REVIEW

Kidneys role in liver transplantation

D.U.S Ratnapala[1], R. Dissanayake[2], P. Phelan[3]
[1]District General Hospital, Chilaw, Sri Lanka
[2]National Hospital Sri Lanka, Colombo, Sri Lanka
[3]Edinburgh Royal Infirmary, United Kingdom

Keywords: Liver Transplantation, Chronic Kidney Disease, Acute Kidney Injury

Abstract

Renal dysfunction in the form of acute kidney injury and chronic kidney disease is abundant in patients with chronic liver cell disease with a negative impact on post liver transplant patient survival. Chronic kidney disease post liver transplantation is another frequently encountered complication associated with adverse allograft and patient survival. Hence, early and precise measurement of renal function is pivotal in pre and post liver transplantation. Nonetheless, the existing methods of renal function evaluation have pros and cons, hence yet to establish complete authority. This review aims at exploring the precise methodology of evaluating renal function in liver disease, the impact and preventive strategies for pre LT AKI, CKD and post LT CKD..

Introduction

Renal dysfunction is commonly observed in patients with liver disease. Wong et al. reported a 46.8% prevalence of chronic kidney disease (CKD) with a significant impact on survival among hospitalized cirrhosis patients in 2019 [1]. Acute kidney injury (AKI) has also displayed a projected prevalence of 20-50% among cirrhosis patients associated with poor prognosis, further to being an important predictor of short term mortality [2]. The liver transplantation remains the gold standard therapy for chronic liver cell disease(CLCD) including hepatocellular carcinoma [3]. Yet, the presence either form of renal dysfunction prior to LT, is associated with reduced patient survival post transplantation [4,5]. Furthermore, CKD has emerged as a major long term complication of post LT despite improvement of mortality over the years [6 ,7].

The liver allocation Model for End-Stage Liver Disease (MELD) score, introduced in 2002 is presently used for assessment of severity of liver disease as well as prioritization of advanced liver disease patients for LT. The inclusion of serum creatinine in MELD score, reflects thefundamental prognostic role of renal function in cirrhosis [8,9]. Hence, early and precise measurement of renal function is pivotal in cirrhosis. Yet, the available methods for the evaluation of renal function ranging from formulas that estimate the glomerular filtration rate(GFR) , to non-invasive markers has not proven their comprehensive authority [10]. Hence, this review article looks at the optimal ways of evaluating renal function in liver disease, and the impact and preventive strategies for pre LT AKI, CKD and post LT CKD.

Evaluation of renal function in liver disease

For the assessment of renal function, serum creatinine (Scr) level based estimated GFR(eGFR) calculations are commonly used in clinical practice. Nonetheless, Scr levels CLCD patients may be variable due to numerous reasons including liver disease causing reduced generation of creatine, decreased skeletal muscle mass resulting in lessened creatine-to-creatinine conversion, augmented tubular secretion of creatinine, and lower estimation of Scr level by hyperbilirubinemia [11,12]. Hence, glomerular filtration rate(GFR) in CLCD is classically overestimated by the Scr based equation, hence a normal Scr level won't exclude kidney dysfunction. Further, Scr is furthermore regarded a late marker of kidney dysfunction, necessitating a reduction of 50% of GFR before a rise in Scr is detected . Regardless of limitations and till better substitutes are developed, the latest Scr based MDRD equation (MDRD-6) is commended by experts to utilize in cirrhotic patients [11].

Accuracy of GFR quantification could improve through measurement of 24 h creatinine clearance, yet limited by been expensive, errors in sample collection (Eg: incomplete bladder emptying) and the effect of tubular secretion of creatinine [14].

Cystatin C is a protein generated by all nucleated cells which is entirely removed by glomerular filtration. It's not affected by muscle mass , sex, hepatic function, hyper-bilirubinemia and tubular secretion. Hence, cystatin C-based eGFR may be

Correspondence: U. Rathnapala
E-mail: udana752@yahoo.com
https://orcid.org/0000-0002-4655-3298
Received: 05-09-2024 Accepted:05-12-2024
DOI:https://doi.org/10.4038/sljs.v43i2.9189

a superior alternate to the Scr-based equation in CLCD [15,16]. However, the level of cystatin C is affected by steroid use, thyroid disease, hypoalbuminemia, raised C-reactive protein and leukocytosis limiting it's use in estimating GFR in cirrhosis [17]. However, cystatin C based eGFR measurement is yet to be agreed for routine utilization in cirrhotic patients .

The utilization of conventional urinary markers like albuminuria is restricted in patients with cirrhosis, due to hypoalbuminemia and relatively increased capillary permeability [11]. The novel urinary biomarkers of renal tubular injury, including interleukin-18, urinary neutrophil gelatinase-associated lipocalin (uNGAL), liver-type fatty acid-binding protein and kidney injury molecule-1, has been studied to identify early renal dysfunction. uNGALis the most extensively evaluated biomarker, which is an inflammatory biomarker generated by damaged renal tubular cells [17]. The usefulness of uNGAL and other urinary and serum biomarkers in predicting AKI following LT remains to be clearly established. Additionally, ideal threshold values and potential confounding variables need to be validated before these biomarkers can be routinely implemented in clinical practice for LT [10].

Inulin renal clearance is the gold standard of GFR quantification. Yet, requirement of standardized environment with continuous intravenous injection of the inulin, and high cost, practically limit the assay in clinical practice, hence mainly utilised for research. The utility of renal and plasma clearance of radioactive isotopes, including [51] Cr-ethylenediamine tetraacetic acid (EDTA), is gaining popularity in practice, as tests are safe, less complex and sufficiently accurate to measure GFR [18].

Pre-transplant kidney dysfunction

Pre transplant AKI

AKI is common in patients with cirrhosis with an estimated prevalence of 20 to 50% among hospitalized patients depicting a substantial impact on survival [2]. Moreover CLCD is a recognized risk factor for AKI, further as a predisposing factor for CKD development [19] . Portal hypertension resulting in accumulation of blood in the splanchnic circulation causes lower effective circulating blood volume risking CLCD patients towards AKI [20].

The aetiology of AKI in cirrhosis could be pre-renal, resulting from volume depletion due to gastrointestinal bleeding, diuretics use, sepsis, aggressive paracentesis, use of vasodilators and hepatorenal syndrome (HRS). Intrinsic renal causes such as nephrotoxics, infections, prolonged pre-renal AKI can result in acute tubular necrosis. Post renal obstruction leading to AKI is very rare [2].

HRS is a significant etiological entity seen in advanced decompensated CLCD, due to circulatory dysfunction induced by portal hypertension [21]. The combined use of albumin and terlipressin can reinstate renal function in 40% to 73% of patients with HRS [22]. Moreover, Piano et al reported that response to terlipressin and albumin was associated with a reduved need of renal replacement therapy after LT and lessened the risk of CKD at 1 year post LT [23]. However, LT is the definitive treatment for HRS. Since hepatorenal syndrome (HRS) is a functional condition without microscopic evidence of structural damage to the glomeruli or tubules, renal function is anticipated to recover following LT alone [24]. However, individuals with underlying tubular or glomerular injury or those experiencing prolonged HRS may not regain renal function through liver LT alone and might require simultaneous liver-kidney (SLK) transplantation or a kidney transplant following LT [25].

Perioperative AKI

Perioperative AKI increases the risk of acute rejection, infection, and mortality [26]. Risk factors for perioperative AKI include sepsis, nephrotoxic drugs, hemodynamic instability and ischemia-reperfusion injury [27]. In a study carried out by Guitard et al. showed that AKI was significantly associated with higher time for Aspartate transaminase peak, decreased post-operative diuresis (< 100 ml/h), post-operative use of vasopressive drugs, increased duration on mechanical ventilation, extended duration in the intensive care unit and overall length of hospital stay [28] . In addition, utilization of more marginal grafts leading to higher ischaemic reperfusion injury could have contributed to higher prevalence of perioperative AKI [29].

Pre transplant CKD

The rising incidence of CKD in cirrhotic patients likely reflects increasing metabolic risk factors—diabetes, hypertension, obesity—and the growing impact of nonalcoholic fatty liver disease (NAFLD) as a key driver of cirrhosis [17]. NAFLD depicts an independent and significant association with a higher incidence and prevalence of CKD [30,31]. Numerous factors like the pro-inflammatory environment, insulin resistance, oxidative stress, and the activated renin-angiotensin system, may contribute to faster CKD onset and progression in NAFLD patients, alongside prevalent diabetes and hypertension.. Moreover, NAFLD accounted for a substantial rise in SLK transplantation, from 8.2% in 2002 to 22% in 2011 [32].

Immune complex glomerulonephritis is seen in certain distinct etiologies of cirrhosis like hepatitis B virus (HBV) or hepatitis C virus (HCV). Further, immunoglobulin A

nephropathy is increasingly seen in alcoholic cirrhosis [21]. Further, there is evidence indicating that the risk of de novo CKD remains elevated. among AKI survivors [33].

Presence of CKD in a CLCD patient can have a significant bearing on clinical manifestations. Anorexia, anaemia, ascites, bleeding, and encephalopathy may stem from hepatic, renal, or combined dysfunction, complicating diagnosis and management. Further, CKD in cirrhosis is linked to worse outcomes and more frequent complications such as higher rates of superimposed AKI, need for dialysis, 30 day mortality rate, refractory ascites, bacterial infections and LT requirement (25% vs 10%) matched with those without CKD [1], [33]. Pre-transplant CKD increases waitlist mortality and worsens post-LT survival. Cullaro et al. reported a one-year post-LT mortality of 12% with CKD vs. 9% without [34]. Presence of CKD in a CLCD patient can have a significant bearing on clinical manifestations. Anorexia, anaemia, ascites, bleeding, and encephalopathy may stem from hepatic, renal, or combined dysfunction, complicating diagnosis and management.

Simultaneous liver kidney transplant

Margreiter et al. introduced SLK transplantation as a treatment strategy for coexistent cirrhosis and kidney dysfunction, which has been performed increasingly since the introduction of MELD scoring system [35]. Five-year survival for SLK recipients ranges from 64% to 76% [20]. At present, there is no global consensus regarding SLK eligibility and organ allocation. The reversibility of kidney dysfunction associated with CLCD is the determinant between LT alone or a SLK transplantation. In 2017, United Network for Organ Sharing (UNOS) implemented a comprehensive SLK policy outlining medical eligibility criteria (Table 1) [36].

Post-transplant CKD

Post LT kidney dysfunction is a frequently encountered complication associated with a significant negative impact on allograft and patient survival [37]. Pre-transplant AKI or CKD is a key risk factor for post-LT CKD [10]. CKD develops in most patients surviving beyond 6 months. The incidence of post LT CKD is higher compared to heart or lung transplanted patients [38]. The prevalence of LT-CKD differ in literature mainly due to differences in definition of CKD [10]. However, Van wagner et al. recently showed a CKD prevalence of 41.5% and a mortality of 6% upon 6 months survival in post LT cohort of 602 patients [39].

Table 1: Medical eligibility criteria for combined SLK.

Candidate's Transplant Nephrologist Confirms a Diagnosis of	Transplant Program Must Document at least 1 of the following
CKD with a measured or calculated GFR ≤60 mL/min for >3 months	Candidate is on regular hemodialysis
	Candidate's most recent GFR is ≤ 30 mL/min at the time of registration for kidney transplant
Sustained AKI	Candidate is on dialysis at least 6 weeks
	Candidate's GFR is ≤ 25 mL/min for at least 6 weeks (as documented in weekly measurements)
	Candidate has any combination of above 2 criteria for 6 weeks
Metabolic disease	Hyperoxaluria
	aHUS from mutations in factor H or I
	Familial nonneuropathic systemic amyloidosis
	Methylmalonic aciduria

Legend: CKD = chronic kidney disease, AKI = acute kidney injury. GFR = glomerular filtration rate, aHUS = atypical hemolytic uremic syndrome.

The main aetiopathological diagnoses of early post LT CKD(<1 year) are calcineurin inhibitors (CNI) toxicity, diabetic nephropathy, and thrombotic microangiopathy [37]. Early CNI nephrotoxicity is a dose-dependent and mainly functional hence; early dose reduction may reverse kidney injury [38]. Vasoconstriction of afferent and efferent arterioles reduces glomerular filtration, causing kidney dysfunction [40].

Iglesias et al. demonstrated that the recovery of pre transplant kidney function is mainly influenced by absence of graft dysfunction followed by anti thymocyte globulin induction and reduction of CNI use [41]. Further, Lin et al demonstrated that the Serum creatinine at the 4th week Post-LT is a strong predictor of CKD over 5 years, highlighting the need for early, aggressive kidney management [42].

CNI toxicity is the leading cause of late onset of CKD (> 1 year post LT) as well. Renal histology would demonstrate obliterative arteriopathy, glomerular ischemic collapse, of precedent renal disease, focal segmental glomerulosclerosis, non-recovered HRS , and acute tubular necrosis of amphotericin were identified as other important causes of late post LT CKD [44]. Diabetes mellitus and hypertension were also causative agents of CKD [21].

Ways to overcome post LT kidney dysfunction

Patients with post-transplant CKD depict a higher risk of hospitalization, infectious complications, and graft dysfunction hence, preventive strategies to preserve kidney function after LT are vital. It is advisable to measure GFR and proteinuria annually to diagnose and prognosticate CKD. Life style modification is of utmost importance. Meticulous control of blood pressure, diabetes mellitus, low salt and low protein intake along with prevention of weight gain to reduce metabolic syndrome are recommended [10].

As CNI-induced nephrotoxicity is the main contributory factor for both early and late post LT CKD, the greatest strategy is to minimize CNI use without affecting graft longevity. One successful strategy was to use induction with monoclonal or polyclonal antibodies(Basiliximab and daclizumab) with late introduction of CNI. Few clinical trials have displayed better renal outcome when used in LT recipients with preoperative renal dysfunction [21], [45]. Early usage of mycophenolate mofetil (MMF) with no or reduced doses of CNI has shown post LT favorable kidney outcomes without allograft rejection [46,47]. The mammalian target of rapamycin inhibitor, everolimus has also revealed a protective renal strategy with reduced dose of CNI [48]. Because of the adverse outcomes associated with Betalecept and Sirolimus in CNI minimizing trials , the use it is not recommended in post LT. Despite the evidence that early MMF and mTor-I usage minimizes renal dysfunction, but proves less effective if started after 1 year post-LT, making it unsuitable for routine practice [49]. To minimize the use of CNI, new drugs are currently being tested, such as CFZ533, an IgG1 anti-CD40 antibody, yet the utiliy in LT is not understood [10].

Conclusion

Pre LT AKI, CKD and post LT CKD have a significant negative impact on post liver transplant outcomes. Hence, meticulous measures should be taken to prevent and manage peri-transplant kidney dysfunction. Probe in to more accurate and readily accessible methods for evaluation of kidney dysfunction in patients with liver disease is a future need.

References

1.Wong F, Reddy KR, O'Leary JG, Tandon P, Biggins SW, Garcia-Tsao G, Maliakkal BJ, Lai JC, Fallon MB, Vargas HE, Subramanian R. Impact of chronic kidney disease on outcomes in cirrhosis. Liver Transplantation. 2019 Jun;25(6):870-80.

2.Bucsics T, Krones E. Renal dysfunction in cirrhosis: acute kidney injury and the hepatorenal syndrome. Gastroenterology report. 2017 May 1;5(2):127-37. https://doi.org/10.1093/gastro/gox009

3.Weber ML, Ibrahim HN, Lake JR. Renal dysfunction in liver transplant recipients: evaluation of the critical issues. Liver transplantation. 2012 Nov;18(11):1290-301.

4.Gonwa TA, McBride MA, Anderson K, Mai ML, Wadei H, Ahsan N. Continued influence of preoperative renal function on outcome of orthotopic liver transplant (OLTX) in the US: where will MELD lead us?. American Journal of Transplantation. 2006 Nov 1;6(11):2651-9.

5.Nair S, Verma S, Thuluvath PJ. Pretransplant renal function predicts survival in patients undergoing orthotopic liver transplantation. Hepatology. 2002 May 1;35(5):1179-85.

6.Durand F. How to improve long-term outcome after liver transplantation?. Liver International. 2018 Feb;38:134-8.

7.Fisher NC, Nightingale PG, Gunson BK, Lipkin GW, Neuberger JM. Chronic renal failure following liver transplantation: a retrospective analysis. Transplantation. 1998 Jul 15;66(1):59-66.

8.Alessandria C, Ozdogan O, Guevara M, Restuccia T, Jiménez W, Arroyo V, Rodés J, Ginès P. MELD score and clinical type predict prognosis in hepatorenal syndrome: relevance to liver transplantation. Hepatology. 2005 Jun;41(6):1282-9.

9.Wiesner R, Edwards E, Freeman R, Harper A, Kim R, Kamath P, Kremers W, Lake J, Howard T, Merion RM, Wolfe RA. Model for end-stage liver disease (MELD) and allocation of donor livers. Gastroenterology. 2003 Jan 1;124(1):91-6.

10.Pacheco MP, Carneiro-D'Albuquerque LA, Mazo DF. Current aspects of renal dysfunction after liver transplantation. World J Hepatol. 2022 Jan 27;14(1):45-61. doi: 10.4254/wjh.v14.i1.45. PMID: 35126839; PMCID: PMC8790396.

11.Francoz C, Nadim MK, Durand F. Kidney biomarkers in cirrhosis. J Hepatol. 2016 Oct;65(4):809-824. doi: 10.1016/j.jhep.2016.05.025. Epub 2016 May 26. PMID: 27238754.

12.Woitas RP, Stoffel-Wagner B, Flommersfeld S, Poege U, Schiedermaier P, Klehr HU, Spengler U, Bidlingmaier F, Sauerbruch T. Correlation of serum concentrations of cystatin C and creatinine to inulin clearance in liver cirrhosis. Clinical chemistry. 2000 May 1;46(5):712-5.

13.Sandilands EA, Dhaun N, Dear JW, Webb DJ. Measurement of renal function in patients with chronic kidney disease. Br J Clin Pharmacol. 2013 Oct;76(4):504-15. doi: 10.1111/bcp.12198. PMID: 23802624; PMCID: PMC3791974.

14.Kashani K, Rosner MH, Ostermann M. Creatinine: From physiology to clinical application. European journal of internal medicine. 2020 Feb 1;72:9-14.

15. Demirtaş S, Bozbaş A, Akbay A, Yavuz Y, Karaca L. Diagnostic value of serum cystatin C for evaluation of hepatorenal syndrome. Clinica Chimica Acta. 2001 Sep 25;311(2):81-9.

16.Mindikoglu AL, Dowling TC, Weir MR, Seliger SL, Christenson RH, Magder LS. Performance of chronic kidney disease epidemiology collaboration creatinine-cystatin C equation for estimating kidney function in cirrhosis. Hepatology. 2014 Apr;59(4):1532-42.

17.Kumar R, Priyadarshi RN, Anand U. Chronic renal dysfunction in cirrhosis: A new frontier in hepatology. World J Gastroenterol. 2021 Mar 21;27(11):990-1005. doi: 10.3748/wjg.v27.i11.990. PMID: 33776368; PMCID: PMC7985728.

18.Soveri I, Berg UB, Björk J, Elinder CG, Grubb A, Mejare I, Sterner G, Bäck SE, SBU GFR Review Group. Measuring GFR: a systematic review. American Journal of Kidney Diseases. 2014 Sep 1;64(3):411-24..

19.Francoz C. Acute kidney injury in cirrhosis: An immediate threat but also a ticking time bomb. Journal of Hepatology. 2020 Jun 1;72(6):1043-5.

20.Singal AK, Ong S, Satapathy SK, Kamath PS, Wiesner RH. Simultaneous liver kidney transplantation. Transplant International. 2019 Apr;32(4):343-52.PMID: 30548094.

21.Nevens F, Pirenne J. Role of Immunosuppression in causing renal failure after liver transplantation. EASL Postgraduate Course: Transplantation & the Liver. Amsterdam. 2013 Apr 24:94-9.

22.Cavallin M, Piano S, Romano A, Fasolato S, Frigo AC, Benetti G, Gola E, Morando F, Stanco M, Rosi S, Sticca A. Terlipressin given by continuous intravenous infusion versus intravenous boluses in the treatment of hepatorenal syndrome: a randomized controlled study. Hepatology. 2016 Mar;63(3):983-92.

23.Piano S, Gambino C, Vettore E, Calvino V, Tonon M, Boccagni P, Gringeri E, Germani G, Burra P, Cillo U, Angeli P. Response to terlipressin and albumin is associated with improved liver transplant outcomes in patients with hepatorenal syndrome. Hepatology. 2021 May;73(5):1909-19.

24.Russ KB, Stevens TM, Singal AK. Acute kidney injury in patients with cirrhosis. Journal of clinical and translational hepatology. 2015 Sep 9;3(3):195.

25.O'Leary JG, Levitsky J, Wong F, Nadim MK, Charlton M, Kim WR. Protecting the kidney in liver transplant candidates: practice-based recommendations from the American Society of Transplantation Liver and Intestine Community of Practice. American Journal of Transplantation. 2016 Sep 1;16(9):2516-31.

26.Biancofiore G, Davis CL. Renal dysfunction in the perioperative liver transplant period. Current Opinion in Organ Transplantation. 2008 Jun 1;13(3):291-7.

27.Jochmans I, Meurisse N, Neyrinck A, Verhaegen M, Monbaliu D, Pirenne J. Hepatic ischemia/reperfusion injury associates with acute kidney injury in liver transplantation: prospective cohort study. Liver Transplantation. 2017 May;23(5):634-44.

28.Leithead JA, Rajoriya N, Gunson BK, Muiesan P, Ferguson JW. The evolving use of higher risk grafts is associated with an increased incidence of acute kidney injury after liver transplantation. Journal of hepatology. 2014 Jun 1;60(6):1180-6.

29.Tokodai K, Lannsjö C, Kjaernet F, Romano A, Januszkiewicz A, Ericzon BG, Nowak G. Association of post-reperfusion syndrome and ischemia-reperfusion injury with acute kidney injury after liver transplantation. Acta Anaesthesiologica Scandinavica. 2020 Jul;64(6):742-50.

30.Sinn DH, Kang D, Jang HR, Gu S, Cho SJ, Paik SW, Ryu S, Chang Y, Lazo M, Guallar E, Cho J. Development of chronic kidney disease in patients with non-alcoholic fatty liver disease: a cohort study. Journal of hepatology. 2017 Dec 1;67(6):1274-80.

31.Musso G, Gambino R, Tabibian JH, Ekstedt M, Kechagias S, Hamaguchi M, Hultcrantz R, Hagström H, Yoon SK, Charatcharoenwitthaya P, George J. Association of non-alcoholic fatty liver disease with chronic kidney disease: a systematic review and meta-analysis. PLoS medicine. 2014 Jul 22;11(7):e1001680.

32.Singal AK, Salameh H, Kuo YF, Wiesner RH. Evolving frequency and outcomes of simultaneous liver kidney transplants based on liver disease etiology. Transplantation. 2014 Jul 27;98(2):216-21.

33.Bassegoda O, Huelin P, Ariza X, Solé C, Juanola A, Gratacós-Ginès J, Carol M, Graupera I, Pose E, Napoleone L, Albertos S. Development of chronic kidney disease after acute kidney injury in patients with cirrhosis is common and impairs clinical outcomes. Journal of hepatology. 2020 Jun 1;72(6):1132-9.

34.Cullaro G, Verna EC, Lee BP, Lai JC. Chronic kidney disease in liver transplant candidates: a rising burden impacting post–liver transplant outcomes. Liver transplantation. 2020 Apr;26(4):498-506.

35.Margreiter R, Kramar R, Huber C, Steiner E, Niederwieser D, Judmaier G, Vogel W. Combined liver and kidney transplantation. The Lancet. 1984 May 12;323(8385):1077-8.

36.Ekser B, Contreras AG, Andraus W, Taner T. Current status of combined liver-kidney transplantation. Int J Surg. 2020 Oct;82S:149-154. doi: 10.1016/j.ijsu.2020.02.008. Epub 2020 Feb 19. PMID: 32084547.

37.Bahirwani R, Reddy KR. Outcomes after liver transplantation: chronic kidney disease. Liver Transplantation. 2009 Nov;15(S2):S70-4.

38.Ojo AO, Held PJ, Port FK, Wolfe RA, Leichtman AB, Young EW, Arndorfer J, Christensen L, Merion RM. Chronic renal failure after transplantation of a nonrenal organ. New England Journal of Medicine. 2003 Sep 4;349(10):931-40.

39.VanWagner LB, Holl JL, Montag S, Gregory D, Connolly S, Kosirog M, Campbell P, Pine S, Daud A, Finn D, Ladner D. Blood pressure control according to clinical practice guidelines is associated with decreased mortality and cardiovascular events among liver transplant recipients. American Journal of Transplantation. 2020 Mar;20(3):797-807.

40.Duvoux C, Pageaux GP. Immunosuppression in liver transplant recipients with renal impairment. Journal of Hepatology. 2011 May 1;54(5):1041-54.

41.Iglesias J, Frank E, Mehandru S, Davis JM, Levine JS. Predictors of renal recovery in patients with pre-orthotopic liver transplant (OLT) renal dysfunction. BMC nephrology. 2013 Dec;14:1-2.

42.Lin YH, Lin CC, Wang CC, Wang SH, Liu YW, Yong CC, Lin TL, Li WF, Concejero AM, Chen CL. The 4-week serum creatinine level predicts long-term renal dysfunction after adult living donor liver transplantation. InTransplantation proceedings 2012 Apr 1 (Vol. 44, No. 3, pp. 772-775). Elsevier.

43.Charlton MR, Wall WJ, Ojo AO, Ginès P, Textor S, Shihab FS, Marotta P, Cantarovich M, Eason JD, Wiesner RH, Ramsay MA. Report of the first international liver transplantation society expert panel consensus conference on renal insufficiency in liver transplantation. Liver Transplantation. 2009 Nov 1;15(11):S1-34.

44.Gonwa TA, Mai ML, Melton LB, Hays SR, Goldstein RM, Levy MF, Klintmalm GB. End-stage renal disease (ESRD) after orthotopic liver transplantation (OLTX) using calcineurin-based immunotherapy: risk of development and treatment. Transplantation. 2001 Dec 27;72(12):1934-9.

45.Millson C, Considine A, Cramp ME, Holt A, Hubscher S, Hutchinson J, Jones K, Leithead J, Masson S, Menon K, Mirza D. Adult liver transplantation: UK clinical guideline-part 2: surgery and post-operation. Frontline gastroenterology. 2020 Sep 1;11(5):385-96.

46.Yoshida EM, Marotta PJ, Greig PD, Kneteman NM, Marleau D, Cantarovich M, Peltekian KM, Lilly LB, Scudamore CH, Bain VG, Wall WJ. Evaluation of renal function in liver transplant recipients receiving daclizumab (Zenapax), mycophenolate mofetil, and a delayed, low-dose tacrolimus regimen vs. a standard-dose tacrolimus and mycophenolate mofetil regimen: a multicenter randomized clinical trial. Liver transplantation. 2005 Sep;11(9):1064-72.

47.Boudjema K, Camus C, Saliba F, Calmus Y, Salamé E, Pageaux G, Ducerf C, Duvoux C, Mouchel C, Renault A, Compagnon P. Reduced-dose tacrolimus with mycophenolate mofetil vs. standard-dose tacrolimus in liver transplantation: a randomized study. American Journal of Transplantation. 2011 May;11(5):965-76.

48.Fischer L, Klempnauer J, Beckebaum S, Metselaar HJ, Neuhaus P, Schemmer P, Settmacher U, Heyne N, Clavien PA, Muehlbacher F, Morard I. A randomized, controlled study to assess the conversion from calcineurin-inhibitors to everolimus after liver transplantation—PROTECT. American Journal of Transplantation. 2012 Jul;12(7):1855-65.

49.Levitsky J, O'Leary JG, Asrani S, Sharma P, Fung J, Wiseman A, Niemann CU. Protecting the Kidney in Liver Transplant Recipients: Practicee-Based Recommendations From the American Society of Transplantation Liver and Intestine Community of Practice. American Journal of Transplantation. 2016 Sep 1;16(9):2532-44.