REVIEW

Simultaneous liver kidney transplantation

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SUMMARY

Kidney injury is frequently seen in patients with end-stage liver disease from cirrhosis and liver failure. Among selected patients, simultaneous liver kidney (SLK) transplantation provides improved post-transplant graft and patient outcomes compared to liver transplantation (LT) alone. We conducted the review of the existing literature on SLK transplant criteria and outcomes. Since the introduction of the model for end-stage disease (MELD) score in 2002, there has been an increased use of SLK transplantation. The criteria for SLK allocation are relatively homogeneous among patients with end-stage renal disease with cirrhosis and among patients with cirrhosis and chronic kidney disease. However, these are quite heterogeneous among patients with cirrhosis and acute kidney injury (AKI), mainly because of inability to accurately differentiate cause of AKI, especially hepatorenal syndrome versus intrarenal aetiology. Clearly, there is an unmet need of urine biomarkers of tubular injury and/or clinical models to accurately stratify AKI aetiology and to predict renal recovery after LT as basis to best utilize the scarce donor kidney pool. In this regard, it remains to be seen whether recently implemented policies by the organ procurement transplant network can fulfil the goal of saving donor kidneys and optimal allocation of SLK.

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Introduction

Portal hypertension with pooling of blood in the splanchnic circulation results in reduced effective circulating blood volume, which puts these patients at risk for renal dysfunction and acute kidney injury (AKI) [1–4]. Comorbidities of diabetes mellitus and/or hypertension in patients with cirrhosis from any aetiology, especially those with nonalcoholic steatohepatitis, are at risk for chronic kidney disease (CKD), Table 1 [5]. About 20% of patients with AKI have features suggestive of prerenal disease, but do not improve with volume replacement, and are diagnosed with hepatorenal syndrome (HRS) [3]. The estimated prevalence of HRS may be higher in the background of proposed new definition of AKI in patients with cirrhosis as given by the international club of ascites, which no longer requires a minimum serum Cr level ≥1.5 before diagnosing AKI [4]. About two-third of patients with AKI have prerenal aetiology, one-third have intrarenal pathology and <1% have postrenal cause from obstructive renal disease. Of patients with prerenal aetiology, about one-third do not respond to fluid administration in the first 24 h and who do not have clinical or laboratory features of intrarenal pathology, and these patients are classified with HRS [1].

Renal dysfunction is associated with worse patient survival and outcome after liver transplantation (LT)

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Table 1. Indications for considering Simultaneous Liver Kidney (SLK) Transplantation.

A. Patients with ESRD listed for kidney and have liver disease (kidney pulling liver)
1. ESRD patients with liver cirrhosis
2. ESRD because of hyperoxaluria
3. Polycystic kidney and liver disease with ESRD
B. Patients with ESLD (cirrhosis and liver failure) listed for liver, who have renal disease (liver pulling kidney)
1. ESLD with chronic kidney disease
2. ESLD with acute kidney injury

ESRD: end-stage renal disease; ESLD: end-stage liver disease.

[6–9]. As HRS is a functional disorder without structural damage to glomeruli or tubules on microscopic examination, renal function is likely or expected to improve after LT alone [3,10]. However, patients with pre-existing tubular or glomerular damage or with prolonged HRS may not recover renal function with LT alone (Table 2) and may require simultaneous liver kidney (SLK) or kidney after LT [9].

This review has been developed for practicing transplant hepatologists and nephrologists with the aims of (i) describing the increasing use of SLK and limitations of current criteria for its allocation; (ii) highlighting new insights published in the literature within the last 5–7 years, as basis for changing paradigm in allocation of SLK; and (iii) recognizing ongoing challenges surrounding the use of SLK and identifying areas of clinical unmet need.

Methods and literature search

PubMed, Embase, PyscINFO, CINAHL, ClinicalTrials.gov and Cochrane Library engines [01/2001 to 06/2018] were used for literature search, using the following Pubmed search strategy: ((((((kidney [tf] OR renal [tf]) AND (hepatic [tf] OR liver [tf])) OR hepatorenal [tf])) AND ((Simultaneous* [tiab] OR slkt [tiab] OR slk [tiab] OR combined [tiab] OR combination [tiab] OR concurrent* [tiab] OR sequential* [tiab]) AND (Graft* [tiab] OR allograft* [tiab] OR allogeneic [tiab] OR homologous* [tiab] OR homograft* [tiab] OR transplant* [tiab] OR Transplants [mh] OR Transplantation [mh]))))) OR (((((Kidney Transplantation [mh] OR Kidney/transplantation [mh]) AND (Liver Transplantation [mh] OR Liver/transplantation [mh])) AND (Simultaneous* [tiab] OR slkt [tiab] OR slk [tiab] OR combined [tiab] OR combination [tiab] OR concurrent* [tiab] OR sequential* [tiab]))) OR ((“liver and kidney” [tiab] OR “kidney and liver” [tiab] OR “liver kidney” [tiab] OR “kidney liver” [tiab]) AND (Simultaneous* [tiab] OR slkt [tiab] OR slk [tiab] OR combined [tiab] OR combination [tiab] OR concurrent* [tiab] OR sequential* [tiab]) AND (Graft* [tf] OR allograft* [tf] OR allogeneic [tf] OR homologous* [tf] OR homograft* [tf] OR transplant* [tf] OR Transplants [mh] OR Transplantation [mh])))). Reviews, animal studies and publications in language other than English were excluded. A total of 751 publications were obtained, with their titles, abstracts and if needed whole manuscript reviewed to select final 55 articles for citation in this article.

Evolution of and criteria for SLK transplantation

Since the introduction of the MELD score in early 2002 to prioritize organ allocation, there has been an over 300% increase for SLK as a proportion of all LT performed in the USA [11]. This has resulted in increase in absolute numbers of donor kidneys diverted to the SLK pool from 138 in 2000 to 738 in 2016 as analysed using the latest UNOS dataset (unpublished data, Fig. 1). Furthermore, about half of SLK patients receive renal grafts with kidney donor profile index <35%, which significantly impacts candidates listed for renal transplantation, especially among paediatric and younger patients [12].

SLK transplantation may be needed among patients with end-stage renal disease (ESRD) with cirrhosis and symptomatic portal hypertension, but more often required for patients who are listed for LT and have concomitant renal dysfunction or injury.

SLK allocation criteria among patients listed for kidney (“Kidney pulling liver”)

This decision is relatively easy among patients with metabolic diseases with primary genetic defect in the liver such as primary hyperoxaluria [13], or for patients with noncirrhotic diseases involving both liver and kidneys such as polycystic kidney and liver disease [14]. Among patients with cirrhosis and ESRD, SLK is recommended (i) if there is clinical evidence of portal hypertension such as ascites or varices or (ii) documentation of clinically significant portal hypertension with hepatic venous pressure gradient ≥10 mm Hg [15].

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Table 2. Characteristics and features comparing hepatorenal syndrome (HRS) and acute tubular necrosis.

	Hepatorenal syndrome	Intrarenal pathology
Pathophysiology	Portal hypertension leads to splanchnic pooling resulting in reduced effective blood volume and renal blood flow	Tubular damage and necrosis from external factors. Glomerulonephritis
Risk factors	Decompensated liver disease and ascites precipitated by any factor causing prerenal azotemia including NSAID or CIN	Sepsis, renal ischaemia, prolonged prerenal azotemia, direct toxicity from drugs
Urine findings	Urine sodium <20 mEq/l FENA < 1% Bland urine no sediment	Urine sodium >40 mEq/l FENA >2% Casts, haematuria, proteinuria
Renal pathology	Normal renal tubules and glomeruli	Abnormal tubules or glomeruli
Response to vasoconstrictors	Reversal of HRS in 60–70%	None
Reversal after LT	Usual but may not be if prolonged prior to transplant and dialysis dependent	None

SLK allocation criteria among patients listed for liver ("Liver pulling kidney")

Among patients listed for LT, criteria for SLK allocation are relatively homogeneous for patients with established CKD (Table 3) [3,16]. However, these criteria are heterogeneous among patients with AKI because of many variables such as GFR, use and duration of dialysis, comorbidities and centre protocol (Table 2). In one study, based on the dialysis duration, one-third of transplant centres reported SLK allocation if the candidate is receiving dialysis >4 weeks, one-third would wait for dialysis duration of at least 6 weeks and another one-third reported that they would wait for at least 8 weeks before considering SLK. Furthermore, 24% of these centres use GFR < 40 ml/min to determine SLK allocation, rather than recommended cut-off of 30 ml/min [17]. The heterogeneity on the criteria for SLK allocation has resulted in extreme variation in use of SLK across centres and UNOS regions. For example, proportion of SLK use varied from 2.2% in regions 6 and 9 to as high as 6.8% in regions 1 and 7 [17]. Even within a given UNOS region, SLK as proportion of all LT has varied from 5% to 45% across various centres in one study and 3–80% in another study [17,18].

Reasons for heterogeneity in allocation of SLK transplantation

Adjudicating aetiology of AKI

The inability to accurately classify AKI into HRS versus an intrarenal aetiology and acute tubular necrosis (ATN) is a major factor for heterogeneity in SLK allocation [19,20]. Renal biopsy is the gold standard for diagnosis of structural damage to kidneys [3,21]. However, this is rarely performed in clinical practice, especially among patients with cirrhosis and liver failure because of the risk of bleeding [3,22].

Underassessment of renal dysfunction in cirrhosis

Reduced muscle mass in patients with end-stage liver disease and cirrhosis can significantly impact serum creatinine measurements and the measured renal function [23]. Other factors because of altered physiology in cirrhosis such as increased volume of distribution and increased tubular secretion may underestimate serum creatinine measurements. Furthermore, the glomerular filtration rate (GFR) may be overestimated in females [24]. Iothalamate clearance is the gold standard and a more accurate measurement of renal function [25]. However, lack of widespread availability, cost and the cumbersome technique for urine collection limit its use in routine clinical practice. Although debated, modified diet for renal disease-6 (MDRD-6) of the various available equations has been found to be most accurate and reliable reflection of renal function in cirrhosis patients, as it incorporates two important variables namely blood urea nitrogen and serum albumin, which can be affected in liver disease [26]. Recently, a model from Royal Free Hospital has been reported to be more accurate than other existing equations including MDRD-6, in predicting the true GFR as measured using the iothalamate clearance [27].

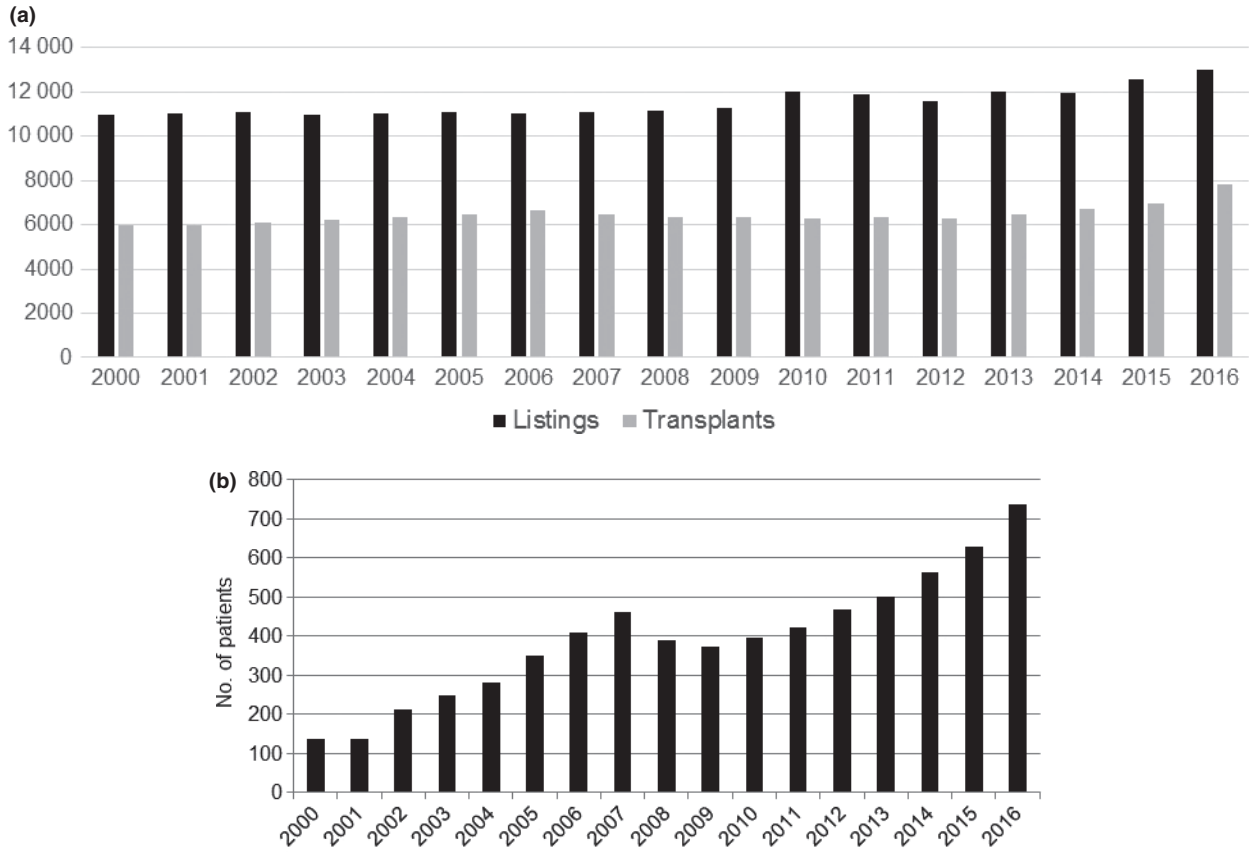

Figure 1 Frequency of liver transplant listings and transplantation (a) and on simultaneous liver kidney transplantation (b) in the USA during 2000 and 2016. The UNOS data show increasing use of simultaneous liver kidney transplantation since the introduction of model for end-stage disease score in 2002.

Difficulties in assessing reversibility of kidney injury

The recovery of renal function among AKI patients depends on many variables, such as degree of renal dysfunction, duration of AKI, need for renal replacement therapy, comorbidities like diabetes and hypertension and age of the transplant recipient [3,28]. Although these variables have been used in developing criteria for SLK allocation, these have suffered from accuracy in predicting renal recovery after LT (Table 2) [29]. Furthermore, renal function is dynamic and changes over time while patients are awaiting LT. For example, about 37% of SLK recipients in one study never required dialysis prior to LT, 22% were on dialysis for <2 months, 9% for 2–6 months and only 23% received dialysis for >6 months [12]. It should also be recognized that these patients frequently develop second or multiple episodes of AKI, with risk for the development of residual renal injury with each AKI episode and subsequent CKD [30]. AKI may also develop on underlying CKD secondary to diabetes and/or hypertension, especially in patients with fatty liver disease [31].

Outcomes of SLK transplantation

Five-year patient survival rates among patients selected to receive SLK range from 64% to 76% in single centre as well as national transplant registry data analyses [11,32–34]. Patients meeting criteria for SLK allocation with serum creatinine >2.5 or dependent on dialysis have better outcomes after receiving SLK compared to LT alone recipients (Fig. 2a) [34,35]. The higher patient and graft loss in the liver alone group compared to SLK persisted even after removing patients dying within the first 48 h from analysis with respective hazard ratios of 1.3 (1.1–1.6) and 2.1 (1.8–2.4) respectively [34]. The renal recovery (<50% increase in mean serum creatinine compared to pretransplant value) at 1 and 3 months after LT is shown to be better for patients with AKI because of HRS as compared to when the AKI because of acute tubular necrosis or ATN (Fig. 2b) [36]. This clinical course was associated with worse outcomes for patients with ATN versus other three groups (risk, injury and HRS) for probability of CKD at 1 year

Table 3. Evolution on proposed criteria for simultaneous liver kidney transplantation.

Author and year	Chronic kidney disease	Acute kidney injury
Davis 2006 [57]	Iothalamate clearance ≤30 ml/min	Dialysis duration ≥ 6 weeks Fixed renal damage on biopsy
Eason 2007 [16]	GFR ≤30 ml/min Renal biopsy with >30% glomerulosclerosis or fibrosis	SC ≥2 mg/dl and dialysis ≥ 8 weeks DM, HTN, age >65 years, proteinuria
OPTN committee 2012	On dialysis GFR ≤ 30 ml/min Proteinuria > 3 g/day Metabolic disease	GFR ≤ 25 ml/min for >6 weeks Dialysis >x2/week for >6 weeks Combination of above two criteria and meeting 6 weeks duration
Nadim 2012 [58]	GFR ≤ 40 ml/min by MDRD or ≤40 ml/min by iothalamate clearance for ≥3 months Proteinuria .2 g/day Renal biopsy >30% glomerulosclerosis or fibrosis Metabolic disease	Duration ≥4 weeks with stage 3 AKI or SC > 4 with increase >0.5 mg/Dl, or on haemodialysis
OPTN policy 2017 [12]	GFR ≤ 60 ml/min for ≥3 months with recent GFR ≤30 ml/min or on haemodialysis Metabolic disease*	Dialysis for >6 weeks GFR ≤ 25 for >6 weeks documented every 7 days Combination of above two criteria and meeting 6 weeks duration

GFR, glomerular filtration rate; DM, diabetes mellitus; HTN, hypertension; MDRD, modified diet for renal disease; OPTN, organ procurement transplant network.

*Hyperoxaluria, atypical haemolytic uraemic syndrome, familial non-neuropathic systemic amyloidosis and methylmalonic aciduria.

(>50% vs. 10–20%, $P < 0.001$) and lower 5-year survival for patients with ATN (<45% vs. 75–80%, $P < 0.001$) [36]. While the outcomes of liver and SLK transplants have traditionally been poorer among patients transplanted for hepatitis C virus (HCV)-related cirrhosis compared to other indications of liver disease [11], the emergence of direct antiviral agents for the treatment of chronic HCV infection has revolutionized and changed this paradigm [37–39].

The liver graft among SLK recipients confers an immunological privilege to the kidney graft, especially among recipients with preformed donor-specific anti-HLA antibodies, with reduced risk of acute cellular as well as antibody-mediated rejection, and better preservation of long-term renal function compared to patients receiving a kidney alone [40]. The mechanism of this protection of kidney graft by the implanted liver is mediated through class I antibodies. Apart from large surface area of the liver absorbing these antibodies, transplanted liver by an unknown mechanism shifts the gene expression within the kidney, from pro-inflammatory to tissue regeneration pattern [41]. Whether these benefits are maintained among SLK transplants for non-alcoholic steatohepatitis (NASH)-related cirrhosis remains a testable hypothesis, as renal graft outcomes among NASH transplants are reported to be worse compared to SLK for other liver disease aetiologies [31].

Based on surgeon's choice, liver can be placed by caval transposition or piggyback technique. Kidney is then placed in the retroperitoneal or abdominal space. Intraoperative haemodialysis may be used to manage fluid shifts, continuous veno-venous haemodialysis if haemodynamic instability. Kidney placement is often delayed in this case or when the liver transplant takes unusually long time. Cold storage in such a case is fine, but invariably machine perfusion is preferred which has benefits to better maintain graft integrity [42].

Recent updates for optimal allocation of SLK transplantation

Patients who are listed for SLK, but receive LT alone for any reason, have been shown to become dialysis dependent with high mortality from cardiovascular-

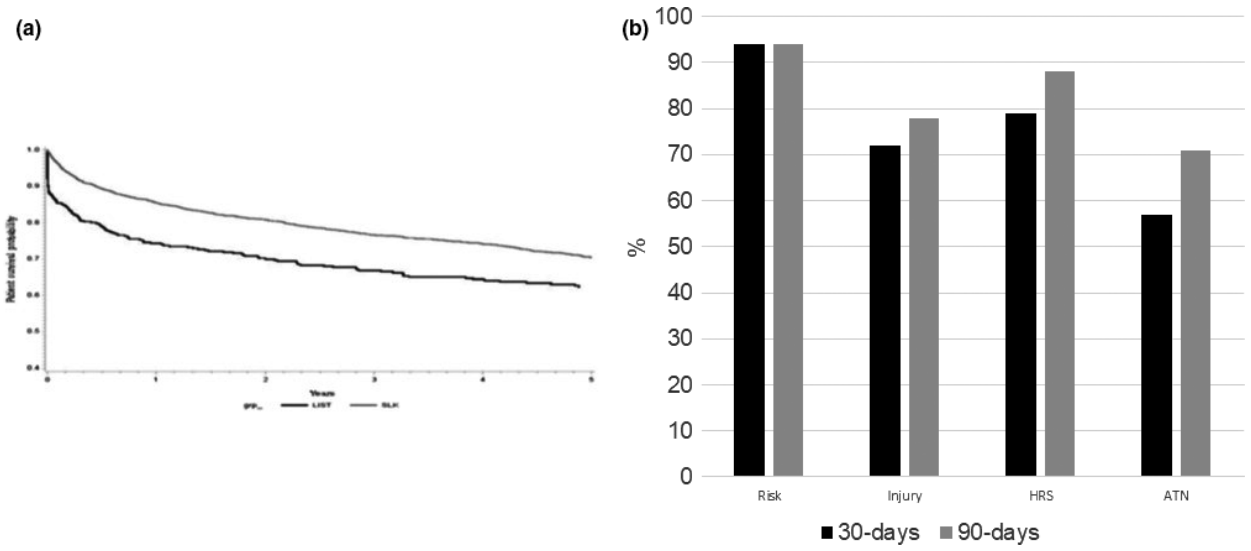

Figure 2 Kaplan–Meier curve showing 5-year patient survival to be better among patients receiving simultaneous liver kidney (SLK) transplantation compared to those who are listed for SLK (LIST) but getting liver alone (a), reproduced with permission from Hmoud et al. [34] Transplantation 2015. Kaplan–Meier curves on patient survival after liver transplantation stratified for aetiology of acute kidney injury. The results show that the outcomes are poor for patients with acute tubular necrosis (ATN) compared to patients with hepatorenal syndrome or HRS (b), reproduced with permission from Nadim et al. [36] Liver Transpl 2012.

related causes within 48 h after surgery [34]. More than 30% of patients who survived the post-transplant hospitalization recovered renal function in the long term, with GFR > 60 ml/min. The frequency of ESRD at 1 year after LT alone is only 6–10% among various reports, even among high risk group of patients who were listed for SLK [34,43]. A recent analysis of UNOS data showed a shorter 10-year kidney allograft lifespan in SLK transplants compared with kidney alone and simultaneous pancreas kidney transplants. This difference was 0.99 years in the Model for End-stage Liver Disease era and 1.71 years in the pre-Model for End-stage Liver Disease era. Death was also higher in SLK recipients relative to the other two groups. Both these findings are sobering and reflective of the trade-off between allocating organs based on medical urgency and maximizing utility [44].

In the background of ongoing shortage of donor kidneys in the USA, with over 90 000 candidates awaiting kidney transplants (about half of which are active on the list) in 2008, it clearly becomes critical to select the right patients who will benefit from SLK [45]. Furthermore, apart from impact on national donor pool, SLK allocation becomes relevant and complicated since the introduction of Share-35 rule. Within this rule, regional candidates with MELD ≥ 35 receive higher priority than local candidates with MELD < 35 [19]. While this rule allows sharing of local liver with a patient in the region with MELD > 35, it does not allow similar regional sharing of kidneys [20]. Options for transplant centres are to use regional livers and wait for local kidneys to be available, or to use both liver and kidney from the region.

In this regard, latest updates and emerging data and/or policies will be helpful to address these concerns and optimal allocation for SLK.

1. *Organ Procurement Transplant Network (OPTN) policy* for homogeneity on SLK listing (Table 2). Criteria for SLK allocation in the setting of CKD in liver patients include (i) GFR < 60 ml/min for >90 days and subsequent GFR < 30 ml/min or requirement for dialysis and (ii) CKD because of metabolic disease that can be corrected with a liver transplant (hyperoxaluria, atypical haemolytic uraemic syndrome, familial non-neuropathic systemic amyloidosis and methylmalonic aciduria) [12]. Criteria for SLK allocation in the setting of AKI in liver patients include (i) duration of AKI >6 weeks with persistent GFR < 25 ml/min, (ii) dialysis dependence or (iii) a combination of both. Under this policy which has been implemented since August 2017, criteria need to be documented every 7 days to maintain listing for SLK [12].

It is unknown as to how this new OPTN policy compares with SLK allocation in European countries. This can only be answered in the next few years whether this new policy has any benefits in saving donor kidneys. A recent study examined the potential impact of this new policy by analysing non-status one adults listed for LT (5/2007-7/2014) with eGFR < 60 ml/min for 90 days,

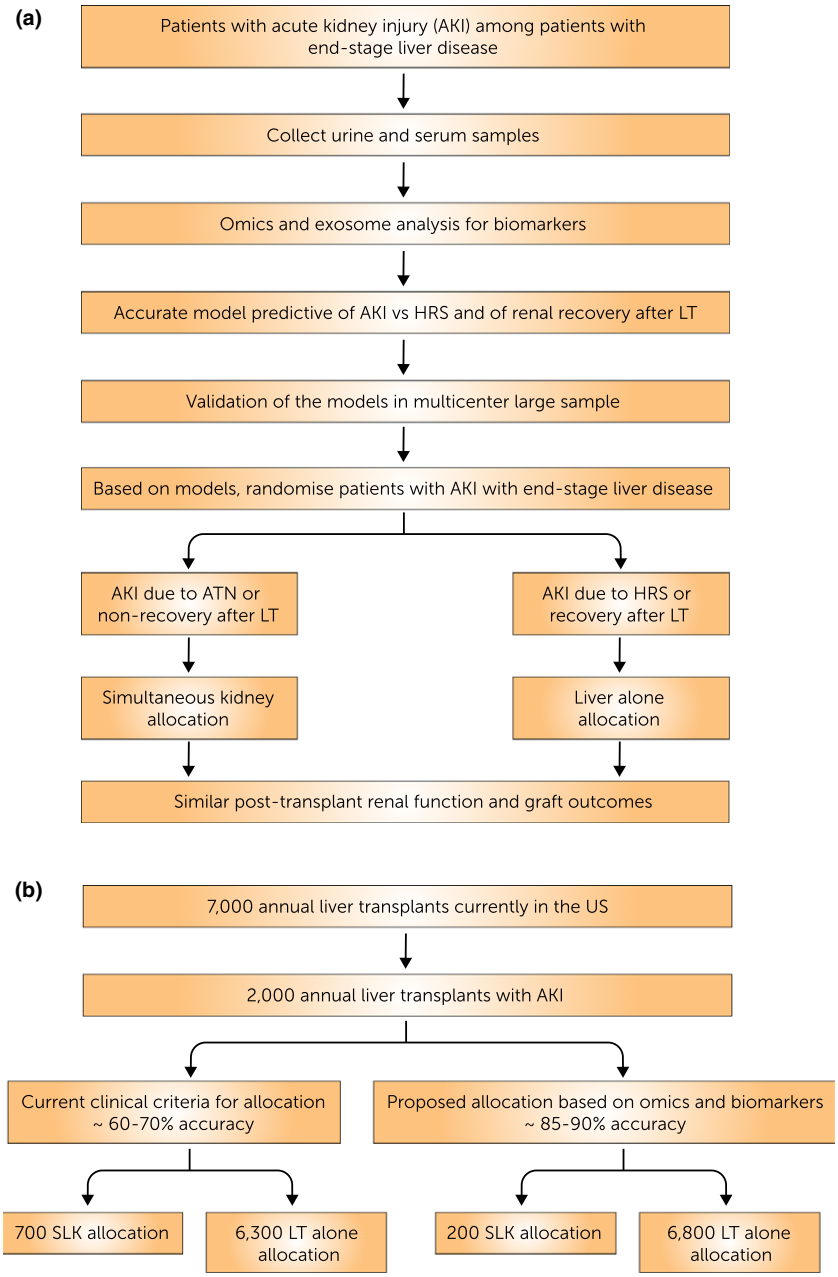

Figure 3 Proposed strategy and future of biomarkers for accurate stratification of acute kidney injury (AKI) to acute tubular necrosis (ATN) versus hepatorenal syndrome (HRS) and for prediction of renal recovery after receipt of liver transplantation (LT) as basis for optimal allocation of simultaneous liver kidney (SLK) transplantation (a). Presuming availability of model with biomarkers of renal tubular injury with or without clinical variables with an accuracy of 85–90%, we will be able to save about 500 donor kidneys without jeopardizing the patient outcomes, and hopefully this will increase kidney donor pool for patients listed for kidney alone (b).

with a final eGFR < 30 ml/min. Among 1683 candidates meeting these new criteria compared to 2452 candidates meeting the old criteria and 1878 candidates meeting both the criteria were more likely to be female (52 vs. 36 vs. 39%, $P < 0.001$) and less likely to die post liver transplant (HR 0.03, $P < 0.001$) [46].

2. *Kidney after* LT is a potential viable approach as the cumulative probability ESRD within first year of LT is low with rate of only 5–10% even among high risk candidates [47]. About 1% of all renal transplants performed in the USA are among patients with previous LT [48]. Limitations of this approach are relatively poorer outcomes of patients undergoing renal transplant after receiving LT compared to patients receiving SLK transplantation [48]. In this regard, continuous renal replacement therapy used intraoperatively during

LT has shown to be a feasible, safe and effective approach to manage fluid shifts and electrolyte imbalance during surgery, with outcomes as good as SLK transplantation. However, these scant data are limited by the retrospective and observational studies and lack of randomized data [49,50]. Another issue to tackle with this approach is that these patients have to compete with already registered individuals on the renal transplant list. The new OPTN policy described above also introduces the safety net approach to overcome this limitation. Under this policy and approach, patients who develop renal failure (either haemodialysis dependence or GFR ≤20 ml/min) between 60 and 365 days after LT are granted priority for kidney listing.

3. *Extended donor criteria kidneys* can be used for patients needing SLK. This approach has been used with transplanting liver along with two kidneys from the same donor, or also known as liver double kidney transplantation (LDKT). Preliminary data in a case–control study including four LDKT showed shown outcomes similar to 11 SLK transplants [51]. The decision to use kidney for SLK or LDKT was made using the Remuzzi score obtained on donor kidney biopsy [45]. With mean MELD score of only 22 in this study of patients undergoing SLK transplantation, more data are needed among patients with higher MELD score before recommending this approach in routine practice.

Biomarkers and future directions on SLK transplantation

Allocation for SLK transplantation among patients listed for liver remains an ongoing challenge for hepatologists and nephrologists alike. In this regard, data have emerged on the utility of plasma and urine biomarkers of renal injury such as neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1), interleukin-18 (IL-18), human endothelin-1 (HE-1), uromodulin, epidermal growth factor and fatty acid-binding protein (FABP). These biomarkers have been shown to (i) diagnose AKI earlier than serum creatinine increase, (ii) differentiating HRS from ATN and (iii) predict recovery of renal function in patients with AKI, AKI during LT and graft function after kidney transplantation [8,52–55]. For example, in one study on 79 patients with cirrhosis and progressive AKI, the accuracy of differentiation between ATN and HRS increased linearly with number of biomarkers above optimal diagnostic cut-offs [54].

Data on association of these biomarkers with post-LT recovery of renal function are limited and scanty. In a prospective study at our centre, none of these biomarkers was associated with renal function recovery after LT alone [30]. Biomarkers levels were measured in this study within a month prior to LT and were examined for association with renal function recovery at 6 months after LT. As renal function is dynamic and potentially confounded by variables in the pre-transplant and post-transplant period, true association of cross-sectional measurement of biomarkers may not reflect renal function after LT. Studies using other biomarkers of renal injury or exploring markers based on metabolomics or exosome analysis of urine samples may be designed to examine novel biomarkers for accurate prediction of renal recovery after LT alone. In one study, a model including elevated osteopontin and tissue inhibitor of metalloproteinase-1, age >57 years and the absence of diabetes was 82% accurate in predicting renal recovery after LT, and this combined model was more accurate compared to models including only biomarkers levels or only clinical variables [56].

Emerging data on the improving outcomes of SLK, new OPTN policy for SLK listing, safety net approach for patients developing ESRD after LT and extended criteria for donor kidneys provide ray of hope for optimal use of donor kidneys for SLK transplantation. Data from the experience from real world will demonstrate the impact of the new OPTN policy on the optimal use of SLK transplantation. In the meantime, research studies are needed aiming to derive accurate models including biomarkers to accurately stratify AKI patients to ATN or HRS and to predict recovery of renal function after LT (Fig. 3a). Presuming availability of a model using biomarkers of tubular injury with and without clinical variables with an accuracy of 85–90%, we will be able to save over 500 donor kidneys keeping the same patient outcomes (Fig. 3b). Hopefully, this will increase the donor kidney pool for patients listed for kidney alone where the average wait time is around 6–7 years. However, currently, the field is still in its infancy with many hurdles to be overcome before their availability for use in clinical practice. These hurdles include but are not limited to derivation of accurate biomarkers, validation of these markers in large multicentre studies and confirming their utility in randomized clinical trials (Fig. 3a).

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Conflict of interest

The authors have declared no conflicts of interest.

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