Overview of Pre and Intraoperative Risk Factors for Acute Kidney Injury after Deceased-Donor Liver Transplantation

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Abstract

Acute Kidney Injury (AKI) is characterized by the abrupt loss, or a worsening of the kidney function, which has serious consequences on the prognosis of patients undergoing Liver Transplantation (LT). Identifying pre and intraoperative risk factors for the occurrence of the AKI after Deceased-Donor Liver Transplantation (DDLT) enables potential interventions on patients at risk immediately after the end of the surgery. The MELD score, preoperative renal dysfunction, graft macrosteatosis, Extended Criteria Donors (ECD), Intraoperative Arterial Hypotension (IOAH) with compromised tissue perfusion, and intraoperative Massive Blood Transfusion (MBT) have already been highlighted as strong predictors of postoperative AKI. Moreover, the definition of AKI to be adopted in this population must be uniform, and it would be reasonable that diagnostic and staging AKI criteria must consider haemodynamic repercussions of cirrhosis. Finally, AKI is a very common complication after DDLT, and identifying potential pre and intraoperative risk factors may lead to a construction of an effective model risk that would ultimately aim to improve perioperative management of these patients in risk, preventing this serious complication.

Keywords: Acute kidney injury; Deceased-donor; Liver transplantation; Risk factors

Introduction

Currently, Liver Transplantation (LT) is the treatment of choice for a wide variety of terminal liver diseases such as liver cirrhosis in its most varied etiologies, primary tumors (benign or malignant), secondary malignant tumors of the liver and metabolic diseases. LT may also be necessary to manage complex cystic liver diseases and some situations of liver trauma. With the refinement of the surgical technique, the improvements in the selection of patients who are candidates for the procedure, the advances in anesthetic support and preoperative care, this surgical intervention, traditionally complex and feared, has become a routine procedure in the last 20 years [1]. Among the possible complications of major procedures, Acute Kidney Injury (AKI) should be considered an important cause of increased postoperative morbidity and mortality [2,3], with an incidence ranging from 10% to 30% after major operations [4,5]. The AKI is characterized by the deterioration of the renal function over a period of hours to days, which results in the failure of the kidneys to excrete nitrogenous waste and maintain fluid and electrolyte homeostasis [6]. Updated data report a 1% incidence of AKI in the postoperative period of major noncardiac surgery without liver resection, about 20% after cardiac surgery [7-9], and 4% up to 94% after LT [10-16].

In the specific scenario of Deceased-Donor Liver Transplantation (DDLT), the difficulties in analyzing data related to postoperative AKI are mainly due to the multiplicity of factors to be considered in these surgical patients, such as: general clinical conditions and comorbidities of patients with liver disease, low physiological reserve of the systems, pre-existing renal dysfunction, graft functional quality and ischemia times, and perioperative hemodynamic events [16]. In addition, there is a lack of a reported standard definition of postoperative AKI after LT [17-20]. Despite this multiplicity of risk factors for postoperative AKI after LT, there are determining factors that clearly contribute to its occurrence, and often, patients may have more than one injury promoter [21-23]. In face of this serious postoperative complication, identifying pre and intraoperative predictive factors for the occurrence of AKI after DDLT is crucial.
**Definition of Renal Dysfunction in Cirrhotic Patients**

It is extremely important to point out that in the case of patients with chronic liver disease, isolated dosages of serum creatinine (sCr) levels cannot reveal the actual renal function of the patient, because: (1) there is a decreased creatine formation in the secondary muscles loss of muscle mass; (2) there is an increased renal tubular secretion of creatinine (Cr); (3) the increased circulating volume of distribution in cirrhosis can dilute e sCr; and (4) there is interference in the measurement of Cr due to elevated bilirubin. As a result, the sCr in patients with cirrhosis overestimate Glomerular Filtration Rate (GFR) [22,23]. Therefore, a dynamic definition referring to the elevation of sCr of ≥50% of preoperative levels to a final value ≥1.5 mg/dL (133 mol/L) could be more suitable for these patients [22,23], and the current criteria suggested by the “International Club of Ascites” (ICA) for definition of AKI in cirrhotic patients do not include unreal measurements for these patients, and apparently would be the most appropriate criteria for the diagnosis and management of AKI after LT, especially DDLT with underlying chronic liver disease. Thus, kidney dysfunction subtypes are best defined according to Wong, et al. (Table 1) [22] and the (ICA) definitions (Table 2), [23] and both the acute deterioration in renal function and the background CKD could be structural or functional in nature, including HRS types 1 and 2 (Table 3) [23]. Estimated Glomerular Filtration Rate (eGFR) can be calculated by the Diet in Renal Disease 6 (MDRD6) formula: eGFR = 198×[serum creatinine(mg/dL)]^{−0.858}×[age]^{−0.167}×[0.822 if patient is female]×[1.178 if patient is black]×[serum urea nitrogen concentration (mg/dL)]^{−0.293}×[urine urea nitrogen excretion (g/d)]^{0.249} [24].

| Diagnosis | Definition |
|-----------|------------|
| AKI       | Rise in serum creatinine of ≥50% from baseline or a rise of sCr by >26.4 mmol/l (≥0.3 mg/dl) in < 48 hours |
| HRS type 1 | is a specific form of AKI |
| CKD       | eGFR of <60 ml/min for >3 months calculated using MDRD6 formula |
| HRS type 2 | is a specific form of CKD |
| ACKD      | Rise in serum creatinine of ≥50% from baseline or a rise of sCr by >26.4 mmol/l (≥0.3 mg/dl) in < 48 hours in a patient with cirrhosis whose eGFR of <60 ml/min for >3 months calculated using MDRD6 formula |

AKI: Acute Kidney Injury; sCr: Serum Creatinine; HRS: Hepatorenal Syndrome; CKD: Chronic Kidney Disease; eGFR: Estimated Glomerular Filtration Rate; ACKD: Acute On Chronic Kidney Disease; MDRD6: Modification of Diet in Renal Disease 6.

**Table 1:** Diagnostic criteria of kidney dysfunction in cirrhosis (Wong et al, 2011).

| Baseline sCr | A sCr value obtained in the three months prior to hospital admission, with preference to the value dated the closest to hospital admission. In patients without a previous sCr value, the value on admission should be used. |
|-------------|----------------------------------------------------------------------------------------------------------------------------------|
| AKI definition | Increase in sCr ≥0.3 mg/dl (≥26.5 µmol/L) within 48 hours; or the percentage increase in sCr ≥50%, which occurred in the last 7 days. |
| Stage 1 AKI | Increase in sCr ≥0.3 mg/dl (26.5 µmol/L) or an increase of 1.5 to 2 times the baseline value. |
| Stage 2 AKI | Increase of sCr 2 to 3 times the baseline value. |
| Stage 3 AKI | Increase in sCr >3 times the baseline or sCr ≥4.0 mg/dl (353.6 µmol/L), with acute increase in sCr ≥0.3 mg/dl (26.5 µmol/L) or onset of RRT. |

AKI: Acute Kidney Injury; ICA: International Club of Ascites. sCr: Serum Creatinine; HRS: Hepatorenal Syndrome; CKD: Chronic Kidney Disease; RRT: Renal Replacement Therapy.

**Table 2:** Definition and classification of AKI for patients with liver cirrhosis according to the ICA (Angeli et al, 2015).
Diagnostic criteria for HRS

1. Presence of cirrhosis or ascites
2. sCr > 1.5 mg/dL or 133 µmoles/L
3. No improvement in sCr (below 1.5 mg/dL) after at least 48 hours of diuretic withdrawal and volume expansion with albumin
4. Absence of shock
5. Has not undergone recent treatment with nephrotoxic drugs
6. Absence of parenchymal kidney disease as indicated by proteinuria less than 500 mg/day, microhematuria (less than 50 erythrocytes / high-magnification field) and/or abnormal renal ultrasound.

HRS Subtypes

**HRS Type 1** - Progressive renal failure rapidly defined as the doubling of initial serum creatinine to a level greater than 2.5 mg/dl or 220 µmoles/L in less than two weeks, and is associated with a very poor prognosis.

**HRS Type 2** - Moderate renal failure (sCr > 1.5 mg/dl or 133 µmoles/l), follows a stable or slowly progressive course, often associated with refractory ascites.

HRS: Hepatorenal Syndrome; sCr: Serum Creatinine.

**Table 3**: Diagnostic criteria and HRS subtypes (Angeli et al, 2015).

**Pre and Intraoperative Predictors of AKI**

Deterioration of renal function in the scenario of DDLT is associated with a substantial increase in 30-day and 1-year mortality rates, [25] therefore, a comprehensive analysis of characteristics of the recipient, the donor, the graft, and surgical events, can enable the identification of patients at risk immediately after the end of the surgery (Table 4) [26].

| Factors modificáveis | OR (95% CI) |
|----------------------|-------------|
| **Recipient factors** |             |
| High MELD score      | 1.98 (1.47-2.67) |
| Preoperative sCr     | 2.33 (1.21-4.49) |
| Overweight           | 2.44 (1.63-3.65) |
| Preoperative use of diuretic | 2.73 (1.30-5.74) |
| Preoperative hyponatremia | 1.61 (1.19-2.17) |
| Preoperative cerebrovascular diseases (including SAH) | 2.06 (1.12-3.80) |
| Preoperative anemia  | 1.62 (1.07-2.45) |
| **Donor and graft factors** |             |
| DCD organ            | 2.70 (1.94-6.09) |
| Donor BMI >30 Kg/m²  | 2.67 (1.17-6.09) |
| WIT (anhepatic time) | 3.59 (1.37-9.39) |
| **Intraoperative factors** |             |
| IOAH                 | 5.58 (3.93-7.92) |
| Major bleeding       | 2.90 (1.50-5.63) |
| Intraoperative use of vasopressors | 2.08 (1.49-2.90) |
| Large intraoperative RBC transfusion | 3.12 (1.99-4.91) |
Preoperative Renal Dysfunction

The increased susceptibility to renal hypoperfusion in patients with structural previous renal dysfunction occurs in elderly patients, atherosclerosis, Systemic Arterial Hypertension (SAH), and pre-existing Chronic Kidney Disease (CKD), due hyalinosis and myointimal hyperplasia. This increased susceptibility to renal ischemia can also occur in malignant hypertension as a result of thickening of the intima and fibrinoid necrosis of the small arteries and arterioles, in addition, the afferent arterioles in the glomeruli dilate with impaired kidney capacity to self-regulate the Glomerular Filtration Rate (GFR) in low perfusion states [22].

In addition to structural chronic deterioration of renal function, the functional disorders can be added as risk factors for AKI, such as HRS. This syndrome is a reversible functional renal failure that occurs in patients with advanced liver cirrhosis, often present at the time of LT, and it is characterized by a marked decrease in GFR and renal plasma flow in the absence of other causes of renal failure. The pathophysiological changes of HRS consist of intravascular hypovolemia with the activation of the renin-angiotensin-aldosterone system and the sympathetic vasoconstrictor nervous system, leading to renal vasoconstriction of the afferent vessels [23]. Thus, renal injury in patients with end-stage liver disease is closely related to the severity of liver disease, as in cases of massive and refractory ascites, which result from the activation of endogenous vasoactive systems released during and after transplantation and circulatory disorders related to portal hypertension [27,28].

Preoperative Severity of Liver Disease (MELD Score)

The MELD (Model for End-Stage Liver Disease) score was initially created to predict survival in patients with liver cirrhosis with complications of portal hypertension, who underwent elective intra-hepatic Transjugular Intra-Hepatic Shunts (TIPS) [29,30]. The MELD formula includes objective parameters (sCr, serum bilirubin and International Normalized Ratio), and the score is considered in the allocation of the liver grafts, identifying those patients with the greatest immediate need for LT, and predicting post-transplant survival [31]. Several other authors described the association between the pre-transplant MELD score and post-LT AKI, and studies have shown that higher MELD scores were associated with AKI after LT, [20] and in patients with MELD scores >30, the most required RRT [26]. Preoperative sCr values have already been identified elsewhere as an independent predictor of post-transplant mortality before the introduction of the MELD score, with higher mortality on the waiting list [32].

Marginal Grafts

Marginal liver grafts of Extended Criteria Donor (ECD) can be defined as a graft with 3 or more of the following donor features: >60 years, BMI >27-30 kg/m², macrovesicular steatosis >30%, Intensive Care Unit (ICU) stay >4 days, sustained arterial hypotension >1 hour, Cold Ischemia Times (CIT) >8 hours, Warm Ischemia Times (WIT) >40-45 minutes, controlled sepsis, history of alcoholism, sCr >1.2 mg/dL, arterial hypotensive episodes <60 mmHg >1 h, bilirubin >2.0 mg/dL, ALT >170 U/l, and AST >140 U/l, the use of dopamine doses >10 microg/kg per min and peak serum sodium >155 mEq/l [4,33-35]. Routine biopsy must be always be performed on the donor allograft for all patients. Liver specimens must be evaluated with hematoxylin and eosin staining as either frozen and permanent section, and macrovesicular steatosis was defined as a single vacuole larger than the nucleus, replacing most of the hepatocytes cytoplasm and displacing the nucleus to the cell membrane [36] Macrosteatosis was categorized as no steatosis (<5%), mild steatosis (10%-29%), moderate steatosis (30%-60%), and severe steatosis (>60%) [37] (Figure 1).

Marginal liver grafts of Extended Criteria Donor (ECD) were identified elsewhere as strong predictors of PGD [4,33-35] and post-LT AKI, [20] and a marginal graft can be defined as a graft with 3 or more of unfavorable features. [4,33-35] In the specific case of graft steatosis, a liver with mild steatosis (<30%) is considered to be completely safe for LT; a liver with severe steatosis (>60%) should be ruled out and, in cases of moderate steatosis (between 30% and 60%), its use is recommended in a individual basis, mainly recipients with low MELD scores and ischemia times [4].
Intraoperative Hemodynamic Instability

Patients undergoing DDLT frequently experience IOAH as a result of various factors, including the duration of surgery, the severity of bleeding, the severity of the Postreperfusion Syndrome (PRS) and the severity of the end-stage liver disease, characterized by a hyperdynamic state (high cardiac output and low SVR) [38-43]. The longer a patient spent with a MAP < 65 mmHg during DDLT, the greater the risk of developing AKI in the immediate postoperative period [16]. Serum lactate is a marker of poor tissue perfusion, present in circulatory shock of different etiologies, indicating end-organ injury, mainly in consequence of hemodynamic instability and IOAH, and can be considered as predictor for the occurrence of AKI [44].

It is important to note that irrespective of the event that results in renal hypoperfusion during DDLT, such as massive bleeding with IOAH, it can results in post-transplant AKI. Sustained hypotension, requiring the infusion of large volumes of crystalloid, promotes a decrease in Systemic Vascular Resistance (SVR), an increase in pulmonary resistance and impaired cardiac output, leading to ischemia. This reperfusion of ischemia leads not only to the release of cold and acidic components by the graft, but also to pro-inflammatory cytokines that trigger inflammatory response and subsequent cell damage, especially tubular injury, further increasing the risk of AKI [27]. Therefore, aggressive bleeding control in the intraoperative period, optimization of cardiac output, hemodynamic stabilization and control of hydroelectrolytic disorders are extremely important measures for the prevention of AKI in cases of LT [16].

Hemodynamic Status and Monitoring During DDLT

Hemodynamic maintenance during DDLT consists of a baseline infusion of a balanced crystalloid (Plasmalyte®, Baxter, Belgium) with or without 4% albumin (depending on patient conditions). Rapid infusers, perfusion heaters, and a Cell Saver® (Haemonetics, Massachusetts, EUA) for blood recovery must be ready for use prior to induction, In accordance to American Society of Anaesthesiologists (ASA) guidelines, Cell Saver® has effectiveness in reducing the volume of allogeneic blood transfused [45]. A Flow Trac/EV1000 System® (Edwards Lifesciences, Irvine, USA) is inserted and hemodynamic interventions were guided using Continuous Cardiac Index (CCI), stroke volume index (SVI), mixed Venous Oxygen Saturation (SvO₂), Central Venous Pressure (CVP), and Mean Arterial Pressure (MAP). Fluids must be administered if SVI <30 ml/m² and/or CCI <2 L/min/m² for compensation for blood loss via 250-500 ml fluid boluses of Plasmalyte®,[16] to strictly maintain MAP >65 mmHg, avoiding hemodynamic instability as described elsewhere [46].
Intraoperative Arterial Hypotension (IOAH) is defined as MAP less than 65-60 mmHg for at least 5 minutes, or any exposure to MAP less than 55-50 mmHg [16], irrespective of the cause; prolonged surgery time, massive bleeding, RPS and/or hemodynamic instability because of end-stage liver disease. Blood loss monitoring consists of visual assessment of the surgical field, including the extent of blood present, presence of microvascular bleeding, surgical sponges, clot size and shape, and volume in suction canister. In case of active haemorrhage, blood products administration can be guided by using rotational thromboelastometry monitoring via ROTEM® (Tem Innovations GmbH, Munich, Germany), hemoglobin/hematocrit monitoring, coagulation tests (International Normalized Ratio [INR], Activated Partial Thromboplastin Time [aPTT], fibrinogen concentration), and platelet count [45]. Whereas there’s no clear evidence that ROTEM® improved survival in LT patients, it was effective in reducing bleeding and fewer patients required both platelets and fresh frozen plasma (FFP) transfusion [47]. Monitoring for perfusion of vital organs includes standard ASA monitoring, renal monitoring (urine output), and analysis of arterial blood gasses [45].

Postreperfusion Syndrome

The PRS following revascularization of the liver graft during LT is described in terms of cardiovascular collapse, with bradyarrhythmia, decreased MAP, and SVR, along with an increased mean pulmonary artery pressure, pulmonary capillary wedge pressure, and CVP, and as a cause of major hemodynamic instability with IOAH, is defined as a decrease in MAP >30% below the baseline value, for at least 1 minute, occurring during the first 5 minutes after reperfusion of the liver graft, asystole, or hemodynamically significant arrhythmias, or the need to start the infusion of vasopressors during the postreperfusion period. The etiology of this syndrome had been attributed to acute acidosis, hyperkalemia, hypothermia, and vasoactive substances released from the liver graft may be involved [48].

The occurrence of PRS correlates with postoperative renal dysfunction as well as higher intraoperative and postoperative mortality. Management of PRS includes pretreatment of the patient with the antihistamines (ranitidine and diphenhydramine) in the 15 minutes prior to reperfusion, and close hemodynamic monitoring at the time of graft outflow unclamping. Hypotension is treated with volume resuscitation and vasopressor agents, including infusion of phenylephrine, norepinephrine, vasopressin, and epinephrine. Treatment of electrolyte abnormalities (hypocalcemia, hyperkalemia, etc) is also necessary [49].

Massive Intraoperative Hemotransfusion

In addition to the deleterious effect of hemodynamic instability on renal perfusion, massive transfusion of red blood cells, which may be necessary in the case of hemorrhage, may be an additional risk factor for postoperative AKI [50]. MBT protocol can be activated when hemorrhage is expected to be massive (anticipated need to replace 50% or more of blood volume within 2 hours), bleeding continued after the transfusion of 4 units of packed Red Blood Cells (RBC) within a short period of time (1-2 hours), or SBP is below 90 mmHg and heart rate is above 120 beats per minute in the presence of uncontrolled bleeding [51]. With more rapid and effective therapy, alternative definitions such as three units of red blood cells over one hour or any four blood components in 30 minutes are more sensitive in identifying patients needing rapid issue of blood products for serious injuries because of uncontrolled hemorrhage [52]. With the findings of the Pragmatic Randomized Optimal Platelet and Plasma Ratios (PROPPR) study group published in 2015, many hospitals have decided on a 1:1:1 ratio of products [53].

Although the exact causal relationship between RBC transfusion and postoperative AKI is not yet fully understood, there are several mechanisms that may be involved: 2,3-diphosphoglycerate deficiency with consequent decrease in hemoglobin oxygen release, stored red blood cells with obstruction of small capillaries and stored red blood cell hemolysis with an increase in free iron circulation [54]. Other mechanisms may include the loss of the nitric oxide generation capacity, the release of pro-coagulant phospholipids, the increase in adhesion to the vascular endothelium and the accumulation of pro-inflammatory phospholipids [55].

Final Considerations

The reported high incidence of AKI after DDLT in numerous studies highlights the importance of this issue. The identification of predictors may provide a focus for further research, mainly in the development of predictive models that may be applied immediately after DDLT. A effective model risk may ultimately aim to improve perioperative management of these patients in risk, preventing this serious complication.

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