ORIGINAL ARTICLE

Combined liver–kidney transplantation versus liver transplant alone based on KDIGO stratification of estimated glomerular filtration rate: data from the United Kingdom Transplant registry – a retrospective cohort study

Francesca Tinti[1,2,*], Anna Paola Mitterhofer[2,*], Ilaria Umbro[2], Peter Nightingale[3], Nicholas Inston[4], Mohammed Ghallab[1], James Ferguson[1], Darius F. Mirza[1], Simon Ball[4], Graham Lipkin[4], Paolo Muiesan[1] & M. Thamara P. R. Perera[1]

1 The Liver Unit, Queen Elizabeth Hospital Birmingham, Birmingham, UK
2 Nephrology Unit, Department of Translational and Precision Medicine, Sapienza University of Rome, Rome, Italy
3 Medical Statistics Unit, Queen Elizabeth Hospital Birmingham, Birmingham, UK
4 Department of Nephrology and Transplantation, Queen Elizabeth Hospital Birmingham, Birmingham, UK

Correspondence
M. Thamara P. R. Perera FRCS, Queen Elizabeth Hospital Birmingham, Mindelsohn Way, Birmingham B15 2TH, UK.
Tel.: 0044 1213714657;
fax: 0044 1214141833;
e-mail: thamara.perera@uhb.nhs.uk

This data was presented at the ERA-EDTA Annual Scientific sessions and The European Society of Organ Transplantation (ESOT) Biennial Symposiums in 2015.
*These authors contributed equally to this work.

SUMMARY

Patient selection for combined liver–kidney transplantation (CLKT) is a current issue on the background of organ shortage. This study aimed to compare outcomes and post-transplant renal function for patients receiving CLKT and liver transplantation alone (LTA) based on native renal function using estimated glomerular filtration rate (eGFR) stratification. Using the UK National transplant database (NHSBT) 6035 patients receiving a LTA ($N = 5912$; 98%) or CLKT ($N = 123$; 2%) [2001–2013] were analysed, and stratified by KDIGO stages of eGFR at transplant (eGFR group-strata). There was no difference in patient/graft survival between LTA and CLKT in eGFR group-strata ($P > 0.05$). Of 377 patients undergoing renal replacement therapy (RRT) at time of transplantation, 305 (81%) and 72 (19%) patients received LTA and CLKT respectively. A significantly greater proportion of CLKT patients had severe end-stage renal disease (eGFR < 30 ml/min/1.73 m^2) at 1 year post-transplant compared to LTA (9.5% vs. 5.7%, $P = 0.001$). Patient and graft survival benefit for patients on RRT at transplantation was favouring CLKT versus LTA ($P = 0.038$ and $P = 0.018$, respectively) but the renal function of the long-term survivors was not superior following CLKT. The data does not support CLKT approach based on eGFR alone, and the advantage of CLKT appear to benefit only those who are on established RRT at the time of transplant.

Transplant International 2019; 32: 918–932

Key words
combined liver–kidney transplantation, liver transplantation, model for end-stage liver disease, National Health Service Blood and Transplant, post-transplant renal function

Received: 19 September 2018; Revision requested: 29 October 2018; Accepted: 18 February 2019; Published online: 28 March 2019

doi:10.1111/tri.13413

Introduction

The introduction of the model for end-stage liver disease (MELD), which is a system used to decide liver transplant allocation, has coincided with a rise in combined liver–kidney transplantation (CLKT). A majority of the data supporting this approach originates from database analyses using the United Network for Organ Sharing (UNOS)/Organ Procurement and Transplantation Network (OPTN) [1]. Despite imprecise methods for classifying severity of renal dysfunction [2], it is clear that the degree and duration of renal insufficiency while in liver pretransplant status have a major impact on post-transplant survival and renal function recovery [3–5].

However, the incremental benefit solely attributable to kidney transplantation in CLKT recipients is largely unknown, and difficult to assess despite a growing evidence base to support that there may be increased mortality in combined organ transplant patients [6]. Opponents also argue that CLKT reduces availability of donor kidneys for candidates awaiting kidney-only transplantation resulting in suboptimal utilization of organs. However, current guidelines devised by the OPTN liver and kidney advisory committees recommend CLKT for patients with chronic kidney disease (CKD), which is defined by the National Kidney Foundation as individuals demonstrating an estimated glomerular filtration rate (eGFR) ≤40 ml/min for three consecutive months or with acute kidney injury (AKI) lasting for ≥4 weeks [1]. A more robust clinical workup algorithm for CLKT has been proposed using GFR measured via the iodine-125 iothalamate test, duration of renal insufficiency and renal biopsy findings, although this is yet to be validated [7]. There is limited consensus regarding a specific GFR threshold that represents insufficient native functional recovery for which CLKT is warranted. Meanwhile the definitive need for CLKT in individuals undergoing chronic renal replacement therapy (RRT) as well as for patients with advanced polycystic disease is well recognized, concerns are raised when RRT is temporary or recently started [e.g. hepatorenal syndrome (HRS), those with an eGFR < 40 ml/min and in the presence of comorbidities such as diabetes] [1].

The aim of this study was to compare outcome in terms of survival (patient and liver graft survival) and renal function for patients receiving liver transplantation alone (LTA) with those receiving CLKT on the basis of KDIGO stages of pretransplant eGFR [8]. Secondarily, because the data for this analysis came from the National Health Service Blood and Transplant (NHSBT) database of the United Kingdom, this study sought to identify predictor variables for such outcomes for application to a European Transplant registry.

Materials and methods

Data were collected from the NHSBT database of the United Kingdom, which contained records of all liver graft alone and combined liver and kidney transplantations from January 2001 to December 2013. Patients were divided into groups of either LTA or CLKT. Excluded from analysis are paediatric recipients (defined as aged <16 years) and recipients of other solid organs in combination with liver/kidney (e.g. lung, heart, intestine). Demographics and clinical characteristics of the participants included in this study were: age, gender, ethnicity, body mass index (BMI), indication for liver transplantation (LT), liver failure grading, hepatitis C virus (HCV) status, diabetes mellitus and hypertensive status, time spent on the transplant waiting list, indications for CLKT, RRT at time of transplantation, MELD, United Kingdom End Stage Liver Disease (UKELD) score and single laboratory elements (e.g. INR, bilirubin, serum creatinine) and serum sodium concentration. Other data collected included donor and organ characteristics such as age, gender, donor-BMI, type of donor, liver cold ischaemia time (CIT) and liver reperfusion time. eGFR has been estimated on the basis of serum creatinine using the MDRD formula [9].

Patients were stratified into groups (eGFR group-strata) on the basis on pretransplant eGFR based on Chronic Kidney Disease KDIGO guidelines [8] as follows: Stage 1 = eGFR ≥ 90 ml/min/1.73 m^2; Stage 2 = eGFR 60–89 ml/min/1.73 m^2; Stage 3a = eGFR 45–59 ml/min/1.73 m^2; Stage 3b = eGFR 30–44 ml/min/1.73 m^2; Stage 4 = eGFR 15–29 ml/min/1.73 m^2; and Stage 5 = eGFR < 15 ml/min/1.73 m^2. Patients on RRT were considered as a distinct group (Table 1). Renal function outcome was evaluated at 1 year post-transplantation with severe end-stage renal disease (sESRD) defined as eGFR < 30 ml/min/1.73 m^2 [10].

Statistical analysis

Comparison of baseline patient characteristics between LTA and CLKT groups were performed by a chi-square or Fisher's exact test when the actual number was <5 within a group, and Student's *t* test, Wilcoxon or Mann–Whitney, as appropriate.

Patient and liver graft survival analysis was performed via Kaplan–Meier with log-rank tests, after patient stratification on the basis of renal function at

Table 1. Distribution of KDIGO [8] stages at transplantation in liver transplant alone and combined liver kidney patients (total number of patients 6035).

KDIGO stage	eGFR, ml/min/1.73 m^2	LTA (5907), %	CLKT (123), %	Total no. of patients by KDIGO stage
Stage 1	≥90	1988 (33.6)	–	1988
Stage 2	60–89	2384 (40.3)	–	2384
Stage 3a	45–59	794 (53.8)	6 (4.9)	800
Stage 3b	30–44	344 (5.8)	10 (8.1)	354
Stage 4	15–29	79 (1.3)	22 (17.9)	101
Stage 5	<15	13 (0.2)	13 (10.5)	26
RRT		305 (5.2)	72 (58.5)	377

eGFR, estimated glomerular filtration rate; RRT, renal replacement therapy.

The value of serum creatinine at transplantation was missing in five patients.

transplantation. Graft failure was defined both as graft failure or patient death irrespective of graft status at the time of death. Death censored liver graft survival was also performed.

Univariate Cox regression analyses were performed to identify factors predicting patient and liver graft survival. All clinically relevant variables were included for multivariate model [11].

Statistical analysis was performed with SPSS 20.0 (IBM Corp., New York, NY, USA). Significance was determined using $P < 0.05$.

Results

This study included a total of 6035 patients who underwent organ transplantation between 2001 and 2013 recorded in the NHSBT database. Among these patients, 123 (2%) individuals received a CLKT and 5912 (98%) underwent LTA. Of the retrieved records, there was a variable percentage of missing data. For the variables used in the multivariable analyses, the highest proportion of missing data was 4.3%. Cases with missing data have been excluded from the analysis.

Distribution of renal function at transplantation

Table 1 presents the number of patients receiving LTA or CLKT according to eGFR stratification. Understandably, no patients demonstrating an eGFR ≥ 60 ml/min/1.73 m^2 underwent CLKT. Six patients demonstrating an eGFR between 45 and 59 ml/min/1.73 m^2 underwent CLKT, which accounted for <1% of transplant volume within the Stage 3a KDIGO group; yet as this is the deviation of common practice, these six individuals were also excluded from comparative analyses. We included in the analysis, all patients with eGFR ≤ 44 ml/min/1.73 m^2 [KDIGO Stage 3b; $n = 858$; of whom $n = 741$ LTA and $n = 117$ CLKT (Table 1)]. Current consensus suggests a threshold of eGFR < 40 ml/min/1.73 m^2 to consider a patient for CLKT, a threshold that falls within the KDIGO CKD Stage 3b (eGFR 44–30 ml/min/1.73 m^2); a separate analysis was conducted for patients with eGFR ranging between 40 and 44 ml/min/1.73 m^2 that did not demonstrate substantially different results (data not shown); hence the aforementioned approach of treating all patients on Stage 3b as a single group.

Three hundred and seventy seven ($n = 377$) patients were undergoing RRT at time of transplantation. Of these, 305 (80.9%) received LTA and 72 (19.1%) received CLKT (Table 1).

Demographics stratified on the basis of eGFR at transplantation

Demographic and clinical characteristics of patients stratified on the basis of pretransplant eGFR, including those on RRT, were compared and reported in Table 2. These were significantly different between patients receiving LTA compared to CLKT patients.

Both MELD and UKELD scores were higher in LTA patients as well as INR and bilirubin at time of transplant, indicating a higher severity of end-stage liver disease (ESLD) for these patients. Additionally, the LTA group presented with a higher incidence of ascites and variceal bleeding.

Indication for liver transplantation was also significantly different in Stage 4 and RRT groups, with a predominance of congenital/inherited diseases in patients receiving CLKT, whereas in patients receiving LTA a

Table 2. Demographic and clinical characteristics of LTA and CLKT patients stratified by stages of renal function (GFR < 44/ml/min/1.73 m^2) and RRT at time of transplantation (eGFR group-strata; total no. of patients 858).

KDIGO stage (eGFR ml/min/1.73 m^2)	3b (44–30)			4 (15–29)			5 (<15)			RRT		
number of patients	354			101			26			377		
	LTA (n = 344)*	CLKT (n = 10)*	P-value	LTA (n = 79)*	CLKT (n = 22)*	P-value	LTA (n = 13)*	CLKT (n = 13)*	P-value	LTA (n = 305)*	CLKT (n = 72)*	P-value
Recipient characteristics												
Age in years	56 [48–62]	62 [53–64]	0.152	56 [47–59]	55 [50–59]	0.808	54 [42–62]	52 [39–60]	0.614	53 [44–65]	52 [45–58]	0.400
Male gender	156 (45.3)	6 (60.0)	0.522	35 (44.3)	8 (36.4)	0.505	5 (38.5)	7 (53.8)	0.695	195 (63.9)	46 (63.9%)	0.548
Recipient body mass index	26 [23–30]	26 [24–29]	0.867	26 [24–29]	25 [23–27]	0.524	26 [23–30]	26 [22–30]	0.801	26 [22–30]	25 [23–29]	0.504
Ethnicity			0.660			0.125			–			0.193
Caucasian	315 (91.6)	8 (80.0)		77 (97.5)	21 (95.5)		13 (100.0)	13 (100.0)		270 (88.5)	59 (81.9)	
Asian	21 (6.1)	2 (20.0)		2 (2.5)	–		–	–		22 (7.2)	11 (15.3)	
Black	3 (0.9)	–		–	1 (4.5)		–	–		7 (2.3)	2 (2.8)	
Other	5 (1.5)	–		–	–		–	–		6 (2.0)	–	
Indication for LT			0.477			**0.001**			0.519			**<0.0001**
Alcoholic cirrhosis	83 (24.1)	3 (30.0)		**21 (26.6)**	**1 (4.5)**		1 (7.7)	2 (15.4)		**80 (26.2)**	**9 (12.5)**	
HCV cirrhosis	44 (12.8)	–		**5 (6.3)**	**1 (4.5)**		2 (15.4)	2 (15.4)		**29 (9.5)**	**6 (8.3)**	
PBC	45 (13.1)	–		**10 (12.7)**	**1 (4.5)**		–	1 (7.7)		**40 (13.1)**	–	
PSC	19 (5.5)	–		**6 (7.6)**	–		3 (23.1)	–		**30 (9.8)**	**1 (1.4)**	
NASH	17 (4.9)	–		–	–		1 (7.7)	–		**10 (3.3)**	–	
HBV cirrhosis	4 (1.2)	–		–	–		–	–		**7 (2.3)**	**1 (1.4)**	
Autoimmune	9 (2.6)	1 (10.0)		**1 (1.3)**	–		1 (7.7)	–		**11 (3.6)**	–	
Re-OLT	43 (12.5)	3 (30.0)		**15 (19.0)**	**2 (9.1)**		1 (7.7)	1 (7.7)		**33 (10.8)**	**6 (8.3)**	
Polycystic	8 (2.3)	1 (10.0)		–	**9 (40.9)**		2 (15.4)	2 (15.4)		–	**14 (19.4)**	
Other	65 (18.9)	3 (30.0)		**18 (22.8)**	**10 (45.5)**		3 (23.1)	5 (38.5)		**39 (12.8)**	**18 (25.0)**	
Unknown/not specified	15 (4.4)	–		**3 (3.8)**	**7 (31.8)**		1 (7.7)	2 (15.4)		**26 (8.5)**	**17 (23.6)**	
Liver failure grading			0.808			0.344			0.174			0.185
Hyperacute/acute /subacute	9 (2.7)	–		3 (3.9)	–		2 (15.4)	–		19 (6.4)	2 (2.8)	
Not acute	328 (97.3)	8 (100.0)		73 (96.1)	22 (100.0)		11 (84.6)	11 (100.0)		278 (93.6)	70 (97.2)	
MELD score	20 [16–25]	15 [14–24]	0.215	**29 [23–34]**	**20 [17–22]**	**<0.0001**	**36 [29–40]**	**22 [20–28]**	**0.001**	**29 [26–35]**	**22 [20–27]**	0.667
UKELD score	56 [52–61]	53 [49–59]	0.136	**62 [57–66]**	**49 [46–52]**	**<0.0001**	**66 [59–69]**	**51 [48–58]**	**<0.0001**	**59 [55–63]**	**50 [48–57]**	**<0.0001**
INR at transplant	1.4 [1.2–1.7]	1.2 [1.1–1.6]	0.106	**1.4 [1.2–1.8]**	**1.1 [1.0–1.5]**	**0.005**	1.7 [1.2–1.9]	1.3 [1.0–1.5]	0.118	**1.4 [1.2–1.8]**	**1.0 [0.9–1.4]**	**<0.0001**
Bilirubin at transplant (μmol/l)	50 [24–153]	19 [9–102]	0.062	**134 [37–481]**	**9 [7–19]**	**<0.0001**	**229 [49–575]**	**14 [5–41.5]**	**0.001**	**67 [35–85]**	**15 [7–50]**	**<0.0001**
Serum sodium at transplant (μmol/l)	136 [133–139]	136 [134–137]	0.833	**135 [131–138]**	**140 [138–142]**	**<0.0001**	**132 [129–136]**	**138 [135–139]**	**0.005**	**137 (133–139)**	**139 (136–140)**	**<0.0001**
Recipient prior to tx ascites	221 (64.2)	7 (70.0)	1.000	**52 (65.8)**	**9 (40.9)**	**0.035**	**12 (92.3)**	**5 (41.7)**	**0.011**	**199 (65.5)**	**26 (36.1)**	**<0.0001**
Recipient prior to tx variceal bleeding	85 (24.7)	2 (20.0)	0.225	**24 (30.8)**	**3 (13.6)**	**0.013**	2 (15.4)	–	0.170	**94 (30.9)**	**17 (23.9)**	**0.002**
No bleeding	141 (41.0)	2 (20.0)		**31 (39.7)**	**5 (22.7)**		5 (38.5)	9 (69.2)		**126 (41.4)**	**19 (26.8)**	
No varices	118 (34.3)	6 (60.0)		**23 (29.5)**	**14 (63.6)**		6 (46.2)	4 (30.8)		**84 (27.6)**	**35 (49.3)**	
Hypertension	31 (23.3)	–	0.457	**2 (6.9)**	**4 (57.1)**	**0.008**	–	1 (20.0)	0.217	**15 (9.8)**	**8 (26.7)**	**0.017**
Diabetes mellitus	43 (32.1)	–	0.320	5 (17.9)	–	0.198	3 (42.9)	1 (20.0)	0.576	25 (16.8)	3 (10.0)	0.264
Serum creatinine at transplant (μmol/l)	153 [130–167]	160 [149–195]	0.072	**229 [188–272]**	**259 [229–316]**	**0.026**	373 [323–468]	461 [388–509]	0.186	**RRT**	**RRT**	**<0.0001**
eGFR at transplant (ml/min)	**39 [36–42]**	**33 [32–41]**	**0.036**	**24 [20–27]**	**19 [17–23]**	**<0.0001**	13 [12–14]	12 [11–13]	0.091			

Table 2. Continued.

KDIGO stage (eGFR ml/min/1.73 m^2)	3b (44–30) 354			4 (15–29) 101			5 (<15) 26			RRT 377		
number of patients	LTA (n = 344)*	CLKT (n = 10)*	*P*-value	LTA (n = 79)*	CLKT (n = 22)*	*P*-value	LTA (n = 13)*	CLKT (n = 13)*	*P*-value	LTA (n = 305)*	CLKT (n = 72)*	*P*-value
Time on the waiting list (days)	74 [30–172]	81.5 [31–145]	0.985	**56 [9–151]**	**253 [56–490]**	**0.004**	**29 [6–54]**	**195 [56–422]**	**0.001**	**51 [15–142]**	**187 [55–333]**	**<0.0001**
Indication for KT			–			–			–			–
Tubulointerstitial nephropathy	1 (12.5)			2 (13.3)		–	1 (9.1)					
Glomerular disease	3 (37.5)				–		2 (18.2)					
Diabetic nephropathy					–		–					
Congenital disease					–		1 (9.1)					
Polycystic disease	1 (12.5)			10 (66.7)			3 (27.3)					
Other and unknown	3 (37.5)			3 (20.0)			4 (36.4)					

CIT, cold ischaemia-time; CLKT, combined liver–kidney transplants; DBD, donation after brain death; DCD, donation after cardiocirculatory death; eGFR, estimated glomerular filtration rate; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; KT, kidney transplantation; LT, liver transplantation; LTA, liver transplant alone; MELD, model for end-stage liver disease; NASH, nonalcoholic fatty liver disease; RRT, renal replacement therapy; WIT, warm ischaemia time.

Results are expressed as number of patients (percentage) or median (interquartile range), as appropriate.

*The amount of numbers does not always return the total number of patients, because of missing data.

high prevalence of alcoholic cirrhosis was observed (Table 2). There were no differences for HCV infection or incidence of pretransplant diabetes. Patients who received CLKT were more likely to be hypertensive and spent a significantly longer time on the waiting list.

A higher percentage of CLKT patients received calcineurin inhibitors (CNIs) based immunosuppression compared with LTA patients at 1 (83.3% vs. 71.5%; $P = 0.040$) and 3 years (62.5% vs. 47.5%; $P = 0.022$), but not at 5 years post-transplantation (43.1% vs. 31.5%; $P = 0.061$).

Recipient and liver graft survival

Patient survival at 1, 3 and 5 years between LTA versus CLKT was 90.4% vs. 91.4% ($P = 0.766$), 84.7% vs. 88.0% ($P = 0.449$) and 78.5% vs. 83.7% ($P = 0.347$) respectively. Liver graft survival at 1, 3 and 5 years between LTA versus CLKT was 85.5% vs. 87.6% ($P = 0.617$), 79.5% vs. 84.4% ($P = 0.241$) and 73.1% vs. 77.6% ($P = 0.368$) respectively.

Infections were the main reported cause of death in LTA patients on RRT (48/305; 15.7%), whereas mortality because of sepsis was less common in CLKT patients (2/72; 2.8%; Table 3). Renal dysfunction was recognized as the cause of death in a marginal number of patients (7/858; <0.01%).

Survival stratified on the basis of eGFR at transplantation

Patient and liver graft survival were analysed after patient stratification on the basis of pretransplant kidney function as reported by KDIGO guidelines [8]. The cumulative survival showed no significant differences between the LTA and CLKT groups on patient or graft survival for KDIGO Stages 3b–5 (Fig. 1).

Significantly higher patient survival was noted for patients on RRT at time of transplantation undergoing CLKT in comparison to those on RRT receiving LTA ($P = 0.038$; Fig. 2a). Similarly, higher liver graft survival was observed in patients on RRT receiving CLKT compared with those receiving LTA ($P = 0.018$; Fig. 2b).

Importantly, there was improved patient and liver graft survival beyond the third year post-transplantation in those maintained on RRT at transplantation receiving CLKT compared with LTA ($P < 0.05$), whereas there was no difference in short-term survival at 1 year ($P = 0.108$; Table 4). Higher liver graft survival following a combined transplant is illustrated early at 1-year post-transplant ($P = 0.023$), which was maintained long-term up to

Table 3. Post-transplant cause of death in LTA and CLKT recipients stratified by stages of renal function (GFR < 44/ml/min/1.73 m^2) and RRT at time of transplantation (eGFR group-strata).

KDIGO stage (eGFR ml/min/1.73 m^2)	3b (44–30)			4 (15–29)			5 (<15)			RRT		
	LTA (n = 344)*	CLKT (n = 10)*	*P*-value	LTA (n = 79)*	CLKT (n = 22)*	*P*-value	LTA (n = 13)*	CLKT (n = 13)*	*P*-value	LTA (n = 305)*	CLKT (n = 72)*	*P*-value
Recipient cause of death			**0.002**			0.765			0.513			0.206
Cardiovascular	7 (2.0)	2 (20.0)		2 (2.5)	–		–	–		5 (1.6)	2 (2.8)	
Renal dysfunction	6 (1.7)	–		–	–		–	–		1 (0.3)	–	
Respiratory failure	4 (1.2)	–		–	–		–	–		2 (0.7)	–	
Haemorrhage	3 (0.9)	1 (10.0)		2 (2.5)	–		–	–		3 (1.0)	–	
Infection	42 (12.2)	–		9 (11.4)	4 (18.2)		2 (15.4)	1 (7.7)		48 (15.7)	2 (2.8)	
Liver cause	12 (3.5)	–		3 (3.8)	–		–	–		8 (2.6)	2 (2.8)	
Other	20 (5.8)	–		4 (5.1)	–		–	–		15 (4.9)	3 (4.2)	
Malignancy	5 (1.5)	1 (10.0)		3 (3.8)	1 (4.5)		–	1 (7.7)		10 (3.3)	1 (1.4)	
Unknown	12 (3.5)	–		1 (1.3)	–		–	–		6 (2.9)	2 (2.8)	
Alive	233 (67.7)	6 (60.0)		55 (69.6)	17 (77.3)		11 (84.6)	11 (84.6)		207 (67.9)	60 (83.3)	

CLKT, combined liver–kidney transplants; LTA, liver transplant alone.

Results are expressed as number of patients (percentage). Significant differences are highlighted in bold numbers.

*The amount of numbers does not always return the total number of patients, due to missing data.

5 years (P = 0.006). However, no differences in liver graft or patient survival were detected at 1-, 3- and 5-year time points for the other eGFR stratifications at time of transplant (Table 4). Death censored graft survival was not different between patients receiving CLKT or LTA for any KDIGO stage or RRT.

The analysis of combined group 3b and 4 (eGFR 15–44 ml/min/1.73 m^2) did not show significant difference in terms of patient (P = 0.627) or liver graft (P = 0.375) survival between LTA and CLKT.

Moreover, the analysis of patients on RRT (dialysis) compared to non-RRT (no dialysis) showed significant decreased patient survival in LTA (P = 0.040) while no differences were detected in CLKT patients (P = 0.966). Liver graft survival was significantly worst in RRT patient receiving LTA compared to patients in non-RRT (P < 0.001), while no differences were detected in CLKT patients (P = 0.429).

Renal function after transplantation

Kidney graft survival was 90.6% at 1 year, 88.7% at 3 years and 84.0% at 5 years post-transplantation in the CLKT group. Table 5 outlines renal function outcomes at 1, 3 and 5 years post-transplantation for patients undergoing LTA compared with CLKT stratified on the basis of eGFR at time of transplantation. The median eGFR was not significantly different between LTA and CLKT groups at each time point post-transplantation, for patients in Stages 3b–5. Patients undergoing RRT at time of transplantation receiving CLKT compared with LTA showed significantly worse median eGFR at 1, 3 and 5 years post-transplant (P < 0.0001; Table 5).

Recovery of renal function in patients with pretransplant eGFR < 30 ml/min/1.73 m^2 is defined as post-transplant eGFR > 30 ml/min/1.73 m^2 [10] and is reported in Table 6. No difference was found in distribution of recovery of renal function for patients with pretransplant renal dysfunction Stages 4 and 5 or on RRT, when comparing patients receiving LTA versus CLKT (Table 6).

Risk factor analysis

Risk factors for patient survival

For univariate Cox regression analyses, recipient age, male gender, HCV infection, MELD score, RRT at transplant, ascites prior to transplantation, donor age and liver CIT were all significant predictors of nonsurvival in patients receiving LTA, while polycystic disease

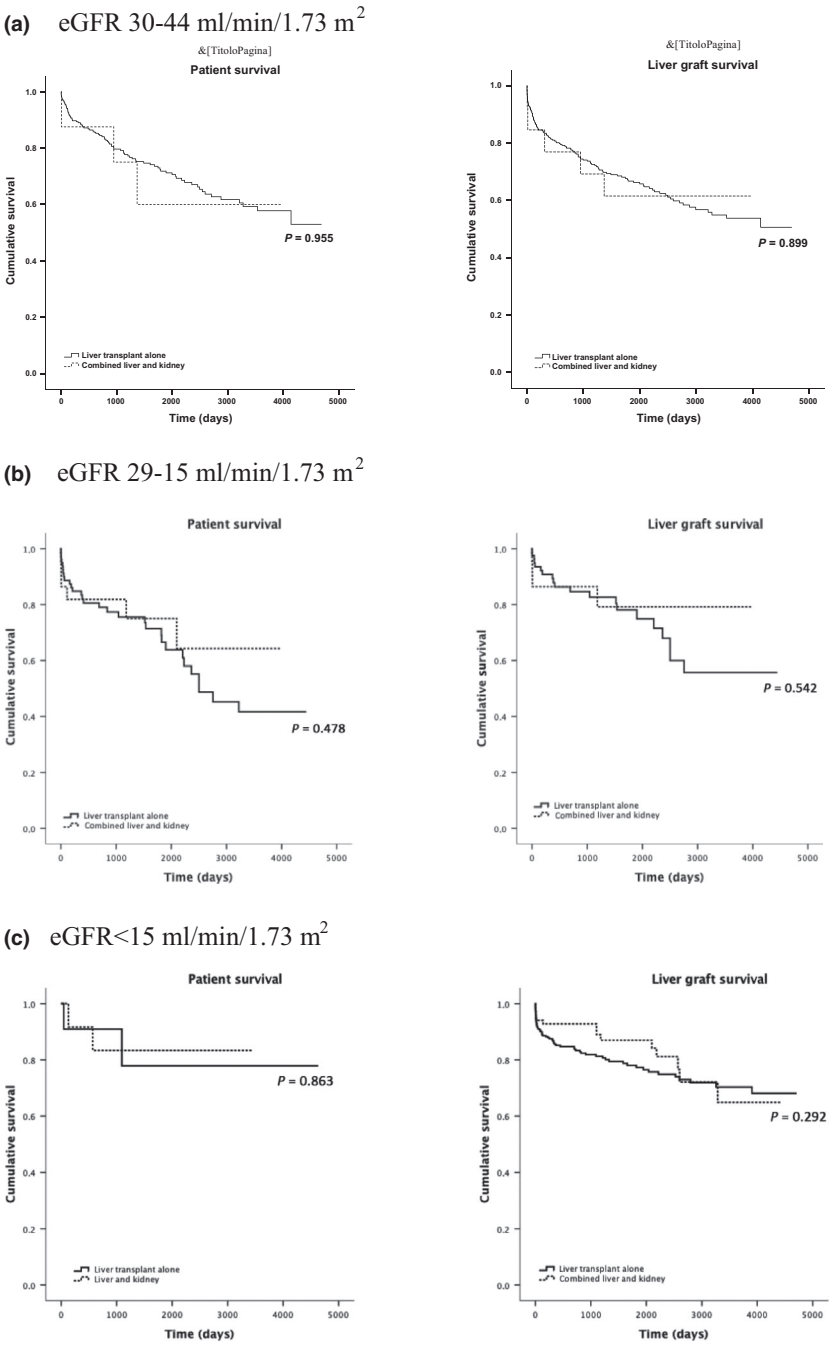


Figure 1 Cumulative patients and graft survival undergoing liver transplant alone compared to combined liver–kidney transplantation for patients stratified by stages of renal function (GFR<44/ml/min/1.73 m^2; estimated glomerular filtration rate group-strata) at transplantation.

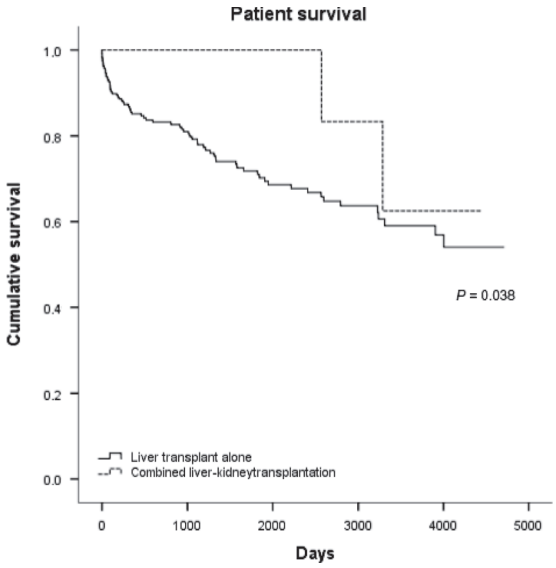
and bilirubin at transplant were associated with improved survival. Recipient age was the only significant factor predicting mortality for CLKT patients, although the statistical power of the latter analyses was lower (Table 7).

In a multivariable model including all clinically relevant variables, significant independent predictors of mortality for patients undergoing LTA were recipient age, HCV infection, higher MELD score, older donor age and longer CIT (Table 7).

Risk factors for liver graft survival

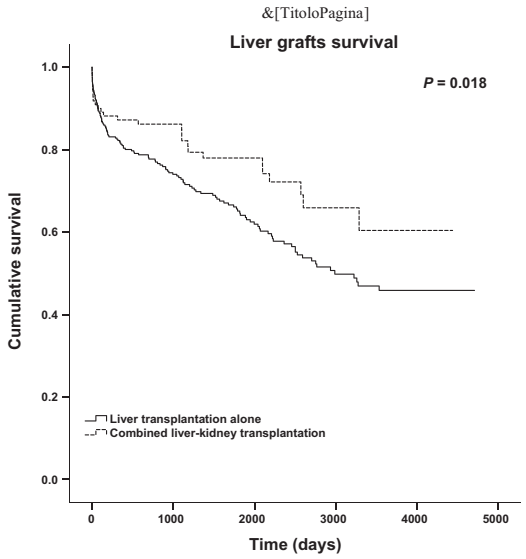
In univariate Cox regression analyses, recipient age, male gender, HCV infection, higher MELD score and bilirubin at transplant, treatment with RRT at time of transplant, older donor age and longer liver CIT were all predictive of liver graft loss for patients receiving LTA, while polycystic disease was associated with improved liver graft survival. In the CLKT group, recipient age and variceal bleeding were predictive factors for

(a) Patient survival



Number at Risk	Transplant	1 year	3 years	5 years	10 years
LTA	305	203	135	99	33
CLKT	25	22	16	10	1

(b) Liver graft survival



Number at Risk	Transplant	1 year	3 years	5 years	10 years
LTA	305	203	135	99	33
CLKT	25	22	16	10	1

Figure 2 Cumulative patient and liver graft survival undergoing liver transplant alone compared to combined liver–kidney transplantation for patients undergoing renal replacement therapy at transplantation.

reduced liver graft survival, although the statistical power of this analysis was low (Table 8).

In a multivariate model including all clinically relevant variables, recipient age, HCV infection, higher bilirubin at transplant, treatment with RRT at time of transplantation, older donor age and longer liver CIT were significant predictors of liver graft loss (Table 8). Polycystic disease was associated with reduced risk of liver graft loss (Table 8).

Discussion

To the best of our knowledge, this is the first data registry-based analyses focusing on CLKT performed in Europe and outside of UNOS/OPTN. Recent evolving trends for CLKT following MELD implementation suggest that kidney grafts may be preferentially allocated to critically ill recipients who may not benefit from such a practice because of advanced disease stage [6]. Combining this understanding with reduced waiting-list time survival for patients listed for kidney transplantation after LTA [12,13] has led to increased number of listings for CLKT. Concerns also continue to be raised regarding the allocation of kidneys to patients who have the potential of renal function recovery following LTA alone. The most recent proposed policy focusing on simultaneous liver–kidney transplantation recommends CLKT for patients with CKD (demonstrating eGFR $\leq$ 40 ml/min for three consecutive months) or AKI lasting for $\geq$4 weeks [1]. While average listings for CLKT has increased up to 11%, particularly in the US [14], this does not seem consistent with our study, with only 2% of the entire cohort of patients receiving CLKT in UK.

In this study, the stratification of renal function in patients receiving LTA and CLKT was based on eGFR as classified by KDIGO guidelines, which provided the basis for analyses in terms of patient and graft survival and recovery of renal function (eGFR > 30 ml/min/1.73 m^2).

The main result from this study highlights no differences in terms of survival benefit for patients presenting with severe KDIGO stages of renal function pre-LTA (Stages 3b–5). Compared to the current consensus, it seems that patients with eGFR < 44 ml/min/1.73 m^2 do not benefit of receiving CLKT in term of patient and liver graft survival. Only those already receiving RRT have a favourable survival outcome from CLKT.

As such, the advantage of CLKT in patients with chronic RRT is well recognized, whereas doubts are still raised when RRT is started because of recent onset of

Table 4. Patients and graft survival rates 1, 3 and 5 years after transplant, stratified by stages (GFR < 44/ml/min/1.73 m^2) and RRT at time of transplantation (eGFR group-strata).

	1 year Survival estimate (%)		3 years Survival estimate (%)		5 years Survival estimate (%)	
	Patients	Grafts	Patients	Grafts	Patients	Grafts
Stage 3b (eGFR 44–30 ml/min/1.73 m^2)						
LTA	88.8	82.8	81.8	76.7	76.9	71.7
CLKT	85.7	70.0	71.4	60.0	57.1	50.0
P	0.765	0.288	0.587	0.263	0.355	0.216
Stage 4 (eGFR 15–29 ml/min/1.73 m^2)						
LTA	89.9	84.8	88.1	77.2	81.4	72.2
CLKT	85.0	81.8	85.0	81.8	80.0	77.3
P	0.523	0.687	0.694	0.719	0.895	0.708
Stage 5 (eGFR < 15 ml/min/1.73 m^2)						
LTA	92.3	90.9	84.6	81.8	84.6	81.8
CLKT	92.3	91.7	84.6	83.3	84.6	83.3
P	0.977	0.895	0.932	0.863	0.932	0.863
RRT						
LTA	85.2	77.6	79.2	70.2	71.0	63.0
CLKT	93.3	90.1	93.3	90.1	90.6	81.3
P	0.108	**0.023**	**0.026**	**0.002**	**0.011**	**0.006**

eGFR, estimated glomerular filtration rate; RRT, renal replacement therapy.

Significant differences are highlighted in bold numbers.

AKI [1]. Contradictory results have been reported for those patients undergoing acute RRT prior to transplantation to which a survival benefit appears to occur only for those patients receiving RRT for intervals ranging between 8 and 12 weeks [15,16]. Recent suggestions have set up a minimum RRT period of ≥4 weeks for a candidate patient awaiting CLKT [1].

Patients on RRT at time of transplantation undergoing LTA compared to CLKT demonstrate more advanced liver disease, as showed higher MELD and UKELD score, mainly related to higher bilirubin and higher INR, that were also associated with lower sodium and more frequent incidence of bleeding varices and ascites in face of lower creatinine. This strongly suggests the occurrence of more severe decompensated cirrhosis in patients receiving LTA and probably a higher incidence of HRS, suggesting the requirement of RRT related more to haemodynamic alterations than to intrinsic renal disease.

Moreover, the indication for LTA or CLKT are dissimilar among the different group-strata of eGFR, with the majority of patients diagnosed with polycystic disease receiving CLKT despite eGFR value, and the majority of patients on RRT before transplantation with alcoholic cirrhosis receiving LTA. This strongly confirms that the aetiology of renal dysfunction related to intrinsic renal disease or functional renal illness related to liver disease, address the decision to candidate patients to LTA or CLKT.

The prognostic outcome for patients from this study appears acceptable in terms of long-term survival, higher than 78% at 5 years. Single centre and US registry analysis challenge the indications for CLKT, reporting controversial results on survival after CLKT, with some reporting increased perioperative morbidity and mortality [17] and others describing a survival benefit at 1 year post-transplantation for patients receiving CLKT compared to LTA [6,18]. No studies have performed an analysis similar to the current study based on stratifications of eGFR at time of transplantation. In this national cohort of patients, no survival difference was demonstrated at 1 year post-transplantation for all stages of eGFR (3b–5 and RRT). Long-term survival mirrors short-term outcomes for all eGFR group-strata, except a survival benefit demonstrated at 3 years post-transplantation for patients on RRT only. There is a clear prevalence of infections and liver dysfunction as cause of death in patients receiving LTA that further confirms the important role of severity of baseline illness on the outcome of these patients.

Several studies have reported different degrees of recovery of renal function post-CLKT, focusing in particular on those cases that would have three functioning

Table 5. Renal function outcome (eGFR ml/min/1.73 m^2) at 1-, 3- and 5-year post-transplant, stratified by stages of renal function at transplantation (eGFR group-strata).

	LTA (no. patients)	CLKT (no. patients)	*P*
Stage 3b (eGFR 44–30 ml/min/m^2)			
1 year post-LT	(294)	(8)	0.381
	49 [41–60]	45 [37–55]	
3 years post-LT	(207)	(7)	0.416
	46 [37–61]	40 [38–52]	
5 years post-LT	(146)	(5)	0.567
	49 [39–61]	38 [34–66]	
Stage 4 (eGFR 15–29 ml/min/m^2)			
1 year post-LT	(65)	(18)	0.500
	51 [34–68]	56 [48–61]	
3 years post-LT	(46)	(14)	0.426
	49 [31–65]	53 [47–61]	
5 years post-LT	(31)	(10)	0.687
	44 [29–67]	52 [38–55]	
Stage 5 (eGFR <15 ml/min/m^2)			
1 year post-LT	(9)	(12)	0.219
	41 [20–63]	60 [45–65]	
3 years post-LT	(8)	(9)	0.321
	39 [21–70]	62 [42–66]	
5 years post-LT	(4)	(7)	1.000
	54 [41–113]	53 [46–73]	
RRT patients			
1 year post-LT	(244)	(63)	**<0.0001**
	63 [50–80]	50 [37–67]	
3 years post-LT	(162)	(47)	**<0.0001**
	60 [48–77]	46 [40–59]	
5 years post-LT	(105)	(32)	**<0.0001**
	61 [49–78]	47 [37–56]	

CLKT, combined liver–kidney transplantation; eGFR, estimated glomerular filtration rate; LT, liver transplantation; LTA, liver transplantation alone; RRT, renal replacement therapy.

Values are expressed as median [interquartile range]; the number of patients reported in round brackets is the number of available data. Significant differences are highlighted in bold numbers.

kidneys [19]. On the other hand, reports have also described the risk of transplanting a functioning kidney to a high mortality risk patient with advanced liver disease and with limited survival as "futility" in transplantation [20]. Patients receiving CLKT demonstrated worst outcome in terms of renal function after transplantation when on RRT before transplant, compared to LTA, while no significant differences were detected in renal function outcome for other different level of pretransplant renal function (Stages 3b–5) within the two groups of patients. Moreover, recovery of renal function equally occurs after transplantation in patients receiving LTA or CLKT. An amount of native renal functional recovery may be supposed in patients receiving LTA when the renal function is not completely deteriorated (Stages 3b–5) probably related to pretransplant dysfunction linked to haemodynamic derangement like HRS, while the renal function resulting from a single kidney with the impact of donor events and ischaemic injury may account for the reduced eGFR in CLKT patients. Moreover, patients receiving CLKT are recognized to receive higher percentage of CNIs based immunosuppression that may account for a certain degree of nephrotoxicity and deterioration of eGFR [21].

There is previously reported evidence suggesting patient survival is inferior when preoperative renal dysfunction persists following LTA [22,23], but renal dysfunction as a cause of death is reported in a minority of patients receiving both LTA and CLKT.

Several previous studies have considered survival of kidney grafts and incidence of renal allograft rejection following CLKT versus kidney transplant alone [24–26]. In the present study, satisfactory kidney graft survival is reported, but unfortunately no data are available

Table 6. Recovery of renal function 1 year post-transplantation stratified on the basis of stages of renal function at transplantation.

eGFR stages [ml/min/1.73 m^2]	Renal function recovery	LTA [number of patients]	CLKT [number of patients]	*P*
Stage 4		[65]	[18]	0.060
[29–15]	eGFR ≥ 30	53 (81.5)	18 (100.0)	
	eGFR ≤ 29	12 (18.5)	–	
Stage 5		[9]	[12]	0.171
[<15]	eGFR ≥ 30	7 (77.8)	12 (100.0)	
	eGFR ≤ 29	2 (22.2)	–	
RRT		[244]	[63]	0.132
	eGFR ≥ 30	230 (94.3)	56 (88.9)	
	eGFR ≤ 29	14 (5.7)	7 (11.1)	

CLKT, combined liver–kidney transplantation; eGFR, estimated glomerular filtration rate; LTA, liver transplantation alone; RRT, renal replacement therapy.

Values are expressed as number of patients (percentage).

Table 7. Cox regression univariate and multivariable analysis of risk factors associated with patients' death following LTA and CLKT.

	LTA		CLKT
	HR (95% CI)		HR (95% CI)
No. patients [no. events]	Univariate 5491 [1224]	Multivariable 4825 [1071]	Univariate 106 [21]
Recipient age (HR for increase of 10)	**1.18 (1.12–1.24)***	**1.14 (1.07–1.21)***	**2.65 (1.43–4.89)***
Male gender	**1.25 (1.11–1.41)***	1.12 (0.98–1.28)	1.47 (0.59–3.66)
Alcoholic cirrhosis	1.13 (0.99–1.28)	1.15 (0.99–1.34)	1.67 (0.61–4.56)
HCV infection	**1.32 (1.15–1.53)***	**1.39 (1.19–1.64)***	1.40 (0.39–5.01)
Polycystic disease	**0.19 (0.05–0.75)***	0.28 (0.07–1.14)	0.32 (0.07–1.38)
Hypertension	1.00 (0.72–1.39)	0.88 (0.61–1.25)	†
Diabetes	1.22 (0.99–1.51)	1.12 (0.89–1.42)	4.78 (0.61–37.36)
MELD-20 squared (HR for increase of 100)	**1.12 (1.03–1.22)***	**1.12 (1.01–1.24)***	0.94 (0.42–2.08)
INR at transplant	0.96 (0.89–1.03)	0.96 (0.89–1.03)	1.10 (0.43–2.82)
Log_{10} (bilirubin at transplant)	**0.81 (0.71–0.91)**	0.92 (0.79–1.08)	0.68 (0.24–1.92)
RRT at transplant	**1.37 (1.08–1.73)***	1.23 (0.93–1.63)	0.56 (0.23–1.32)
Serum sodium at transplant (HR for increase of 10)	0.95 (0.86–1.05)	0.98 (0.87–1.10)	0.38 (0.13–1.11)
Prior to tx ascites	**1.15 (1.02–1.28)***	1.11 (0.97–1.27)	0.65 (0.26–1.61)
Prior to tx no varices	1	1	1
Variceal no bleeding	1.00 (0.87–1.14)	0.94 (0.81–1.09)	0.66 (0.21–2.10)
Variceal bleeding	1.05 (0.91–1.21)	0.96 (0.82–1.12)	1.72 (0.63–4.70)
Time on the waiting list (HR for increase of 100)	0.97 (0.93–1.02)	0.98 (0.93–1.02)	1.01 (0.84–1.22)
Donor age (HR for increase of 10)	**1.08 (1.04–1.13)***	**1.07 (1.03–1.11)***	1.16 (0.82–1.65)
Liver CIT (HR for increase of 100)	**1.04 (1.01–1.08)***	**1.04 (1.00–1.08)***	1.16 (0.91–1.49)

The final model included all clinically relevant variables. Significant differences are highlighted in bold numbers.

CI, confidence interval; CIT, cold ischaemia time; HR, hazard ratio; RRT, renal replacement therapy; tx, transplant.

*$P < 0.05$.

†No deaths were recorded among patients with hypertension receiving CLKT.

regarding the incidence of renal rejection. We identified HCV infection as risk factors that negatively affect recipient survival for patients receiving LTA. Similar to previous studies [4,22], our results confirm the negative impact of HCV on patient survival, but this must be regarded in the context of increasing use of new efficacious treatments against HCV infection [27]. Higher MELD score is a well-recognized predictive factor for

Table 8. Cox regression univariate and multivariable analysis of risk factors associated with graft loss following LTA and CLKT.

	LTA		CLKT
	HR (95% CI)		HR (95% CI)
No. patients [no. events]	Univariate 5906 [1644]	Multivariable 5152 [1430]	Univariate 122 [31]
Recipient age-45 squared (HR for increase of 100)	**1.04 (1.01–1.07)***	**1.04 (1.01–1.07)***	**1.23 (1.00–1.52)***
Male gender	**1.12 (1.01–1.24)***	1.07 (0.96–1.20)	1.42 (0.67–3.02)
Alcoholic cirrhosis	0.98 (0.87–1.10)	1.10 (0.96–1.26)	1.48 (0.60–3.61)
HCV infection	**1.18 (1.03–1.34)***	**1.31 (1.14–1.52)***	0.91 (0.27–3.07)
Polycystic disease	**0.30 (0.11–0.81)***	**0.18 (0.04–0.72)***	0.39 (0.12–1.29)
Hypertension	0.81 (0.60–1.09)	0.78 (0.57–1.08)	†
Diabetes	1.04 (0.86–1.25)	1.08 (0.88–1.32)	2.00 (0.24–16.67)
MELD-20 squared (HR for increase of 100)	**1.13 (1.05–1.21)***	1.01 (0.93–1.11)	1.21 (0.83–1.77)
INR at transplant	0.95 (0.90–1.01)	0.95 (0.89–1.01)	1.28 (0.62–2.64)
Log_{10} (bilirubin at transplant)-1.7 squared	**1.34 (1.16–1.54)***	**1.54 (1.29–1.85)***	1.51 (0.71–3.21)
RRT at transplant	**1.42 (1.17–1.72)***	**1.38 (1.10–1.74)***	0.75 (0.37–1.52)
Serum sodium at transplant (HR for increase of 10)	1.00 (0.91–1.09)	1.06 (0.95–1.18)	0.78 (0.33–1.89)
Prior to tx ascites	1.01 (0.92–1.12)	1.02 (0.91–1.14)	0.82 (0.40–1.70)
Prior to tx no varices	1	1	1
Variceal no bleeding	0.97 (0.87–1.09)	0.95 (0.84–1.08)	1.16 (0.48–2.81)
Variceal bleeding	0.98 (0.87–1.11)	0.96 (0.83–1.10)	**2.44 (1.06–5.58)***
Time on the waiting list (HR for increase of 100)	0.98 (0.94–1.01)	0.98 (0.94–1.02)	1.05 (0.91–1.21)
Donor age (HR for increase of 10)	**1.05 (1.02–1.09)***	**1.06 (1.03–1.10)***	0.94 (0.70–1.25)
Liver CIT (HR for increase of 100)	**1.06 (1.03–1.09)***	**1.06 (1.02–1.09)***	1.13 (0.92–1.39)

CI, confidence interval; CIT, cold ischaemia time; HR, hazard ratio; RRT, renal replacement therapy; tx, transplant.

The final model included all clinically relevant variables. Significant differences are highlighted in bold numbers.

*$P < 0.05$.

†No deaths were recorded among patients with hypertension receiving CLKT.

reduced post-transplant patient survival that confirm how the baseline liver disease affects the outcome of patients undergoing LTA [28]. Moreover, we confirmed the negative role of liver graft quality on the outcome of LTA patients, in particular older donor age and prolonged CIT confirm to be factors that negatively affect patient and graft survival, probably linked to the severe ischaemia reperfusion injury suffered by these organs [29].

Few studies have analysed liver graft survival following CLKT compared with LTA [6,30–32]. We observed an advantage for composite outcome of patient and long-term liver graft survival following transplantation only for patients undergoing RRT at time of transplantation receiving CLKT. No differences were detected for death censored liver graft survival in any of KDIGO stages and RRT, suggesting, in accordance with patient survival results, that the prevalence of liver graft failure in LTA when on RRT is more correlated with patient mortality than to liver graft dysfunction itself. The present results are consistent with one of the larger studies on CLKT where a significant decrease of liver graft loss occurred in recipients of CLKT in comparison to LTA [30]. Less positive results have been reported by others [6,31]. Factors associated to increased risk of graft loss are mainly related to the aetiology of cirrhosis such as the HCV infection, the severity of liver disease, that is higher bilirubin level, and to the ischaemia suffered by the graft, in particular grafts from older donors. Polycystic disease, otherwise, often associated with less severe liver disease, was associated with superior graft survival and this further confirm the pivotal role of liver disease aetiology on patient outcome [33], amongst other known donor characteristics, such as donor age and CIT [29].

There are several limitations of this study that may affect the interpretability of these data. As a retrospective study where data input comes from different National centres, data were not collected for the specific aim of this study hence certain amount of missing data reduces the power of statistical analysis. Unfortunately, some data on renal function prior to transplantation was lacking. For example, data for length of dialysis pretransplantation,

data on pretransplant AKI and delayed graft function post-transplantation were missing. The estimation of renal function for these patients may be questioned because data are based on a single pretransplant measurement of serum creatinine, and inaccuracy of serum creatinine in estimating renal filtration rate in liver disease patients. The exact cause of kidney disease was not always accurately reported and the diagnosis of HRS was also not always available. Data are also missing regarding long-term dialysis status post-transplantation, whereas only serum creatinine values were available. Immunosuppressive medications, such as induction therapy, therapeutic levels of CNI and delayed introduction of CNI immediately post-transplantation were also incomplete. Important limitations regard the small number of CLKT patients. Because of this, a confounder-adjusted comparisons or methods for causal inference were not used and cautions in overinterpret results may be considered.

However as study of varied transplant units across the UK with different policies and protocols, this study represents a real world assessment of CLKT practice, in terms of allocation of the organs and national allocation policy was followed. It is somewhat concerning that a number of patients with elevated eGFR (45–59 ml/min/1.73 m^2) were listed and received CLKT, and this merits further investigation. In the UK the allocation system does not give any priority to patient's with a prior liver transplant. It is noteworthy that both in the United States and Eurotransplant program those patients undergo LTA with borderline renal function are prioritized to receive priority renal transplant within the first year [34,35]. This pragmatic approach enables selecting the group of patients who do not demonstrate renal function recovery, fair allocation of organs based on actual need than perceived demand for a combined simultaneous organ transplant and furthermore opens the avenues for living donor renal transplant options [36]. Interestingly, the paediatric transplant community is adopting a similar approach of a sequential rather than simultaneous approach perhaps it important to revisit the listing criteria for CLKT in the adult population.

In conclusion, this is the first study based on a national European registry focused on CLKT. Our primary observations highlight equivalent outcomes in terms of patient and graft survival and renal function post-transplant for patients undergoing LTA or CLKT when stratified by stages of renal function prior to transplantation. These data suggest that the only patients that benefit from CLKT in terms of patient and graft survival are those already receiving RRT prior to transplant. For patients who are not on RRT receiving LTA did not show reduced survival and or worse post-transplant renal function. The aetiology of liver disease seems to better address the decision process, as this strongly influences the aetiology of renal dysfunction and helps to predict post-transplant recovery of renal function. These results confirm the importance of single patient evaluation, in particular when comorbidities are existing. For those patients with renal dysfunction the decision to list for CLKT rather than LTA appear to be opportunistic as both organs can be transplanted with the kidney as an insurance against future native dysfunction. This study demonstrates that this is unnecessary and actually results in significantly longer wait times for a liver transplant. In addition, it appears that this approach will result in unnecessary kidney transplantation and reduce organ utilization. This has an even greater effect on beneficent and utilitarian organ allocation as donors of CLKT tend to be younger. It may be that a scheme of kidney after liver transplant for those who require it would be a more equitable and effective approach. To better define the indications for CKLT further prospective validation studies are proposed as these may allow better allocation and utilization.

Authorship

FT designed and performed the study, collected and analysed the data, and wrote the paper. APM designed and performed the study, and wrote the paper. IU critically revised the paper. PN performed the statistical review. NI critically revised and edited the paper. MG critically revised and edited the paper. JF critically revised the paper. DFM critically revised the paper. SB critically revised the paper. GL critically revised the paper. PM critically revised the paper. MTPRP critically revised and edited the paper.

Funding

The authors have declared no funding.

Conflicts of interest

The authors of this manuscript have no conflicts of interest to disclose as described by *Transplant International*.

Acknowledgements

The authors acknowledge additional statistical support from James Hodson for the advice and support in

preparation, statistical analysis and interpretation of the manuscript. We also thank the NHSBT data unit; the Liver advisory board for sanctioning the study; the ELITA and ERA-EDTA for travel award and the Euro-liver Foundation.

REFERENCES

1. Nadim MK, Sung RS, Davis CL, *et al.* Simultaneous liver-kidney transplantation summit: current state and future directions. *Am J Transplant* 2012; **12**: 2901.
2. Gonwa TA, Jennings L, Mai ML, Stark PC, Levey AS, Klintmalm GB. Estimation of glomerular filtration rates before and after orthotopic liver transplantation: evaluation of current equations. *Liver Transpl* 2004; **10**: 301.
3. Gonwa T, Klintmalm G, Levy M, Jennings L. Impact of pretransplant renal function on survival after liver transplantation. *Transplantation* 1995; **59**: 361.
4. Nair S, Verma S, Thuluvath PJ. Pretransplant renal function predicts survival in patients undergoing orthotopic liver transplantation. *Hepatology* 2002; **35**: 1179.
5. Campbell MS, Kotlyar DS, Brensinger CM, *et al.* Renal function after orthotopic liver transplantation is predicted by duration of pretransplantation creatinine elevation. *Liver Transpl* 2005; **11**: 1048.
6. Locke JE, Warren DS, Singer AL, *et al.* Declining outcomes in simultaneous liver-kidney transplantation in the MELD era: ineffective usage of renal allografts. *Transplantation* 2008; **85**: 935.
7. Tanriover B, Mejia A, Weinstein J, *et al.* Analysis of kidney function and biopsy results in liver failure patients with renal dysfunction: a new look to combined liver kidney allocation in the post-MELD era. *Transplantation* 2008; **86**: 1548.
8. Levin A, Stevens P, Bilous R. Kidney disease: improving global outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int Suppl* 2013; (Suppl. 3):1.
9. Levey AS, Bosch JP, Lewis JB, Greene T. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. *Ann Intern Med* 1999; **130**: 461.
10. Ojo AO, Held PJ, Port FK, *et al.* Chronic renal failure after transplantation of a nonrenal organ. *N Engl J Med* 2003; **349**: 931.
11. Heinze G, Dunkler D. Five myths about variable selection. *Transpl Int* 2017; **1**: 6.
12. Cassuto JR, Reese PP, Sonnad S, *et al.* Wait list death and survival benefit of kidney transplantation among nonrenal transplant recipients. *Am J Transplant* 2010; **10**: 2502.
13. Srinivas TR, Stephany BR, Budev M, *et al.* An emerging population: kidney transplant candidates who are placed on the waiting list after liver, heart, and lung transplantation. *Clin J Am Soc Nephrol* 2010; **5**: 1881.
14. Nadim MK, Davis CL, Sung R, Kellum JA, Genyk YS. Simultaneous liver-kidney transplantation: a survey of US transplant centers. *Am J Transplant* 2012; **12**: 3119.
15. Ruiz R, Kunitake H, Wilkinson AH, *et al.* Long-term analysis of combined liver and kidney transplantation at a single center. *Arch Surg* 2006; **141**: 735.
16. Ruebner R, Goldberg D, Abt PL, *et al.* Risk of end-stage renal disease among liver transplant recipients with pretransplant renal dysfunction. *Am J Transplant* 2012; **12**: 2958.
17. Moreno-Gonzalez E, Meneu-Diaz JC, Garcia I, *et al.* Simultaneous liver-kidney transplantation for adult recipients with irreversible end-stage renal disease. *Arch Surg* 2004; **139**: 1189.
18. Schmitt TM, Kumer SC, Al-Osaimi A, *et al.* Combined liver-kidney and liver transplantation in patients with renal failure outcomes in the MELD era. *Transpl Int* 2009; **22**: 876.
19. Brennan TV, Lunsford KE, Vagefi PA, Bostrom A, Ma M, Feng S. Renal outcomes of simultaneous liver-kidney transplantation compared to liver transplant alone for candidates with renal dysfunction. *Clin Transplant* 2015; **29**: 34.
20. Lunsford KE, Bodzin AS, Markovic D, *et al.* Avoiding futility in simultaneous liver-kidney transplantation. Analysis of 331 consecutive patients listed for dual organ replacement. *Ann Surg* 2017; **265**: 1016.
21. Campistol JM, Sacks SH. Mechanisms of nephrotoxicity. *Transplantation* 2000; **69**(Suppl. 10): S5.
22. 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? *Am J Transplant* 2006; **6**: 2651.
23. Zand MS, Orloff MS, Abt P, *et al.* High mortality in orthotopic liver transplant recipients who require hemodialysis. *Clin Transplant* 2011; **25**: 213.
24. Hanish SI, Samaniego M, Mezrich JD, *et al.* Outcomes of simultaneous liver/kidney transplants are equivalent to kidney transplant alone: a preliminary report. *Transplantation* 2010; **90**: 52.
25. Hibi T, Sageshima J, Molina E, *et al.* Predisposing factors of diminished survival in simultaneous liver/kidney transplantation. *Am J Transplant* 2012; **12**: 2966.
26. Simpson N, Cho YW, Cicciarelli JC, Selby RR, Fong T-L. Comparison of renal allograft outcomes in combined liver-kidney transplantation versus subsequent kidney transplantation in liver transplant recipients: analysis of UNOS database. *Transplantation* 2006; **82**: 1298.
27. European Association for the Study of the Liver. EASL recommendations on treatment of hepatitis C 2018. *J Hepatol* 2018; **69**: 461.
28. Klein KB, Stafinski TD, Menon D. Predicting survival after liver transplantation based on pre-transplant MELD score: a systematic review of the literature. *PLoS One* 2013; **8**: e80661.
29. Feng S, Goodrich NP, Bragg-Gresham JL, *et al.* Characteristics associated with liver graft failure: the concept of a donor risk index. *Am J Transplant* 2006; **6**: 783.
30. Martin EF, Huang J, Xiang Q, Klein JP, Bajaj J, Saeian K. Recipient survival and graft survival are not diminished by simultaneous liver-kidney trans plantation: an analysis of the united network for organ sharing database. *Liver Transpl* 2012; **18**: 914.
31. Creput C, Durrbach A. Incidence of renal and liver rejection and patient survival rate following combined liver and kidney transplantation. *Am J Transplant* 2003; **15**: 348.
32. Becker T, Nyibata M, Lueck R, *et al.* Results of combined and sequential liver-

kidney transplantation. *Liver Transpl* 2003;**9**: 1067.
33. Coquillard C, Berger J, Daily M, Shah M, Mei X, Marti F. Combined liver – kidney transplantation for polycystic liver and kidney disease: analysis from the United Network for Organ Sharing dataset. *Liver Int* 2016; **36**: 1018.
34. Eurotransplant Manual© – version 5.1; October 2016; page 34. *https://www.eurotransplant.org/cms/.
35. Simultaneous Liver Kidney (SLK) Allocation Policy; pages 73–74. *https://optn.transplant.hrsa.gov/media/1192/0815-12_SLK_Allocation.pdf.
36. Gonwa TA, McBride MA, Mai ML, Wadei HM. Kidney transplantation after previous liver transplantation: analysis of the organ procurement transplant network database. *Transplantation* 2011; **92**: 31.