.ru

Table 1

Incidence of acute kidney injury after liver transplantation

Authors	Year of publication	Country of publication	AKI incidence in %	Remarks
A.G. Barreto et al. [14]	2015	Brazil	46.7	
I.A. Hilmi et al. [25]	2015	USA	52	
M.H. Park et al. [15]	2015	South Korea	27.3	Living liver donors
P. Wiesen et al. [26]	2016	Belgium	58.3	
M. Hamada et al. [27]	2017	Japan	46.2	Pediatric LT
E.C. de Ataide [28]	2017	Brazil	46.84	
T. Mizota et al. [17]	2017	Japan	30.7	Living liver donors
Z.Q. Zhou et al. [29]	2017	China	40.8	
Y. Zongyi et al. [20]	2017	China	3.97	
I. Jocmans et al. [13]	2017	Belgium	26	
M.S. Chae et al. [16]	2017	South Korea	22.7	Living liver donors
E. Trinh et al. [7]	2017	Canada	56.6	
Y. Cheng et al. [30]	2018	China	64.2	
M. Kalisvaart et al. [21]	2018	Netherlands	65	Cardiac death liver donors
C. Pulitano et al. [31]	2018	Australia	32	

post-LT AKI occurrence in studies of other authors. The incidence of post-LT AKI ranges from 3.97% [20] to 65% [21] of liver recipients. Such wide variations in AKI prevalence can be explained by not only population differences, but also inconsistent use of standardized AKI classification criteria. AKI etiology and incidence also vary between high- and low-income countries. The incidence is lower in high-income countries than in low-to-middle-income countries, where contaminated water and endemic diseases, such as malaria contribute to high burden of AKI. Outcomes of AKI are similar to or more severe in low-income patients. Later detection of AKI hinders recovery and leads to high mortality [19].

AKI is often observed not only after LT from donors with advanced criteria, but also from "standard" donors and can lead to CKD and/or death [22].

I.G. Jun et al. [23] retrospectively analyzed the data of 1617 patients who underwent living donor liver transplantation. 271 of the patients received ABO-incompatible (ABOi) living donor liver transplantation (LDLT). AKI incidence was significantly higher after ABOi LDLT than with ABO-compatible LDLT (67.0% versus 48.2%; $p < 0.001$). Besides, length of ICU stay ($p = 0.01$) was significantly prolonged, but there were no significant differences in mortality ($p = 0.74$), graft failure ($p = 0.32$) and postoperative dialysis ($p = 0.74$) between the two groups of patients. Hemoglobin level and duration of surgery were independent risk factors for AKI after ABOi LDLT [23].

A meta-analysis of databases (MEDLINE, EMBASE and Cochrane Databases) from inception until December 2018 showed that the incidence rates of post-LT AKI and severe AKI requiring RRT are 40.8% and 7.0%, respectively are 40.8% and 7.0%, respectively. There is reliable association of AKI with increased mortality and graft failure. Incidence of AKI after LT has remained stable over the last 10 years of the study [24].

ORIGIN AND PATHOGENESIS OF ACUTE KIDNEY INJURY

Acute kidney injury is a syndrome with various etiologies and pathophysiological processes leading to impaired kidney function [1–3, 32]. In addition to retention of waste products, impaired electrolyte homeostasis and altered drug concentrations, AKI induces a generalized inflammatory response that affects many internal organs [19].

According to most researchers, post-LT AKI is multifactorial in origin [1, 2, 19]. It has been causally associated with exposure to high levels of toxic free-radicals, renal ischaemia with hemodynamic instability, effects of end-stage liver disease on the kidney and infectious complications after LT. In addition, AKI has been associated with the severity of native liver disease according to MELD [30], pre-LT renal dysfunction, graft quality, perioperative factors, particularly calcineurin inhibitor nephrotoxicity [11].

One of the main etiological factors of AKI in LT is hepatic IRI [11, 13, 33]. M. Kalisvaart et al. [21] studied the effect of warm ischemia duration on AKI development in 368 recipients who received liver from cardiac death donors. AKI severity significantly increased with longer duration of warm ischemia: from 61 minutes in recipients without AKI up to 69 minutes in recipients with the most severe form of AKI ($p < 0.001$). The length of warm ischemia should ideally not exceed 60 minutes because a longer time will increase the severity of post-LT AKI. It is known that cold storage of donor organs leads to increased ischemic damage. However, M. Kalisvaart et al. [21] found no relationship between length of cold ischemia and severity of AKI.

Vascular pathology can be an etiological factor of AKI. W. Beaubien-Souligny et al. [34] presented a rare observation in which inferior vena cava stenosis was the cause of post-LT AKI. A month after undergoing LT, a 25-year-old man with cirrhosis caused by sclerosing cholangitis and autoimmune hepatitis developed severe AKI in combination with recurrent ascites and lower extremity edema. An ultrasound scan revealed inferior vena cava stenosis. There was rapid improvement in renal function after angioplasty with stent installation.

AKI pathogenesis is still not clear [11]. In the pathogenesis of AKI in hepatic IRI, I. Jochmans et al. [13] distinguish four components. First, the main role is played by systemic inflammatory response as activated Kupffer cells initiate the release of circulating inflammatory and pro-inflammatory cytokines and transcription factors. Increased level of tumor necrosis factor α and other interleukins disrupts regulation of endothelial adhesion molecules in distant organs, particularly in the kidneys, and with that leukocyte recruitment and increased vascular wall permeability occur in them. Activated neutrophils release enzymes and cytokines into the subendothelial space, directly causing kidney injury and recruitment of monocytes and macrophages. Second, hepatic IRI leads to increased endothelial apoptosis, which further promotes leukocyte infiltration of the vessel walls. Third, oxidative stress and reactive oxygen species also contribute to kidney injury. Fourth, damage to the actin cytoskeleton of the tubular and renal endothelial cells can lead to increased apoptosis. According to I. Jochmans et al. [13], reducing hepatic IRI, for example, by using machine perfusion technology, might not only improve graft function but also limit the effect of the injury on the kidney and reduce AKI incidence.

MORPHOLOGY OF ACUTE KIDNEY INJURY

Morphology of kidney in acute injury is poorly studied because biopsies are not performed in AKI patients. In the study of autopsy material in AKI, there are various degrees of dystrophy and necrosis of renal tubular epithelial cells, up to acute tubular necrosis. The glomerular capillaries are anemic, with collapsed lumen.

RISK FACTORS FOR ACUTE KIDNEY INJURY

In a study by P. Wiesen et al. [26] in a univariate analysis, the severity of renal dysfunction was correlated with the presence of ascites and prior bacterial infection, preoperative bilirubin, urea and creatinine levels, use of vasopressors, need for postoperative mechanical ventilation, postoperative bilirubin and urea, aspartate aminotransferase, and hemoglobin levels and the need for transfusion. Multivariate analysis showed that body mass index [BMI] ($p = 0.004$), preoperative creatinine level ($p < 0.0001$), use of vasopressor ($p = 0.0002$), maximal postoperative bilirubin level ($p = 0.044$) and minimal postoperative hemoglobin level ($p = 0.0005$) were independent predictors of early post-LT AKI. In multivariate analysis, neither donor status nor aspartate aminotransferase levels had significant effect on early postoperative renal dysfunction [26].

In another study, univariate analysis showed that preoperative factors (BMI, diabetes mellitus, C-reactive protein), intraoperative factors (packed red blood cell transfusion, furosemide, and oxygen content at the anhepatic phase, five minutes and one hour after graft reperfusion, and at peritoneal closure) and postoperative factors (severe postreperfusion syndrome) were significant AKI risk factors. Multivariate analysis showed that oxygen content 5 minutes after graft reperfusion, BMI, and furosemide administration were independently associated with postoperative AKI. Thus, postoperative AKI was independently associated with oxygen content 5 minutes after graft reperfusion, BMI, and furosemide administration [16].

In a multivariate analysis after living donor liver transplantation, independent risk factors for AKI were: BMI >27.5 kg/m^2; serum albumin <3.5 mg/dl; MELD score >20; operation time >600 min; warm ischemia time >40 min; postreperfusion syndrome; mean blood glucose during the day of surgery >150 mg/dl; cryoprecipitate >6 units; blood loss/body weight >60 ml/kg; calcineurin inhibitor use without combined mycophenolate mofetil [15]. The authors argue that doses of calcineurin inhibitor should be reduced by combined use of mycophenolate mofetil to reduce incidence of postoperative AKI.

Increased preoperative total bilirubin level and increased intraoperative blood loss, as well as prolonged hospitalization were independently associated with the risk of developing AKI after pediatric liver transplantation [27].

Recently, increased intake of serum phosphate was found to be associated with increased risk of AKI at all stages of hospital stay [35].

As can be seen from the above recent reports, there are numerous preoperative, intraoperative and postoperative risk factors for AKI. We will look deeper into AKI risk factors at each of these stages.

Preoperative risk factors

The greatest number of risk factors for post-LT AKI exists in patients before surgery. Reports focus on various factors. Research by H. Aksu Erdost et al. [36] showed that with MELD score >20, the recipient has an increased risk of post-LT AKI. Viral hepatitis in the recipient, longer warm ischemia time (WIT) and high levels of serum lactate are risk factors for AKI before LT in A.G. Barreto et al. [14]. In addition, predisposing factors for development of AKI were female sex, weight (>100 kg), non-alcoholic steatohepatitis, and severity of native liver disease [25]. Post-LT renal dysfunction prevails in patients with decompensated native cirrho-

sis [37]. In the study of H.P. Chen et al. [9], the most significant risk factor for post-LT AKI was preoperative cerebrovascular disease.

An important predisposing factor for development of AKI is diabetes mellitus, which has existed before LT [25]. After LT, progression of kidney injury to end-stage renal disease was particularly pronounced in patients with diabetes mellitus [38]. The authors suggest that diabetes mellitus can be considered as a criterion in making decisions regarding simultaneous liver-kidney transplantation. Every year the number of such operations increases both in CKD and in AKI [39]. Only in a study by O. Komurcu et al. [40], no effect of hyperglycemia (blood glucose >200 mg/dl) on increased risk of AKI, increased postoperative infections, or increased post-LT mortality.

Independent and reliable ($p < 0.05$) risk factors for AKI include high preoperative serum creatinine levels and a long period of treatment with dopamine [20]. Acute kidney damage is associated with high BMI, low urine output [29], low serum albumin and elevated levels of direct bilirubin, alkaline phosphatase and gamma-glutamyltransferase [41].

Inflammatory and anti-inflammatory cytokines play critical roles in the development of AKI. Based on this, a study was undertaken of the role of cytokine gene polymorphisms in kidney deterioration after LT. It was found that the IL4-33 T/T genotype was significantly associated with higher incidence of AKI compared with the other two genotypes ($p = 0.03$). Therefore, the IL4-33 T/T genotype might be a risk factor for post-LT AKI [42].

Donor risk factors

Warm and cold donor liver ischemia is considered as an independent and significant ($p < 0.05$) risk factor for post-LT AKI. The degree of ischemia increases for organs from high-risk donors, especially from asystolic donors [20]. In a study by M.B. Doyle et al. [43], AKI incidence depending on the nature of the donor liver – from a donor with cardiac death or with brain death – was investigated. Although cardiac death liver donors were younger than brain death donors ($p < 0.0001$) and had lower MELDs ($p = 0.03$), AKI was more common in cardiac death livers than in brain death livers (16.3% of recipients required dialysis – against 4.1%, $p = 0.01$).

AKI does not depend directly on high-risk liver donors (asystolic donors or donors older than 65 years) but is associated with the severity of hepatic IRI [13, 25]. J. Roller and M. Glanemann [44] point out that to reduce the likelihood of developing AKI in LT, warm and cold ischemia time of the donor liver should be minimized.

It is difficult to identify which LT candidates with severe kidney injury will have full restoration of renal function after LT alone. H.L. Laskey et al. [45] found that in such recipients, full restoration was the median WIT – 31 minutes (24–46 minutes), and there was no recovery with a WIT of 39 minutes (34–49 minutes; $p = 0.02$). For each minute of increased WIT, there was an 8–9% increase in the risk of lack of renal recovery after LT.

Intraoperative risk factors

Hemodynamic instability during LT is crucial in development of AKI and deserves closer attention. Severe hypotension, even for less than 10 minutes, was significantly associated with severe AKI [17].

Univariate analysis showed that intraoperative factors (red blood cell transfusion, furosemide, and oxygen content at the anhepatic phase, five minutes and one hour after graft reperfusion, and peritoneal closure) were significant AKI risk factors [16].

During LT, an independent and significant ($p < 0.05$) risk factor for AKI was too much blood loss [20], and accordingly, volume of transfused blood and/or its components (red blood cells, freshly frozen plasma) [25, 30, 36]. According to H. Aksu Erdost et al. [36], normalizing hemoglobin levels without transfusion of blood components can prevent AKI.

It is believed that blood transfusion is a risk factor for AKI only if the quantity is large [13, 30]. Besides, transfusion of long-stored red blood cells significantly increases the risk of postoperative AKI in patients after LT. In one study [46], patients who underwent LT were divided into two groups. The first group consisted of patients who received transfused red blood cells that had been stored for less than 14 days, and the second group consisted of patients who received red blood cells that had been stored for 14 days or more. Postoperative AKI was observed in 40.5% of patients of the first group and in 65.1% of the second ($p < 0.01$). The incidence of severe post-LT AKI was significantly higher, and the length of stay in the ICU was much longer in the second group [46]. The risk of developing AKI increases with surgery lasting for more than 480 minutes [29].

In patients after LT, progression of kidney injury to the end-stage renal disease was especially pronounced at glomerular filtration rate (GFR) <60 ml/min during surgery [47]. According to I.A. Hilmi et al. [25], the presence of severe unstable hemodynamics during reperfusion does not affect the incidence of post-LT AKI. In contrast, J. Roller and M. Glanemann [44] emphasize the need to maintain adequate blood pressure during reperfusion to reduce the likelihood of AKI in LT.

Recently, it has been found that indicators such as elevated baseline central venous pressure (CVP), elevated baseline right ventricular end-diastolic volume (RVEDV) after anesthesia induction and decreased mixed venous oxygen saturation (SvO_2) during anhepatic phase in LT, are risk factors for postoperative AKI [48]. Intraoperative oliguria, combined with decreased SvO_2, is a more

accurate predictor of post-LT AKI than just one of these indicators [48].

Postoperative risk factors

Calcineurin inhibitor nephrotoxicity and postoperative infections are independent and significant ($p < 0.05$) risk factors for post-LT AKI [20]. Development of AKI is facilitated by the non-optimal function of the liver graft [29, 49] and use of vasopressors [29]. Peak aspartate aminotransferase, occurring at 6 hours after reperfusion, was the only independent risk factor for AKI. Early liver graft dysfunction occurred more frequently in AKI patients [13]. Postoperative risk factors for AKI also include high preoperative MELD score and native liver cirrhosis [30]. A study by S. Yoo et al. [50] suggested that increased perioperative glucose variability, but not hyperglycemia, was independently associated with increased risk of post-LT AKI.

DIAGNOSTIC CLASSIFICATIONS FOR ACUTE KIDNEY INJURY

The use of standard classifications for AKI diagnosis and stratification has increased detection rates for this syndrome in clinical practice and epidemiological studies [5]. R. Caragata et al. [51] point to gradual changes in the concept of AKI and emphasize the need for standardized definition in subsequent studies. AKI classifications based on the AKIN, RIFLE, and KDIGO criteria enable assessment of the severity of post-LT renal dysfunction in patients [52].

The RIFLE and KDIGO criteria identify more AKI cases than do AKIN criteria (RIFLE 84.2% vs. KDIGO 87.5% vs. AKIN 72.8%, $p < 0.001$), although the prediction of in-hospital mortality was similar between the three classifications. In septic patients, AKI, defined only by a decrease in urine output, was a better predictor of in-hospital mortality than was AKI, determined either by serum creatinine (SCr) itself or by both SCr and urine output ($p < 0.001$), indicating the diagnostic and prognostic importance of diuresis in patients with septic AKI [53]. Other authors have also noted the advantage of RIFLE and KDIGO classifications over the AKIN classification in the diagnosis of AKI in critically ill patients [1, 2, 54]. Most authors prefer the KDIGO classification in diagnosing AKI and predicting in-hospital mortality [55–58].

AKI is defined as an increase in serum creatinine by 50% or more from its preoperative baseline level. Stage 1 AKI is characterized by 0.3 mg/dl of serum creatinine or a 50% increase after LT. Stages 2 and 3 are defined by a two-fold and three-fold increase in serum creatinine levels, respectively [59]. Determination of serum creatinine level is a sensitive and specific method in diagnosis and classification of post-LT AKI [37].

Inclusion of oliguria, which is common after LT, into the diagnostic criteria, dramatically increases the measured incidence of AKI. Oliguria without serum creatinine increase was significantly associated with adverse postoperative outcomes [60].

Post-reperfusion syndrome, which reflects severe IRI, is a predictor of AKI following donation after brain death liver transplantation [22]. At the same time, increased plasma levels of aspartate aminotransferase (AST) is the only reliable predictor of hepatic IRI. Therefore, elevated AST blood levels should also be considered as a predictor of AKI [13, 33].

NEW DIAGNOSTIC APPROACHES IN ACUTE KIDNEY INJURY

A new trend in early diagnosis of various diseases, including in patients after solid organ transplantation, is the search and study of various biomarkers for this purpose [61, 62]. Although serum creatinine remains the gold standard for assessing kidney function, this test has low specificity and sensitivity for ***early detection*** of AKI [63]. Therefore, as well as the fact that modern AKI therapy leaves much to be desired, researchers are currently focusing not on treatment methods, but on prevention and early detection of AKI in critically ill patients, including LT recipients [64, 65]. New biomarkers for predicting or detecting AKI early can potentially increase the possibility of treating this condition in donor liver recipients [66]. Transition to molecular level, particularly to identification of tubular injury biomarkers, permits earlier and more accurate detection of AKI [67].

The diagnostic capabilities of neutrophil gelatinase-associated lipocalin (NGAL) and G1 cell cycle arrest biomarker as biomarkers have been confirmed in many clinical trials involving cardiac patients (B. Wu et al., 2019) [63]. To predict post-LT AKI, it was also proposed to determine NGAL (A.C.Y. Yeung et al., 2018) [68].

Serum and urinary systemic macrophage migration inhibitory factor (MIF) and NGAL levels were used as early predictors of severe post-LT AKI in 45 patients (mean age 55 ± 8 years). Of these, 19 patients (38%) developed severe AKI within 48 hours after reperfusion. At the end of LT operation, serum MIF was predictive of severe AKI ($p = 0.03$), whereas urinary MIF, serum and urinary NGAL were uninformative. On the first postoperative day, serum MIF ($p = 0.006$), urinary MIF ($p = 0.03$) and urinary NGAL ($p = 0.02$) levels predicted severe AKI, while serum NGAL was not indicative [69]. M.A. Kandil et al. [70] also believe that serum NGAL levels are not a predictor of AKI. Nevertheless, A.C.Y. Yeung et al. [68] consider it necessary to conduct further studies to standardize the method for determining NGAL and confirm its clinical usefulness. This was carried out in a recent study [71], which showed that whole-blood NGAL concentration at ICU admission is a good

stratifier of AKI in critically ill patients (Table 2). However, in septic patients, NGAL concentration is higher regardless of the presence or absence of AKI: an average of 481 (247–687) μg/L in those with sepsis and 623.5 (361–798) μg/L in the subgroup of septic shock.

Table 2

Whole-blood NGAL concentration in critically ill patients, depending on the AKI stage based on KDIGO Classification [71]

AKI stage	NGAL average concentration, μg/L	Variation range of NGAL concentration, μg/L
0	78	60–187
1	263	89–314
2	484	333–708
3	623	231–911

Hyperuricemia often occurs after organ transplants and is an independent predictor of renal failure. Hyperuricemia may accompany decreased renal function in this category of patients [38, 47]. In addition, hyperuricemia is an independent predictor of post-LT mortality, especially in patients with an estimated GFR <60, and a predictor of a doubling of creatinine in patients with diabetes mellitus. Treatment of hyperuricemia leads to improved renal function in liver recipients [38].

Determining the concentration of tissue inhibitor of metalloproteinase-2 (TIMP-2) and insulin-like growth factor-binding protein 7 (IGFBP7) in urine is proposed as biomarkers for early detection of AKI in various clinical situations [72]. They have been recognized in many countries of Europe and the USA as a test in assessing the risk of AKI in patients after major surgery, with hemodynamic instability or sepsis [73]. However, these biomarkers have proved ineffective in predicting post-LT AKI, and should not be recommended for use in clinical practice [74].

C. Pulitano et al. [31] conducted a prospective study of the potential relationship between gene expression, serum mediators, and onset of post-LT AKI. Reperfusion liver biopsy specimens in the AKI group showed higher expression of several genes involved in IRI compared with the non-AKI group. Changes in gene expression of ET-1, interleukin (IL) 18, and tumor necrosis factor α (TNF-α) were associated with creatinine peak value. AKI patients also had significantly higher ET-1, IL18, and TNF-α serum levels on the first day after surgery. Multivariate analysis showed that ET-1 and IL18 serum levels are independent predictors of AKI [31].

There were attempts to use preoperative serum D-dopachrome tautomerase concentrations as a predictor of AKI in patients after LT. However, this biomarker was useful only as a predictor of the outcome of operation, but not development of AKI [75].

PREVENTION AND MANAGEMENT OF ACUTE KIDNEY INJURY

There are still no ways for preventing post-LT AKI [11]. Use of continuous veno-venous hemofiltration in LT for patients who need renal replacement therapy before surgery does not reduce the length of ICU or hospital stay, but increases survival rates [76]. Another large retrospective study demonstrated that the use of veno-venous bypass during LT was associated with a significantly lower incidence of posttransplant AKI in patients with compromised pretransplant renal function but did not require renal replacement therapy [77].

In order to reduce the risk of AKI, it is necessary to maintain sufficient oxygen content immediately after graft reperfusion in patients undergoing LT by thorough mechanical ventilation and blood transfusion [16]. Targeting perioperative systemic therapy reduces the risk of AKI [78]. The authors believe that systemic oxygen delivery, by means of fluids and inotropes, can be the best way to increase kidney perfusion and oxygenation in high-risk patients undergoing major surgery.

Analysis of recent reports has shown that there are no major breakthroughs in the treatment of AKI. Early intervention with this formidable complication has both short-term and long-term positive effects. AKI treatment is usually performed in the ICU. First of all, it is aimed at preventing or eliminating pulmonary edema and hyperkalemia. To date, renal replacement therapy remains the gold standard for the treatment of severe AKI, although the ideal timing and technique of this therapy remain under debate [79]. The question of using loop diuretics, which are widely used in emergency and intensive care medicine, in patients with AKI with preserved euvolemia, needs to be determined [80].

OUTCOMES OF ACUTE KIDNEY INJURY

The outcome of post-AKI can vary from complete recovery to death. Acute renal failure causes serious difficulties in the management of these patients, affects the outcome of operation and is an independent risk factor for death [9, 14, 81]. AKI patients require much longer artificial lung ventilation [14], they stay longer in the ICU and hospital [9]. There are also so many complications, such as frequent postoperative bleeding, infections (bacteremia, pneumonia) [9] and early development of LT dysfunction [31] with decreased survival rates in the first few months [25]. Even a mild or transient post-LT AKI can lead to severe complications, prolonged stay in the ICU and hospital, as well as increased morbidity and mortality [13, 25, 59].

One study showed that between 2002 and 2013, there was an increase in the number of patients with severe AKI after LT requiring programmed hemodialysis [12]. High MELD-Na score (≥22) is a predictor of hemodialysis need [14].

Severe AKI requiring renal replacement therapy is a known risk factor for death in the ICU [25]. Of 177 patients who underwent liver transplant, 35 patients (19%) required renal replacement therapy in the early post-transplantation period. The mean patient age was 31.1 ± 20.0 years. The MELD score was 16.7 ± 12.3. In-hospital mortality in the AKI patients who underwent renal replacement therapy was 23.3%, and 40% of patients remained on hemodialysis [82].

IRI is responsible for occurrence of post-reperfusion syndrome, which is the first manifestation of severe AKI [22] and which affects morbidity and mortality after LT [83–85]. Development of moderate or severe hepatic IRI in conjunction with AKI has the greatest negative impact on treatment outcomes in these patients. The 90-day survival of patients sustaining both complications was 89%, compared to 100% in patients with either or neither complication [33].

Late survival rates of patients with post-LT AKI, according to various clinics, varies widely. The 1- and 5-year cumulative survival rates of patients with AKI were 33.95% and 25.24%, respectively, compared with 86.34% and 70.05% in non-AKI patients ($p < 0.001$) [20]. In another study, patient survival one year after surgery was 90% in AKI patients versus 98% in non-AKI patients [13].

More than half and even most AKI patients develop CKD. The risk of death increases exponentially with GFR <30 ml/min/1.73m^2 [12, 14, 22]. Incidence of *de novo* CKD and the need for dialysis three months and one year after liver transplantation were significantly higher among patients who developed AKI [25]. This complication is also an important risk factor for long-term postoperative *de novo* CKD [31, 85].

CONCLUSION

Even though post-liver transplant acute kidney injury is less common than in heavy therapeutic and surgical patients, including after transplantation of other solid organs, the urgency of this problem remains to this day and still attracts major attention from many researchers. Incidence of post-LT AKI varies widely. The origin of AKI is multifactorial, but the main cause is hepatic IRI. Acute tubular necrosis is observed in severe AKI. Acute kidney injury has numerous preoperative, intraoperative and postoperative risk factors. The use of standard classifications, such as AKIN, RIFLE and, to a greater extent, KDIGO has improved post-LT AKI diagnosis. However, serum creatinine levels are used to diagnose AKI only in the later stages of development of this syndrome and this does not meet hospital's needs. Therefore, research is currently underway to find ways of detecting early AKI using biomarkers. Transition to molecular level, particularly to identification of tubular injury biomarkers, permits earlier and more accurate detection of AKI. Currently, the diagnostic capabilities of NGAL are the most studied. To date, there are no known measures of preventing post-LT AKI. Moreover, there is no effective treatment for this condition. Even mild post-LT AKI can be devastating. In severe AKI requiring renal replacement therapy, there is a risk of death in the ICU. Over half of AKI patients develop CKD requiring chronic hemodialysis.

The authors declare no conflict of interest.

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