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Review

Kidney Failure after Liver Transplantation

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Abstract: One-third of patients with cirrhosis present kidney failure (AKI and CKD). It has multifactorial causes and a harmful effect on morbidity and mortality before and after liver transplantation. Kidney function does not improve in all patients after liver transplantation, and liver transplant recipients are at a high risk of developing chronic kidney disease. The causes of renal dysfunction can be divided into three groups: pre-operative, perioperative and post-operative factors. To date, there is no consensus on the modality to evaluate the risk of chronic kidney disease after liver transplantation, or for its prevention. In this narrative review, we describe the outcome of kidney function after liver transplantation, and the prognostic factors of chronic kidney disease in order to establish a risk categorization for each patient. Furthermore, we discuss therapeutic options to prevent kidney dysfunction in this context, and highlight the indications of combined liver–kidney transplantation.

Keywords: liver transplantation; kidney failure; risk factor; cirrhosis; kidney protection

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Highlights

- Kidney failure is very common in liver transplantation.
- It impacts morbidity and mortality pre- and post-liver transplantation.
- The risk of kidney failure for each patient should be categorized.
- Preventive measures should be implemented at an early stage.
- Combined liver–kidney transplantation should be restricted to targeted patients.

1. Kidney Function and Cirrhosis

Cirrhosis is now the 4th leading cause of death in Europe and the main indication for liver transplantation [1]. Regardless of the initial disease, the prognosis for patients with cirrhosis is saddled with numerous complications, one of which is kidney failure. Kidney failure can occur as acute kidney injury with or without dialysis requirement, chronic kidney disease or end-stage kidney disease. It occurs in one-third of patients with cirrhosis [2,3]. Chronic kidney disease (CKD) is responsible for increased mortality [4]. The mechanisms responsible for renal dysfunction in patients with cirrhosis are multifactorial and include a combination of functional and organic renal impairments [5], such as vasodilation of the splanchnic arterial system and intestinal bacterial translocation secondary to the portal hypertension (PHT). These phenomena are responsible for hepatorenal syndrome (HRS) [6]. In addition, there are renal damages associated with cardiovascular morbidities

(diabetes, insulin resistance, hypertension and obesity), renal damage specific to cirrhosis or the initial liver disease (IgA nephropathy, cryoglobulinemic membranoproliferative glomerulonephritis (MPGN)) or repeated renal toxicity of drugs and contrast agents [7]. All these factors contribute to the occurrence of irreversible lesions and impact renal function. It is now widely accepted that pre-transplantation kidney function is a major prognostic factor in pre-transplant mortality [3]. Therefore, in order to integrate this variable in the estimation of the severity of liver disease, the MELD (Model of End Stage Liver Disease) score has been used since February 2002. Unlike the Child–Pugh score, this score takes into account serum creatinine, which has a high impact on the result. Consequently, the proportion of patients with kidney failure with cirrhosis who have received a transplant has increased significantly since the introduction of the score [8]. However, these patients are at a high risk for AKI and CKD after liver transplantation, which is responsible for excess mortality in this population [9].

The aims of this narrative review are: (i) to describe the outcome of kidney function after liver transplantation (AKI and CKD) and the prognostic factors of chronic kidney disease; (ii) to discuss markers and predictive models of post-transplantation renal dysfunction used to establish a risk stratification for each patient; (iii) to discuss therapeutic options to prevent kidney dysfunction; and (iv) finally, to summarize the indications of combined liver–kidney transplantation.

2. Change in Kidney Function Post-Transplantation

The change in kidney function after transplantation is extremely variable and depends on many factors. In general, kidney function deteriorates rapidly during the first year, stabilizes and then decreases more gradually [10].

2.1. Acute Kidney Injury after Liver Transplantation

The risk of post-transplant AKI is significant. However, the variability in incidence across studies is due to the lack of consensus on the diagnostic criteria. In 2004, the second ADQI (Acute Dialysis Quality Initiative) group consensus conference established the RIFLE (Risk of kidney dysfunction, Injury to the kidney, failure of kidney function, loss of kidney function, and end-stage renal disease) classification based on changes in GFR and diuresis, adopted in 2010 by the ICA (International Club of Ascites) for patients with cirrhosis, regardless of the cause of kidney failure. In 2011, the AKIN (Acute Kidney Injury Network) group improved the RIFLE criteria to produce the AKIN classification (Appendix A). With these more sensitive criteria, it takes into account less severe renal impairments and, therefore, increases the incidence of AKI [8]. The ADQI-ICA committee suggests the use of AKIN criteria in patients with cirrhosis for the diagnosis of AKI [9].

A review of 67 observational studies published between 1985 and 2019 showed that over 50% of transplant patients will develop AKI within the early period after transplantation [8,9,11–69]. Fifteen percent will require dialysis [51,70]. Ninety-five percent (95%) of the cases of AKI develop within 7 days of transplantation and are usually attributed to a high MELD score, the presence of ascites or prolonged perioperative hypotension [36]. Late post-operative AKI that occurs after the first week is mainly associated with infectious complications, repeat surgery, or delayed or no recovery of liver function. The recovery rate after AKI with or without the need for dialysis is between 60% and 80% [24,25]. This seems to be associated with the existence of a pre-transplantation hepato-renal syndrome and can occur from a few days to several months after surgery. However, AKI causes a significant risk of CKD which is even greater with a longer period of hemodialysis.

2.2. Post-Transplantation Chronic Kidney Disease and End-Stage Renal Disease

CKD is common after organ transplantation, mainly during recovery from liver transplantation [70]. A review of 46 observational studies between 1990 and 2019 [15,20,24,28,31,43,49–51,66,71–105] showed that CKD is observed in 10% to 75% of liver-transplant patients beyond 20 years post-transplantation. This wide variability is due to inhomo-

geneous definitions, measurement methods, and lengths of follow up between studies. Some use creatinine levels, while others use GFR thresholds or variations. At one year post-transplantation, an average of 19% of patients develops CKD compared to 29% and 69%, respectively, at 5 and 15 years post-transplantation. The incidence of end-stage renal disease follows the same course (an average of 4% and 11%, respectively, at 5 and 15 years post-transplantation). This decrease in GFR has an exponential impact on post-transplantation mortality [93] with an overall risk of mortality increased by a factor of four in the event of CKD [106]. The mechanisms responsible for post-transplantation impairment of kidney function are multifactorial with variable histological manifestations.

2.3. The Contribution of Histology in Post-Transplantation Kidney Failure

Few studies have examined histological renal lesions in liver transplant patients with kidney failure. However, these analyses confirm that renal lesions are numerous, varied, complex and multifactorial. In contrast to renal histological lesions in cirrhotic patients, few specific primary glomerular lesions are detected. Most of the damage consists of vascular lesions, tubular necrosis or non-specific glomerular lesions (thickening of the glomerular basement membrane, fibrous expansion of the mesangium, segmental and focal hyalinosis lesions, nodular diabetic glomerulosclerosis or podocyte depletion observed under electron microscopy) [107]. In 15% to 50% of the cases, there are lesions secondary to calcineurin inhibitor toxicity characterized histologically by nodular arteriolar hyalinosis and/or interstitial fibrosis in bands [108]. Rare cases of membranous glomerulonephritis, oxalate nephropathy or BK virus nephropathy have also been described [109,110]. The high variability of post-transplantation lesions observed and the low rate of pre-transplantation histological lesions suggest the occurrence of new nephrotoxic events [107]. Given the high number of non-specific lesions, histological evaluation constitutes a challenge in the post-transplantation quantification of these lesions. In previous studies, we suggested evaluating the percentage of glomerular obsolescence; acute tubular necrosis; and according to the Banff classification, interstitial fibrosis (ci), tubular atrophy (ct) and intimal thickening (cv) [80,111]. Similarly, Kubal et al. propose a prognostic histological score based on the semi-quantitative staging of histological lesions, such as inflammation, tubular atrophy, interstitial fibrosis, intimal thickness and mesangial thickening. They showed that this histological score is highly correlated with renal survival. It is interesting to note that severe histological lesions, such as glomerulosclerosis, fibrous endarteritis and interstitial fibrosis, were even observed in patients with normal kidney function (GFR $\geq$ 60 mL/min/1.73 m^2) [108].

2.4. The Impact of Kidney Function on Post-Transplantation Mortality

Most studies report a strong relationship between kidney failure and patient survival [93,112]. In fact, as is the case in pre-transplantation, post-transplant renal dysfunction is an independent predictor of immediate and long-term mortality in liver transplant patients [44,47,94,113]. Mainly in AKI that occurs immediately after transplantation, the need for post-operative dialysis is associated with a higher risk of mortality [18,55]. Similarly, persistent CKD after liver-transplantation increases the short-term risk of mortality ($\leq$1 year) by a factor of three (2.55 to 3.20 depending on the study) [36,114], as well as the long-term risk of mortality, as highlighted by a meta-analysis by Fabrizi et al., who showed an increased mortality by a factor of four [106]. This increases with the severity of renal dysfunction, if the onset is late (>1 year after transplantation) or if the patient requires dialysis [113].

Recently, Allen et al. established a mortality risk assessment model based on measured or estimated GFR and creatinine values in a cohort of 1211 liver transplant recipients monitored for 25 years [72]. When GFR decreases below 60 mL/min/1.73 m^2, mortality increases exponentially (the relative risk of death increases by up to 5.5 times). Using serum creatinine, they found a U-shaped curve with an excess risk of mortality for extreme values (<0.75 and >2 mg/dL).

3. Factors Associated with the Risk of Post-Transplantation Renal Dysfunction

The cause of renal dysfunction after liver transplantation is multifactorial. There are many risk factors involved in AKI and CKD [66,78,111]. However, they can be classified into three categories: pre-transplantation, perioperative and post-operative. We identified these predictive factors by uni- or multivariate analysis from 101 observational studies published between 1996 and 2019 [8,10,14–34,36–38,40–46,48,53,56,60–64,70,71,73,76–87,89–97,104,106–108,111–113,115–136] (Figure 1).

3.1. Pre-Operative Risk Factors

3.1.1. Intrinsic Renal Factors

The level of kidney function before transplantation, estimated by creatinine or GFR, is a determining factor for the changes in kidney function after transplantation [122]. In fact, the risk of post-transplantation CKD or AKI is directly correlated with the degree and duration of kidney failure prior to transplantation [75,88,106]. In addition, patients with a pre-transplantation GFR < 60 mL/min/1.73 m^2 may improve after transplantation but remain at high risk for stage IV CKD 5 years post-transplantation [92]. Finally, the presence of proteinuria, microalbuminuria and high Doppler renal resistance indices is associated with an increase in the risk of renal dysfunction after liver transplantation [28,84,94].

3.1.2. Risk Factors Related to the Diathesis

Some studies have identified female gender as a risk factor for CKD after liver transplantation, as is the case in heart and lung transplantation [20,70,73,76,85,104,121]. One of the explanations mentioned is the enhanced sensitivity of women to calcineurin inhibitor toxicity. On the other hand, post-operative AKI is more closely associated with males [17,34,36,43]. Cardiovascular risk factors, such as advanced age, diabetes, high body mass index (BMI), high blood pressure, dyslipidemia and smoking, are also associated with a decline in kidney function after liver transplantation [62,70,82,83,86,90,128].

3.1.3. Risk Factors Related to the Liver Impairment

The severity of liver impairment (high MELD score) has been identified as a risk factor for post-transplantation CKD [112]. Similarly, an elevated Child–Pugh score, hypoalbuminemia, hepato-renal syndrome, hepatic encephalopathy and the need for TIPS are associated with both the development of AKI and the risk of progression to CKD [16,18,26,61,64,81,84,94,115,116,122,130].

At the same time, the risk of developing renal dysfunction is correlated with the type of liver cirrhosis. In fact, viral cirrhosis related to hepatitis [14], non-alcoholic steatohepatitis (NASH), alcoholic cirrhosis and primary biliary cholangitis are recognized as risk factors for post-transplantation renal dysfunction [10,66,70,73,75,122,123,129,131]. Conversely, patients with cirrhosis complicated by hepatocellular carcinoma develop fewer renal dysfunctions after transplantation [42,95]. This can be explained by access to transplantation without decompensated cirrhosis.

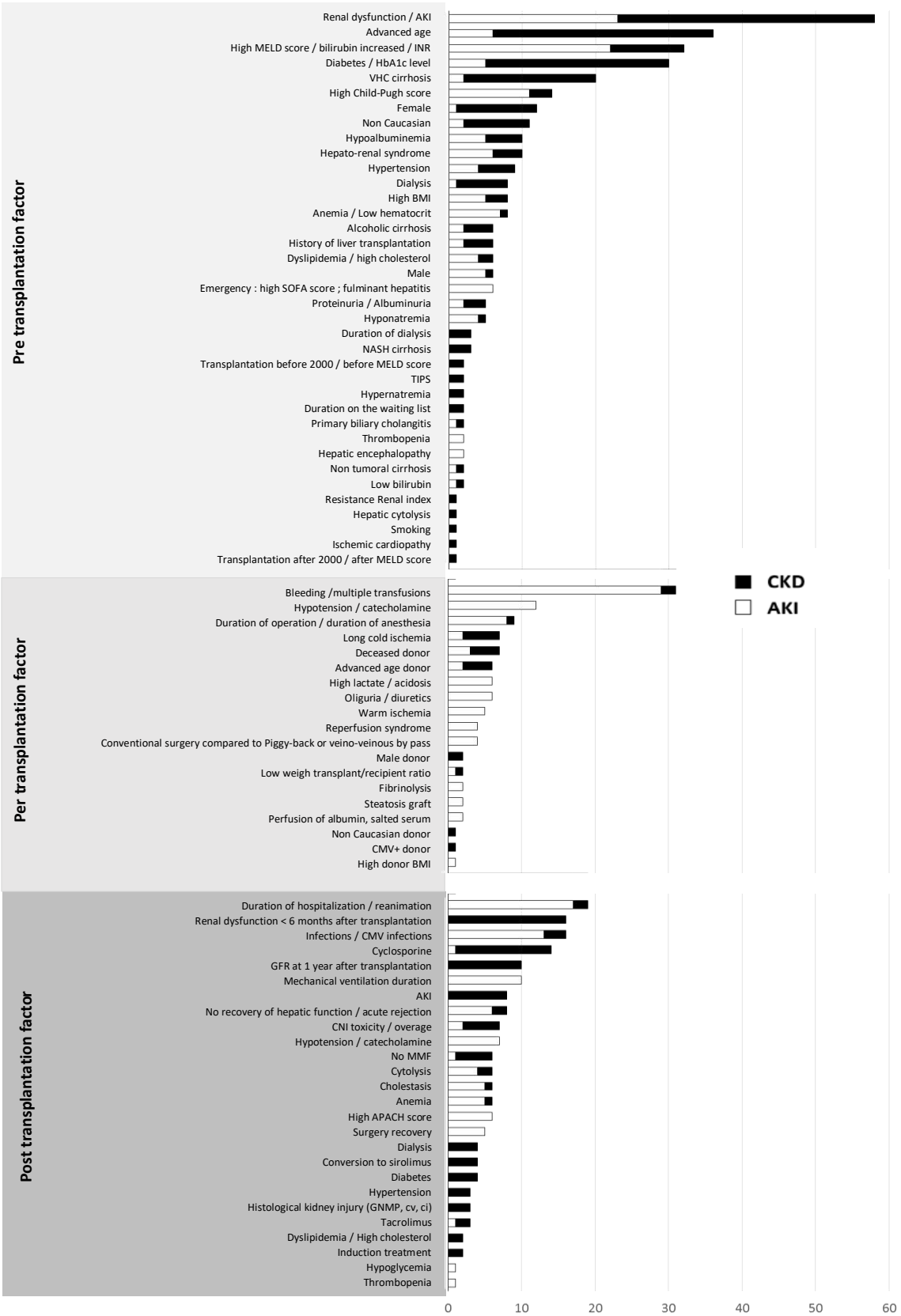

Figure 1. Inventory of the pre-transplantation, perioperative and post-operative risk factors for AKI or CKD according to the number of studies that mention them [8,10,14–34,36–38,40–46,48,53,56,60–64,70,71,73,76–87,89–97,104,106–108,111–113,115–136]. AKI: acute kidney injury; CKD: chronic kidney disease.

3.2. Perioperative Risk Factors

Perioperative risk factors are mainly associated with the development of post-operative AKI, mainly related to kidney hypoperfusion. Severe portal hypertension (PHT) with collateral circulation, portal vein thrombosis and a history of abdominal surgery can lead to perioperative collapse and hemorrhage, which reduce renal perfusion and increase the risk of AKI [8,13,14,20,21,37,38,40,42]. The surgical technique and, therefore, the vascular clamping time are determinants, similarly to warm and cold ischemia duration [137]. Therefore, the more the period of renal congestion is extended, the greater the risk of kidney failure in post-transplantation [53] due to decreased blood flow, peripheral resistance and decreased contractility. This results in hemodynamic instability and acute renal injury [18,32,34]. Similarly, post-reperfusion syndrome after the unclamping of the portal vein is a source of hemodynamic instability [74] and the release of cold and acidotic components and pro-inflammatory cytokines, such as interleukin-6 (IL-6) or Tumor Necrosis Factor alpha (TNF-α), which are responsible for acute tubular lesions and renal vasoconstriction, are linked to the activation of endogenous vasoactive systems [138]. Liver transplantation with the preservation of the inferior vena cava, known as the "piggy-back" technique, reduces the risk of hemodynamic instability and prevents renal congestion [139]. Other surgical options available to preserve kidney function after transplantation are the creation of a veno-venous extracorporeal membrane oxygenation circuit or of a temporary portacaval shunt in patients with PHT [140]. By the same token, perioperative hypothermia could reduce the risk of post-operative AKI [141], but the massive transfusion of red blood cells (>10) induces a proinflammatory state that impacts kidney oxygenation [142]. The quality of the graft is also crucial. Leithead et al. found that the increasing use of marginal liver transplants is associated with an increase in the incidence of AKI and dialysis requirement [21,136], but this does not seem to have a harmful impact on the long-term (5 years) risk of CKD [105]. However, transplants from donors after circulatory death compared with those after brain death and size mismatch between donors and recipients are more often associated with post-LT AKI [143]. Similarly, the late recovery of liver function, advanced age non-Caucasian male donors, CMV-positive transplants, prolonged cold and warm ischemia are factors of post-transplantation CKD [89,128,129]. However, the current utilization of liver graft machine perfusion allows a reduction in ischemia perfusion injury and seems to reduce early allograft dysfunction and the amount of post-operative AKI for the liver with extended criteria [141].

3.3. Post-Operative Risk Factors

Post-operative risk factors for AKI are represented by markers of the severity of the condition, such as mechanical ventilation, length of hospitalization (including in intensive care unit), infectious complications, hemodynamic instability or a high APACHE II score [8,23,25,36,60]. The importance of liver function is also accentuated since the occurrence of AKI is predicted by a lack of recovery of liver function, acute rejection, cholestasis and peak cytolysis [31,42,116]. The occurrence of AKI within 6 to 12 months after transplantation is associated with an increase in the risk of chronic renal disease within 5 years after transplantation [46,62,71,75,76,79,83,87]. Several studies have shown the importance of GFR monitoring during the first year after surgery as it allows the identification of patients at risk for CKD in the long term. However, we were able to demonstrate that very early creatinine elevation between D3 and D5, which did not meet the criteria for AKI as they are not sensitive enough, was correlated with poorer kidney function at 6 months to 1 year [66,131]. Similarly, the need for temporary dialysis has been identified as a source of CKD [51] in the long run. Cardiovascular risk factors, such as hypertension, dyslipidemia and diabetes, may be present before transplantation but may also appear after transplantation, mainly as a result of immunosuppressive treatments (calcineurin inhibitor, mTOR inhibitor and corticosteroids). They play an important role in the progression of chronic kidney disease [62,78,95,107,111]. The choice of immunosuppressive treatment is

also crucial to prevent deterioration in kidney function [84,85,88,93,95] since calcineurin inhibitors are a source of nephrotoxicity in the long run.

4. Markers and Predictive Models of Post-Transplantation Renal Dysfunction

Therefore, there are many risk factors that expose patients to post-transplantation CKD. Some factors are non-modifiable (age, hepatopathy or cardiovascular comorbidity), and it is, therefore, crucial to determine modifiable and preventable risk factors. Consequently, over the past 10 years, new concepts have focused on the detection of non-invasive markers of nephrotoxicity and the establishment of predictive models of post-transplantation CKD. This enables the pre-transplantation or early post-transplantation identification of patients at high risk for renal dysfunction in order to prevent kidney failure as much as possible [144].

4.1. Markers of Post-Transplantation Renal Dysfunction

Early post-transplantation serum creatinine (D5) is associated with an excess risk of CKD [66]. The use of biomarkers (blood or urine) is an interesting innovative approach for early diagnosis, characterization of renal impairment (pre or intrarenal) and quantification of irreversible renal lesions [145]. Among the most promising are interleukin 18 (IL-18), kidney injury molecule 1 (KIM-1), liver-type fatty acid binding protein (L-FABP), osteopontin, TIMP-2 and neutrophil gelatinase-associated lipocalin (NGAL). In patients with cirrhosis, an elevation in these biomarkers seems to be more closely associated with structural kidney lesions than with functional impairment [146]. In certain studies, they are even considered as predictive factors of AKI after liver transplantation, but the results remain inconsistent. However, some plasma biomarkers, such as NGAL, are associated with a risk of early post-transplantation CKD [117]. Similarly, Levitsky et al. showed an association between a specific plasma proteome profile and the development of chronic kidney disease after transplantation [126]. However, these promising tools are not yet validated and at present remain in the realm of research [147].

4.2. Long-Term CKD Prediction Models

In order to improve the identification of patients at risk, certain teams have developed formulas to predict the risk of CKD after liver transplantation. Giusto et al. established and validated a model for predicting CKD 12 months post-transplantation, based on a regression analysis that takes into account GFR, hypertension and episodes of severe infection [78]. However, this model is limited by a small number of variables that contrast with all the risk factors identified to date. Israni et al. propose a model for ESRD prediction at 6 months and 5 years post-transplantation. This model takes into account more variables, such as age, history of diabetes, cancer or dialysis, ethnicity, hepatitis C status, BMI, donor risk index, albumin, bilirubin and creatinine levels. It has the advantage of being more complete and, therefore, more precise in terms of risk analysis [125]. However, given the complexity of the model and the failure to take into account post-transplantation risk factors, it seems difficult to use in clinical practice. Sharma's team suggests calculating a Renal Risk Index (RRI) to predict the risk of end-stage renal disease following liver transplantation [96]. It estimates the cumulative incidence of ESRD at 1, 3 and 5 years post-liver transplantation by taking into account age; BMI; ethnicity; UNOS status; the presence of TIPS; and laboratory values, such as serum creatinine, bilirubin, albumin and natremia. Finally, the AKI score, which is more recent, categorizes risks into three distinct groups based on five factors: the BMI of the donor and the recipient, the time of warm ischemia, the characteristic of the graft (deceased donors) and the need for fresh frozen plasma during the procedure [148]. However, these scores are still rarely used on a daily basis and still need to be validated in routine practice.

5. Prevention of Post-Liver Transplantation Kidney Failure

The prevention of CKD after liver transplantation should be considered a priority due to the considerable impact on patient morbidity and mortality. Therefore, the early management of modifiable risk factors in these patients is essential.

5.1. Pre-Transplantation Prevention

Preventing pre-transplantation AKI is a major factor in the prevention of post-transplantation kidney failure. This implies limiting the use of nephrotoxic treatments (NSAIDs, iodinated contrast products and aminoglycosides), compensating ascites and treating ascetic fluid infections (AFI) by albumin infusion, the early treatment of all infections, the implementation of antibiotic prophylaxis for AFI and the early management of episodes of hemodynamic instability or hepato-renal syndrome. In this regard, the O'Leary team proposes an algorithm for the management of AKI in patients with cirrhosis regarding the mechanisms of the AKI (pre-renal, renal and post-renal) and the AKI evolution at 48 h after treatment [149].

5.2. Post-Transplantation Prevention

5.2.1. Control of Cardiovascular Risk Factors

Cardiovascular risk factors are very frequent in liver transplant patients. First of all, cirrhosis is responsible for hypermetabolism associated with insulin resistance. Second, immunosuppressive drugs, such as tacrolimus or corticosteroids, cause high blood pressure, dyslipidemia and diabetes. These complications are associated with a decline in kidney function after liver transplantation. Consequently, strict control is required before and after transplantation to minimize the impact on kidney function [20]. Therefore, immunosuppression without corticosteroids is preferable. Two meta-analyses have shown that an immunosuppressive regimen without corticosteroid therapy has no impact on renal function, patient survival or short- and long-term liver transplant survival, but can limit the occurrence of diabetes or dyslipidemia [150,151]. Finally, hyperuricemia, a frequent complication after organ transplantation, seems to be correlated with the development of CKD in liver transplant patients. Similarly, treatment with allopurinol leads to a significant decrease in creatinine level after liver transplantation [88,152].

5.2.2. Optimization of Immunosuppressive Treatment

Calcineurin inhibitors (CNIs) (cyclosporine and tacrolimus) are the cornerstone of immunosuppressive treatment in organ transplantation, despite their nephrotoxicity. This chronic nephrotoxicity is characterized by arteriolar hyalinosis, which leads to a variety of tubulointerstitial and glomerular lesions with an essentially hemodynamic and ischemic mechanism. Acute rejection is less likely with liver transplants than other organ transplants. Therefore, the current dynamic is to decrease exposure to CNIs to minimize kidney toxicity (9). At present, the available strategies are (1) promoting the use of tacrolimus over cyclosporine; (2) reducing CNIs by adding mycophenolic acid (MPA) or mTor (mammalian target of rapamycin) inhibitor; (3) delaying the introduction of CNIs after induction therapy (basiliximab or antilymphocyte serum); (4) complete weaning from CNIs by early conversion to mTor inhibitors or antimetabolites.

- *Promoting the use of tacrolimus*

It is now acknowledged that tacrolimus improves patient survival and prevents acute rejection after liver transplantation compared to cyclosporine. In a literature review and meta-analysis of 32 randomized controlled trials and 32 observational studies, Rodríguez-Perálvarez et al. determined that reduced residual tacrolimus concentrations (6–10 ng/mL) in the first month after liver transplantation are associated with fewer renal dysfunctions at 1 year (RR = 0.51), with no significant effect on acute rejection compared to the recommended residual tacrolimus concentrations (>10 ng/mL) [153]. On the other hand, it increases the risk of post-transplantation diabetes [154]. Similarly, the use of sustained-

release formulations of tacrolimus ((Envarsus® *(Veloxis Pharmaceuticals A/S, North Carolina, USA)*, Advagraf® (*Astellas Pharma Inc, Ireland*)) limits peak concentrations and, therefore, reduces the toxicity of calcineurin inhibitors without excess risk in terms of rejection, even in the event of very early initiation [155–158].

- *Decreasing or weaning from calcineurin inhibitors*

Due to the absence of nephrotoxicity, MPA has shown protective effects on kidney function in CNI reduction or weaning strategies in liver transplantation [81,95,153,159–162]. However, the use of MPA in monotherapy is accompanied by a higher risk of rejection [159,161]. Several studies have demonstrated a favorable effect of everolimus (EVR) in preserving renal function [163]. A reduction in CNIs with an early [164–174] or delayed [39,175,176] introduction of EVRs is associated with improved kidney function (GFR increase by +5 to +10 mL/min/1.73 m^2) without excess risk of rejection or mortality [162,172]. On the other hand, conversion after the first year of transplantation has shown no benefit for kidney function [149,164]. However, EVR is associated with side effects that limit its use in at least 20% of cases (aphtha, edema, proteinuria and dyslipidemia). Similarly, complete weaning from CNIs to EVR alone exposes the patient to an excess risk of early rejection, unless it is combined with MPA after induction treatment with basiliximab [173]. The use of sirolimus in liver transplantation is less clearly defined. Some studies found a nephroprotective effect [177], while other studies noted no improvement in renal function, or even a higher risk of rejection [164,178,179]. The use of Belatacept in the calcineurin-inhibitor-sparing strategy is not currently recommended. In a randomized controlled trial, Klintmalm et al. showed a higher rate of death, rejection, graft loss and viral and fungal infections during immunosuppression with belatacept and MPA compared to an immunosuppressive regimen that combines tacrolimus and MPA. This led to the early termination of the study, despite an estimated 1-year improvement in GFR of +15–34 mL/min/1.73 m^2 [180].

- *Delaying the introduction of calcineurin inhibitors*

Induction immunosuppressive therapies, such as anti-thymocyte globulin and basiliximab, can be used to delay the introduction of calcineurin inhibitors, particularly in patients at high risk for kidney failure. Four of the five randomized controlled trials show that the delayed introduction of CNIs after basiliximab induction is beneficial for kidney function and has no impact on the incidence of short-term rejection (<12 months) [155,158,181–185]. The impact of these different therapeutic strategies is summarized in Figure 2.

Therefore, based on the data in the current literature, the standard immunosuppressive regimen in liver transplantation includes tacrolimus and MPA associated with corticosteroids. Early conversion to everolimus and basiliximab induction with a delayed introduction of CNIs can be considered for nephroprotective purposes.

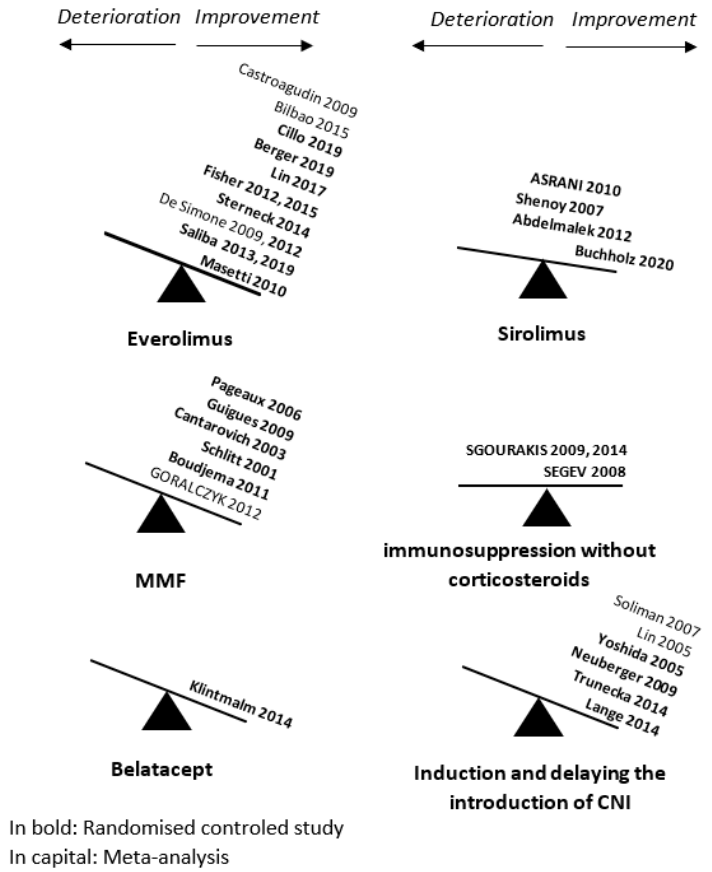

Figure 2. Review of the main studies on possible immunosuppressive regimens in liver transplantation and their effects on kidney function compared to standard immunosuppressive therapy. MMF: mycophenolate mofetil; CNI: calcineurin inhibitors.

6. The Indication for Liver–Kidney Transplantation

With the increase in the incidence of kidney failure in patients awaiting liver transplantation and with the use of the MELD score, the indication for combined liver–kidney transplantation has been on the rise since 2002 [186]. However, it is often difficult to decide whether a dual transplantation is necessary as the assessment of the reversibility of kidney damage is complex, as is the risk of post-transplantation ESRD. Hmoud et al. showed that among patients listed for combined transplantation but who finally received liver transplantation alone, one-third exhibited recovered kidney function with a GFR of more than 60 mL/min/1.73 m^2 [187]. Similarly, the survival benefit of a combined liver–kidney transplant is currently uncertain. Some studies have shown an advantage of combined transplantation in terms of survival, while others have shown no superiority [188–190]. However, most of these are observational monocentric studies conducted in a small number of subjects. In a study of 5609 patients who received combined or isolated liver transplant, Sharma et al. showed that the 5-year survival in patients on dialysis before transplantation was similar in both groups. On the other hand, there is a slight improvement in survival in favor of combined transplantation in patients not on dialysis at the time of transplantation (+3.7 months concentrated mainly in the first year). This is partly due to a better quality of kidney and liver transplants in combined transplants [191]. However, renal transplantation performed in a certain period of time after liver transplantation or staggered for 24–48 h (kidney on perfusion machine) appears to cause less morbidity and to have a protective effect on the renal transplant. This is partly explained by less exposure to SIRS in the post-liver transplantation period, which is responsible for early and late renal dysfunction [192]. A recent study reports better survival for patients who receive a liver transplant and then a kidney transplant within 3 years compared to patients who receive a liver and a kidney

transplant simultaneously [193]. However, one of the advantages of combined transplantation remains immunological with a reduced risk of rejection in patients with pre-formed DSAs that allow the long-term preservation of kidney function [194]. In order to limit the indications for dual transplantation and to standardize the practices of each center, in 2017, an expert committee published the latest recommendations for combined liver–kidney transplantation in patients with cirrhosis who are on the waiting list (Table 1) [69]. It can be noted that the indications for dual transplantation in the case of CKD are relatively homogeneous over time, in contrast to the indications for combined transplantation for AKI, which remain more heterogeneous [195].

Table 1. Current indications for combined liver–kidney transplantation (OPTN 2017 recommendations) [69].

Indications for a Combined Liver–Kidney Transplantation
Patients with AKI associated with: ■ A need for dialysis ≥6 weeks; ■ GFR estimated according to MDRD-6 ≤ 25 mL/min for more than 6 weeks.
Patients with CKD (eGFR < 60 mL/min for at least 3 months) associated with: ■ Recent worsening of GFR ≤ 30 mL/min estimated according to MDRD6; ■ A need for hemodialysis; ■ A metabolic disease (hyperoxaluria, methylmalonic aciduria, atypical HUS with factor H or I mutation or hereditary amyloidosis).

AKI: acute kidney injury; GFR: glomerular filtration rate; MDRD: modification of diet in renal disease; CKD: chronic kidney disease; HUS: hemolytic uremic syndrome.

This illustrates the difficulties in establishing the indications for dual transplantation considering the individual risk factors for the progression of kidney failure, mainly in the case of AKI. Therefore, it would appear that risk stratification is important in this type of reflection. Renal biopsy, as proposed by Tanriover et al., appears to be an objective means of assessing renal impairment and the possibility of a combined transplantation [7]. The percentages of glomerulosclerosis (>30%) and interstitial fibrosis (>40%) and the degree of nephroangiosclerosis are indicators of a poor prognosis and the non-reversibility of renal impairment, which should be a basis for combined transplantation. Similarly, Wadei et al. showed that in 41 patients with renal dysfunction (GFR measured with iothalamate <30 mL/min) but with a percentage of glomerulosclerosis <30–40% and interstitial fibrosis <30%, only 22% had an indication for kidney transplantation at 1 year after liver transplantation [196]. However, given that hemostasis disorders are frequently observed in this population, this cannot be offered to all patients. Transjugular biopsy seems to be the method of choice because it has fewer complications but should be performed by experienced physicians due to a higher rate of failures or uninformative samples than transcutaneous biopsy. One potential solution is to use biomarkers to indicate the cause of kidney failure (functional or organic) and determine the capacity for recovery [137,197]. However, these tools are not yet available in current practice and need to be supported by further studies.

Future research is necessary to better understand and characterize kidney function during liver cirrhosis and after liver transplantation. First, the development of a new equation of estimated glomerular filtration rate is essential due to the over- or underestimation of kidney function with the standard equation. The GRAIL equation, for example, proposed by Asrani and al., seems to be more accurate for low GFR but must be confirmed in clinical practice [198,199]. Second, it is necessary to develop a validated model of individual risk stratification for AKI or CKD after liver transplant. This would allow an appropriate transplant protocol to be established for each patient (indication of liver–kidney transplant, immunosuppression and surgical mode) to prevent kidney dysfunction. Lastly, in the near future, the emergence of new biomarkers or a new algorithm of biomarkers will be very important to better characterize kidney dysfunction during liver cirrhosis [147,197].

This will help for diagnostic (organic or pre-renal dysfunction), prognostic and recovery potential after kidney injury and for the prediction of kidney function after liver transplant.

7. Conclusions

Kidney function plays a central role in liver transplantation. It inevitably progresses to impaired kidney function more or less rapidly in the post-transplantation period and has a high impact on patient morbidity and mortality. There are multiple causes of degradation. Therefore, any AKI should be prevented before transplantation, and all pre-, peri- and post-operative factors associated with the risk of CKD should be identified. By combining them with histological and biological tools, it is possible to rank the level of risk of developing CKD after liver transplantation for each patient. This allows the implementation of prevention strategies adapted to the risk level, such as the surgical protocol and immunosuppressive regimen. It also allows the best possible selection of patients eligible to receive a combined liver–kidney transplant. In the near future, biomarkers are likely to be an additional aid when considering the best ways to identify organic kidney failure and reversibility.

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Appendix A. AKI Classification according to RIFLE and AKIN Criteria Based on Serum Creatinine, Baseline GFR or Hourly Urine Output

Stages	Criteria According to Creatinine or Baseline GFR	Criteria According to Hourly Urine Output
	RIFLE	
Risk Injury Failure Loss End stage renal disease	↑ serum creatinine 1.5× or ↓ GFR > 25% ↑ serum creatinine 2× or ↓ GFR > 50% ↑ serum creatinine 3× or ↓ GFR > 75% or ↑ serum creatinine > 44 µmol/L if serum creatinine ≥ 354 µmol/L Complete loss of kidney function > 4 weeks Dialysis dependence for 3 months	Urine output < 0.5 mL/mg/h × 6 h Urine output < 0.5 mL/mg/h × 12 h Urine output < 0.5 mL/mg/h × 24 h *Or* anuria × 12 h
	AKIN	
1 2 3	↑ serum creatinine ≥26.4 µmol/L or ↑ serum creatinine 1.5–2× ↑ serum creatinine >2–3× ↑ serum creatinine > 3× or ↑ serum creatinine > 44 µmol/L if serum creatinine ≥ 354 µmol/L or need for dialysis	see RIFLE criteria

AKI: acute kidney injury; RIFLE: risk of kidney dysfunction, injury to the kidney, failure of kidney function, loss of kidney function and end-stage renal disease; AKIN: Acute Kidney Injury Network; GFR: glomerular filtration rate.

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