

ORIGINAL ARTICLE

Split liver transplant recipients do not have an increased frequency of acute kidney injury

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Introduction

The growing discrepancy between supply and demand for liver transplantation has necessitated the search for measures to increase the donor pool [1]. Split liver transplantation (SLT) is recommended as one such strategy, allowing usually both an adult recipient and paediatric recipient to benefit from a single organ [2,3]. In the UK, 15% of all deceased donor liver transplants now use split livers [4]. However, in other countries such as the USA, SLT has been less widely accepted because of inferior graft and recipient survival compared with full-size donation after brain death liver transplantation (FSLT) [5,6]. Larger volume centres report acceptable outcomes [7–9]. Nevertheless, concerns remain regarding the ethical implications of benefiting a second recipient by increasing the morbidity and mortality of the first [10].

Summary

Small series have suggested that split liver transplantation (SLT) has an increased frequency of peri-operative acute kidney injury (AKI). However, the optimal donor selection in this setting could have a favourable impact on renal outcomes. This was a retrospective single-centre study of 76 adults who underwent SLT (right extended lobe) and 301 adults who underwent elective full-size donation after brain death liver transplantation (FSLT). SLT recipients were less likely than unmatched FSLT recipients to develop AKI (\geq stage 1 KDIGO criteria) (40.3% vs. 56.1%, $P = 0.016$) and had a reduced frequency of renal replacement therapy (11.8% vs. 21.9%, $P = 0.049$). In 72 pairs of SLT patients and propensity score-matched FSLT controls the incidence of AKI was not significantly different (40.3% vs. 47.2%, $P = 0.473$). However, SLT patients were less likely to require renal replacement therapy (11.1% vs. 23.6%, $P = 0.078$; adjusted OR 0.32; 95% CI 0.11–0.87, $P = 0.026$). There was no association between SLT and the development of chronic kidney disease (eGFR < 60 ml/min/1.73 m², log rank $P = 0.534$). In conclusion, SLT is not associated with an increased frequency of AKI. These observations support the postulation that the optimal donor status of SLT may result in less graft injury with renal sparing effects.

Acute kidney injury (AKI) is a major cause of morbidity and mortality after liver transplantation [11–14]. In addition to the prolonged recovery period and greater financial cost, AKI is increasingly recognised as an independent risk factor for short term mortality in the Intensive Care setting [11,12,14,15]. Moreover, AKI can cause permanent structural damage, with progressive tubulo-interstitial fibrosis and long-term implications for renal function [13,16–18]. Liver transplant recipients with postoperative acute renal failure are twice as likely to develop chronic kidney disease, which is associated with a 5-fold increased risk of death [13].

The major reported morbidity of SLT relates to biliary and vascular graft complications [6]. Renal outcomes after SLT have been less well described. In two small studies totalling 26 SLT recipients greater renal dysfunction was demonstrated during the immediate post-operative period

when SLT recipients and FSLT recipients were compared [19,20]. Yet, the cohorts were not ideally matched, and the observation was in the setting of an increased rate of graft-related complications, including the need for re-operation and sepsis. We have previously postulated that hepatic ischaemia–reperfusion injury may play a critical role in the pathogenesis of AKI following donation after circulatory death (DCD) liver transplantation [14]. Following on from this, we hypothesised that in SLT the optimal donor selection could have a beneficial renal sparing effect.

Our aim was to compare renal outcomes following SLT with FSLT patients.

Methods

This was a retrospective single-centre study of 76 consecutive adults who underwent SLT with a right extended lobe graft (segments I and IV–VIII, split *ex situ*) and 301 consecutive patients who underwent FSLT for chronic liver disease between January 2007 and March 2011. The implantation technique was piggyback in all cases. No SLT or FSLT patient had a previous history of renal transplantation, and no patient received a combined liver–kidney transplant. In view of the differing baseline clinical characteristics of the two cohorts, a detailed comparison was performed of 72 SLT patients and a control group of 72 FSLT patients matched by propensity risk score (PRS).

Data were collected on the following donor and graft variables: age, gender, height, aspartate aminotransferase (AST), inotropes, warm ischaemic time and cold ischaemic time. Donor risk index (DRI) was calculated as previously described [21]. An allograft biopsy was performed immediately after reperfusion (time zero) in 28 SLT patients (36.4%) and 217 FSLT patients (72.1%) and was graded by an independent histopathologist.

The following recipient characteristics at the time of admission for transplantation were recorded: age, gender, ethnicity, additional co-morbidity including need for haemodialysis, international normalised ratio (INR), serum bilirubin, serum creatinine, serum sodium and presence of ascites (past history or ultrasonographic evidence). Refractory ascites was defined according to the International Ascites Club criteria [22,23]. The MELD (Model for End-Stage Liver Disease) score was determined [24]. The UK Score for Patients with End-Stage Liver Disease (UKELD), a recently devised scoring system that incorporates serum sodium in addition to the MELD variables that is now used routinely in the UK to prioritise graft allocation, was also calculated [25]. Intra-operative red cell concentrate (RCC), fresh-frozen plasma (FFP) and platelet transfusion requirements, and need for intra-operative inotropes (noradrenaline/adrenaline infusion at time of admission to the Intensive Care Unit). Docu-

mented peri-operative variables (following transplantation but prior to hospital discharge) were peak serum AST, peak serum creatinine, need for renal replacement therapy and sepsis. Renal function was then recorded at 1, 3, 6, 9, 12, 18, 24, 30, 36, 42 and 48 months following transplantation. Patients receiving renal replacement therapy during the immediate post-operative period were given a peak serum creatinine of three times baseline if the actual recorded value was less [26]. Similarly, beyond the peri-operative period patients on haemodialysis were given an estimated glomerular filtration rate of 15 ml/min/1.73 m² [27].

Peri-operative acute renal dysfunction (following transplantation but prior to hospital discharge) was defined according to the KDIGO criteria for acute kidney injury (AKI) and recent Working Party proposal: a rise in serum creatinine by $\geq 26.5 \mu\text{M}$ in <48 h and/or peak serum creatinine ≥ 1.5 times the baseline level [28,29]. Stage 1, AKI was defined as a rise in serum creatinine by $\geq 26.5 \mu\text{M}$ in <48 h and/or peak serum creatinine 1.5–1.9 times baseline; stage 2, AKI was defined as peak serum creatinine 2.0–2.9 times baseline; stage 3, AKI was defined as peak serum creatinine ≥ 3.0 times baseline and/or increase in serum creatinine $\geq 353.6 \mu\text{M}$ and/or renal replacement therapy [28]. The main measure of renal function thereafter was estimated glomerular filtration rate (eGFR), determined using the Modification of Diet in Renal Disease (MDRD) Study 4-variable equation ($\text{eGFR} = 186 \times \text{creatinine}(\text{mg}/\text{dl})^{-1.154} \times \text{age}(\text{years})^{-0.203} \times 1.212$ (if black) $\times 0.742$ (if female) [30]. Chronic kidney disease was defined as eGFR <60 ml/min/1.73 m² on at least two occasions and sustained from 6 months post-transplant onwards: stage 3, stage 4 and stage 5 chronic kidney disease were defined as eGFR 30–59 ml/min/1.73 m², 15–29 ml/min/1.73 m², and <15 ml/min/1.73 m² or on dialysis, respectively [27].

Immunosuppression was noted and calcineurin inhibitor trough levels at day-7, day-30 and 12-months. Standard immunosuppression was tacrolimus aiming for a trough level of 8–10 within the first 3 months of transplantation, azathioprine and reducing dose steroid discontinued by 3 months. Renal sparing immunosuppression consisted of half dose tacrolimus aiming for a trough level of 5–8, mycophenolate and reducing dose steroid discontinued by 3 months. In a single patient (FSLT recipient), renal sparing with delayed introduction of calcineurin inhibitor and interleukin-2 receptor antagonist cover was employed. No patient received sirolimus. All immunosuppression choices were Physician and Surgeon dependent and made either prior to transplantation or in the event of complications including AKI. The tacrolimus trough levels on day 30 (renal

sparing, 5.9 (2.4) µg/l; no renal sparing, 7.7 (4.1) µg/l, mean (SD); $P = 0.008$) were lower in the patients discharged on renal sparing immunosuppression, but not at 12 months post-transplant (renal sparing, 6.9 (2.4) µg/l; no renal sparing, 6.1 (2.8) µg/l, mean (SD); $P = 0.161$) ($P < 0.025$ considered significant).

Hepatic ischaemia–reperfusion injury minimising strategies were not used in any donor. The decision to administer intravenous n-acetylcysteine to the recipient was Surgeon dependent and in all cases precipitated by clinical evidence of initial poor graft function such as hemodynamic instability, lactic acidosis and/or high serum AST.

Statistical analyses

Matching patients by PRS is a recognised method of controlling for selection bias [31,32]. A PRS for the allocation of a split liver over a full-size liver amongst the 377 whole liver transplant recipients (single organ) in our unit during the time period studied was generated by nonparsimonious multiple logistic regression. This model included all recipient variables of clinical relevance to the outcome measure post-transplant AKI (age, gender, ethnicity, diagnosis, BMI, diabetes mellitus, hypertension, ascites, eGFR, MELD and waiting list time). The nearest available matching on the

Table 1. Clinical characteristics of split liver transplant and full-size liver transplant recipients at time of hospital admission for transplantation.

	Pre-match		P value	Post-match		P value	Effect size
	SLT (no:76)	FSLT (no:301)		SLT (no:72)	FSLT (no:72)		
Age (years)	51.9 (13.5)	52.7 (11.0)	0.578	52.0 (13.4)	52.2 (11.4)	0.928	0.016
Gender (male:female)	1:1	1.9:1	0.011	0.9:1	1.1:1	0.839	0.056
Ethnicity:							
Caucasian	68 (89.5)	263 (87.4)		64 (88.9)	62 (86.1)		0.085
Asian	6 (7.9)	28 (9.3)		6 (8.3)	6 (8.3)		0.000
Other	2 (2.6)	10 (3.3)	0.88	2 (2.8)	4 (5.6)	0.494	0.140
Height (cm)	169 (10)	170 (14)	0.8	169 (10)	169 (10)	0.950	0.000
Body mass index	25.2 (4.6)	27.5 (5.0)	<0.001	25.2 (4.6)	25.1 (4.1)	0.853	0.023
Aetiology of liver disease:							
Alcoholic cirrhosis	8 (10.5)	74 (24.6)		7 (9.7)	8 (11.1)		0.046
Hepatitis C cirrhosis	14 (18.4)	61 (20.3)		14 (19.4)	17 (23.6)		0.102
Primary biliary cirrhosis	14 (18.4)	41 (13.6)		14 (19.4)	14 (19.4)		0.000
Primary sclerosing cholangitis	13 (17.1)	25 (8.3)		12 (16.7)	13 (18.1)		0.037
NASH cirrhosis	6 (7.9)	20 (6.6)		6 (8.3)	7 (9.7)		0.049
Hepatitis B cirrhosis	2 (2.6)	15 (5.0)		2 (2.8)	3 (4.2)		0.076
Autoimmune hepatitis	4 (5.3)	10 (3.3)		4 (5.6)	3 (4.2)		0.065
Other	15 (19.7)	55 (18.3)	0.077	13 (18.1)	7 (9.7)	0.273	
Hepatocellular carcinoma	15 (19.7)	76 (25.2)	0.316	14 (19.4)	14 (19.4)	1.000	0.000
MELD score	17 (8)	16 (7)	0.24	16 (7)	17 (8)	0.440	0.127
UKELD	52 (7)	51 (6)	0.577	51 (7)	52 (7)	0.460	0.133
Regraft	4 (5.3)	12 (4.0)	0.408	0 (0)	0 (0)		0.000
Measures of renal function							
Creatinine (µm)	81 (65–96)	85 (67–99)	0.201	80 (22)	82 (25)	0.654	0.085
eGFR (ml/min/1.73 m ²)	90 (40)	89 (34)	0.759	91 (41)	90 (34)	0.870	0.027
Sodium (mm)	138 (136–141)	138 (134–140)	0.144	138 (136–141)	137 (135–140)	0.626	0.067
Haemodialysis	0 (0)	0 (0)	1	0 (0)	0 (0)	NA*	0.000
Ascites	33 (43.4)	176 (58.5)	0.018	32 (44.4)	37 (51.4)	0.473	0.140
Refractory ascites	7 (9.2)	60 (19.9)	0.029	6 (8.3)	10 (13.9)	0.424	0.179
Hepatorenal syndrome (type 2)	0 (0)	7 (2.3)	0.204	0 (0)	1 (1.4)	NA*	0.169
Co-morbidity							
Diabetes mellitus	13 (17.1)	74 (24.6)	0.167	12 (16.7)	15 (20.8)	0.648	0.105
Insulin-dependent diabetes	9 (11.8)	34 (11.3)	0.893	9 (12.5)	8 (11.1)	1.000	0.040
Hypertension	13 (17.1)	42 (14.0)	0.487	12 (16.7)	11 (15.3)	1.000	0.038
Waiting list time (days)	59 (22–173)	71 (25–185)	0.638	59 (25–174)	53 (26–167)	0.904	0.000
Followup time (days)	962 (507–1323)	880 (449–1364)	0.894	932 (445–1271)	666 (314–1314)	0.373	0.000

Values expressed as mean (standard deviation), median (interquartile range) and number (per cent) where appropriate. Follow-up time defined as duration from transplant to present day (patients not censored at time of death or regraft).

*P value incalculable due to the small sample size.

Significant values are shown in bold.

estimated PRS method was used to construct the control group with a caliper width of 0.2 of the standard deviation of the logit of the propensity score [31,33]. Balance was achieved between the SLT and FSLT groups on the recognised confounders only when the single statistically significant interaction term was excluded from the model (Table 1) [34].

Pre-PRS matching, normally distributed continuous variables and nonparametric continuous variables were compared using the Student's t-test and Mann-Whitney test, respectively. Chi-squared analysis or Fisher's exact test were used for comparison of categorical data. After PRS matching, the paired t-test was used with nonparametric variables transformed into their natural logarithms and the McNemar test's for dichotomous variables. Survival was estimated using Kaplan-Meier plots with log-rank test for differences. Cumulative incidence of chronic kidney disease was estimated using the Kaplan-Meier method. Variables associated with AKI and renal replacement therapy were assessed in the propensity score-matched patients using backward sequential logistic regression of clinically relevant variables. SLT status was forced into the final model to determine any association with renal dysfunction. To account for the superior donor quality of the SLT grafts, the relationship between SLT and renal outcomes was then determined in patient subgroups, stratified according to the median values of the donor indices that differed most between SLT and FSLT recipients. In these logistic regression models, SLT status and the statistically significant variables in the entire PRS-matched cohort were included simultaneously. Cox proportional hazards analysis was used to examine the relationship between SLT and chronic kidney disease. $P < 0.05$ was considered statistically significant unless otherwise stated.

Data were analysed using the SPSS (SPSS Inc., Chicago, IL, USA) 18 package. All values are expressed as mean and standard deviation (SD), and median and interquartile range (IQR) as appropriate.

Results

Unmatched patients

Baseline clinical characteristics of all SLT and unmatched FSLT patients are outlined in Table 1. SLT recipients were more likely to be female ($P = 0.011$), to have cholestatic disease (SLT, 38.2%; FSLT, 24.9%; $P = 0.021$) and had a lower BMI ($P < 0.001$). Serum creatinine ($P = 0.201$) and serum sodium ($P = 0.144$) were similar for both groups. SLT patients were less likely to have refractory ascites ($P = 0.029$), although the prevalence of type 2 hepatorenal syndrome was the same ($P = 0.204$). The frequency of an eGFR <60 , 60–89 and ≥ 90 ml/min/1.73 m² was 13.9%, 47.2% and

38.9% for SLT patients, respectively, and 18.3%, 43.9% and 37.9% for FSLT patients ($P = 0.659$).

The overall incidence of AKI in SLT recipients ($n = 76$) was 43.4%, and in FSLT recipients ($n = 301$) was 55.8% ($P = 0.053$). When regrafts were excluded SLT patients ($n = 72$) were less likely than FSLT patients ($n = 289$) to develop AKI (SLT, 40.3%; FSLT, 56.1%; $P = 0.016$). SLT recipients demonstrated a lower frequency of renal replacement therapy (SLT, 11.8%; FSLT, 21.9%, $P = 0.049$).

PRS-matched patients

In view of the differing baseline clinical characteristics of the two groups, more detailed analyses were then per-

Table 2. Donor, graft and intra-operative characteristics of split liver transplant and full-size liver transplant recipients.

	SLT (n:72)	FSLT (n:72)	P value
Donor characteristics			
Age (years)	28.5 (9.7)	48.4 (14.7)	<0.001
Gender (male: female)	1.6:1	0.8:1	0.015
Height (cm)	175 (12)	167 (9)	<0.001
AST (u/l)	38 (21–64)	42 (24–85)	0.664
Inotrope	58 (80.6)	63 (88.7)	0.332
Graft characteristics			
>30% macrovesicular steatosis	0/26 (0)	3/54 (5.6)	NA*
>30% microvesicular steatosis	4/26 (15.4)	10/54 (18.5)	0.625
Cold ischaemic time (hours)	9.2 (1.8)	8.4 (2.3)	0.056
Recipient warm ischaemic time (mins)	38.9 (8.6)	40.5 (6.2)	0.246
Donor risk index	1.75 (1.55–1.83)	1.43 (1.21–1.71)	<0.001
Donor risk index excluding split status	1.14 (1.02–1.20)	1.43 (1.21–1.71)	<0.001
Recipient characteristics			
RCC transfusion (units)	2 (0–3)	2 (0–3)	0.653
FFP transfusion (units)	6 (3–10)	7 (4–10)	0.182
Platelets transfusion (units)	5 (0–10)	5 (0–10)	0.594
Inotropes	51 (70.8)	50 (69.4)	1.000
N-acetylcysteine	1 (1.4)	5 (6.9)	0.219

Values expressed as mean (standard deviation), median (interquartile range) and number (per cent) where appropriate.

*P value incalculable due to the small sample size.

Significant values are shown in bold.

formed comparing the renal outcomes of SLT patients ($n = 72$) with a PRS-matched control group of FSLT patients ($n = 72$). The groups were matched with regard to recipient characteristics (Table 1). Donor and graft characteristics are outlined in Table 2. When compared with FSLT patients, the SLT recipients had a younger donor age ($P < 0.001$), a trend towards a longer cold ischaemic time ($P = 0.056$) but similar recipient warm ischaemic time ($P = 0.246$). DRI excluding split status was lower in the SLT group ($P < 0.001$).

There was no difference in the proportion of SLT and FSLT patients who were prescribed renal sparing immunosuppression immediately post-transplant (SLT, 13.9%; FSLT, 18.1%, $P = 0.648$) or at time of hospital discharge (SLT, 24.3%; FSLT, 34.3%, $P = 0.248$). Tacrolimus trough levels at day 7 (SLT, 7.6 (3.9) $\mu\text{g/l}$; FSLT, 8.1 (4.2) $\mu\text{g/l}$, mean (SD); $P = 0.423$), day 30 (SLT, 7.2 (4.0) $\mu\text{g/l}$; FSLT, 7.1 (3.4) $\mu\text{g/l}$, mean (SD); $P = 0.878$) and 12 months (SLT, 6.1 (2.7) $\mu\text{g/l}$; FSLT, 6.5 (2.6) $\mu\text{g/l}$, mean (SD); $P = 0.330$) were similar ($P < 0.017$ considered significant).

Nonrenal morbidity and graft and patient survival

During the immediate postoperative period, the median peak serum AST was 1156 (IQR 757–1675) u/l for SLT recipients and 1124 (IQR 699–2239) u/l for FSLT controls ($P = 0.828$). The frequency of re-laparotomy for bleeding (SLT, 1.4%; FSLT, 4.2%; $P = 0.625$), primary nonfunction (SLT, 1.4%; FSLT, 1.4%; $P = 1.000$), hepatic artery thrombosis (SLT, 1.4%; FSLT, 0%; P value incalculable), sepsis (SLT, 16.7%; FSLT, 13.9%; $P = 0.791$) and biliary complications (SLT, 5.6%; FSLT, 5.6%; $P = 1.000$) were comparable in both groups. The estimated 1-year and 3-year graft survival were 87.3% and 85.5% for the SLT patients respectively, and 92.6% and 90.4% for the FSLT controls (log rank $P = 0.292$).

Duration of ITU stay (SLT, 3 (2–4) days; FSLT, 3 (2–5) days, median (IQR); $P = 0.300$) and hospital stay (SLT, 11 (9–14) days; FSLT, 11 (9–18) days, median (IQR); $P = 0.062$) were comparable for the two cohorts. An equal proportion of SLT patients (95.8%) and FSLT patients (95.8%) survived to hospital discharge ($P = 1.000$). Estimated 1- and 3-year patient survival were 90.0% and 88.2% for SLT patients, respectively, and 94.0% and 91.8% for FSLT controls (log rank $P = 0.400$).

Peri-operative renal function

Baseline serum creatinine ($P = 0.654$), eGFR ($P = 0.870$), serum sodium ($P = 0.626$), and the prevalence of ascites ($P = 0.473$), refractory ascites ($P = 0.424$) and type 2 hepatorenal syndrome (P value incalculable) were the same for both SLT and FSLT groups (Table 1).

Immediately after transplantation the median peak perioperative serum creatinine was 113 (IQR 85–177) μM for SLT patients and 116 (IQR 81–223) μM for FSLT controls ($P = 0.415$). The median peak peri-operative change in serum creatinine from baseline was +27.0 (IQR 11.9–145.1) % for SLT patients and +43.6 (IQR 6.8–197.3) % for FSLT patients ($P = 0.721$). 40.3% of SLT patients developed AKI compared with 47.2% of FSLT controls ($P = 0.473$, Fig. 1).

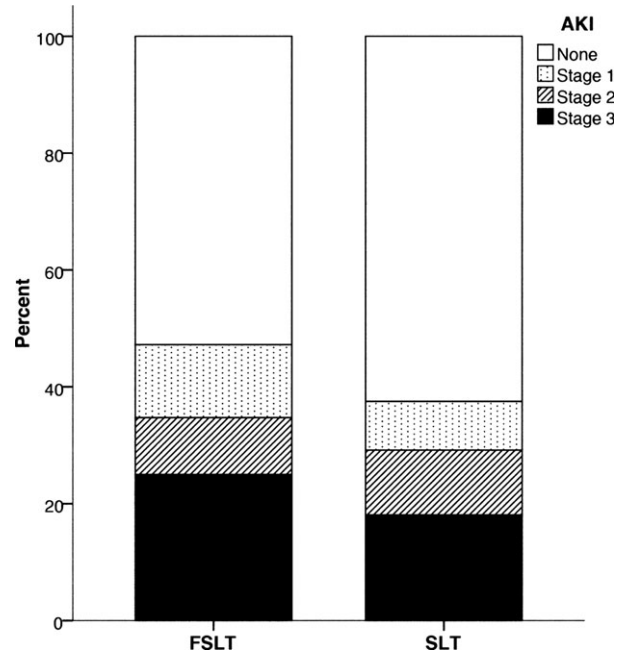


Figure 1 Stacked bar graph demonstrating the proportion of split liver transplant recipients (SLT) and full-size liver transplant recipients (FSLT) who developed acute renal dysfunction during the immediate postoperative period. Renal dysfunction defined according to KDIGO criteria as: Stage 1, rise in serum creatinine by $\geq 26.5 \mu\text{M}$ in < 48 h and/or peak serum creatinine 1.5–1.9 times baseline; Stage 2, peak serum creatinine 2.0–2.9 times baseline; Stage 3, peak serum creatinine ≥ 3.0 times baseline and/or increase in serum creatinine $\geq 353.6 \mu\text{M}$ and/or renal replacement therapy. $P = 0.743$.

Table 3. Logistic regression analysis of variables associated with peri-operative acute kidney injury after first elective donation after brain death liver transplantation in propensity score-matched patients.

	OR	95% CI	<i>P</i> value
Pretransplant refractory ascites	3.96	1.15–13.69	0.030
≥ 5 units RCC intra-operative	5.01	1.63–15.40	0.005
Log peak postoperative AST (u/l)	2.11	1.25–3.54	0.005
SLT	0.76	0.37–1.56	0.454

Reference group (relative risk 1.00): No refractory ascites, 0–4 units RCC intra-operative, FSLT recipient. Additional variables entered into the model: age, pretransplant eGFR, pretransplant MELD. Significant values are shown in bold.

Table 4. Logistic regression analysis of variables associated with renal replacement therapy after first elective donation after brain death liver transplantation in propensity score-matched patients.

	OR	95% CI	P value
Age (years)	1.06	1.01–1.12	0.023
≥5 units RCC intra-operative	6.04	1.89–19.31	0.002
Log peak postoperative AST (u/l)	2.14	1.12–4.10	0.022
SLT	0.32	0.11–0.87	0.026

Reference group (relative risk 1.00): 0–4 units RCC intra-operative, FSLT recipient.

Additional variables entered into the model: pretransplant eGFR, pretransplant MELD, pretransplant refractory ascites.

Significant values are shown in bold.

Table 5. Adjusted association between split liver transplantation and peri-operative renal outcomes (acute kidney injury and renal replacement therapy) in patient subgroups.

	No (%) with renal outcome	OR(95% CI)*	P value
Acute kidney injury			
Donor age <38 years	26 (34.7)	0.82 (0.23–2.94)	0.765
Donor age ≥38 years	37 (53.6)**	1.96 (0.56–6.84)	0.290
Donor risk index <1.60	32 (45.1)	0.58 (0.18–1.86)	0.360
Donor risk index ≥1.60	30 (42.9)	0.65 (0.22–1.95)	0.439
Donor risk index excluding split status <1.22	24 (32.9)	0.74 (0.20–2.74)	0.647
Donor risk index excluding split status ≥1.22	38 (55.9)***	3.11 (0.82–11.83)	0.097
Renal replacement therapy			
Donor age <38 years	6 (8.0)	2.05 (0.15–28.59)	0.593
Donor age ≥38 years	19 (27.5)**	0.32 (0.07–1.50)	0.148
Donor risk index <1.60	12 (16.9)	0.09 (0.01–1.05)	0.055
Donor risk index ≥1.60	13 (18.6)	0.29 (0.08–1.07)	0.062
Donor risk index excluding split status <1.22	7 (9.6)	0.54 (0.07–4.32)	0.564
Donor risk index excluding split status ≥1.22	18 (26.5)***	0.51 (0.12–2.32)	0.368

Cut-off values for subgroups were based on the median of the PRS-matched patients.

*Adjusted for refractory ascites, ≥5 units RCC intra-operative and log peak postoperative AST (u/l) when the renal outcome is acute kidney injury and adjusted for age (years), ≥5 units RCC intra-operative and log peak postoperative AST (u/l) when the renal outcome is renal replacement therapy.

**P < 0.05 for renal outcome in donor age ≥38 years vs. <38 years groups.

***P < 0.05 for renal outcome in donor risk index excluding split status ≥1.22 vs. <1.22 groups.

On multivariate analysis, there was no association between SLT and AKI (OR 0.76; 95% CI 0.37–1.56, P = 0.454, Table 3).

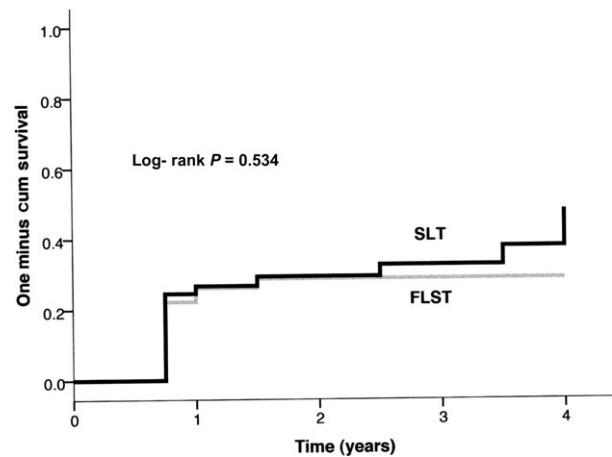


Figure 2 Cumulative incidence of stage 3–5 chronic kidney disease following liver transplantation subdivided into split liver transplantation recipients (SLT) and full-size liver transplantation recipients (FSLT).

Table 6. Cox regression analysis of variables associated with chronic kidney disease after first elective donation after brain death liver transplantation in propensity score-matched patients.

	OR	95% CI	P value
Age (years)	1.05	1.01–1.09	0.021
Pretransplant eGFR	0.99	0.97–1.00	0.080
SLT	1.18	0.59–2.36	0.649

Reference group (relative risk 1.00): FSLT recipient.

Additional variables entered into the model: pretransplant MELD, pretransplant diabetes mellitus, day 7 tacrolimus trough.

Significant values are shown in bold.

On univariate analysis, there was a trend towards less renal replacement therapy in the SLT group (SLT, 11.1%; FSLT, 23.6%, P = 0.078). The median renal replacement therapy duration was 19 (IQR 3–34) days for SLT patients and 6 (IQR 4–15) days for FSLT patients. On multivariate analysis, SLT patients were less likely to require renal replacement therapy (OR 0.32; 95% CI 0.11–0.87, P = 0.026, Table 4).

Given the superior donor quality of the SLT grafts, the relationship between SLT and renal outcomes was determined in patient subgroups, stratified according to the donor indices that differed most between SLT and FSLT recipients (Table 5). The frequency of renal outcomes was higher in patients who received an older donor liver (AKI, P = 0.022; renal replacement therapy, P = 0.002) and a higher DRI (excluding split status) graft (AKI, P = 0.006; renal replacement therapy, P = 0.009). When the patients were stratified based on these donor quality indices, SLT was no longer associated with a reduced risk of renal replacement therapy (donor age <38 years, P = 0.593; donor age ≥38 years,

$P = 0.148$; $\text{DRI} < 1.22$, $P = 0.564$; $\text{DRI} \geq 1.22$, $P = 0.368$). This suggests that donor quality may underlie the lower rate of renal replacement therapy in SLT recipients.

Long-term renal function post-transplant

By 1 month post-transplant the mean eGFR was similar in SLT and FSLT patients (SLT, 83 [35] ml/min/1.73 m²; FSLT, 81 (37) ml/min/1.73 m², mean (SD), $P = 0.688$). Furthermore, the mean change in eGFR by 12 months from baseline was no different for the two groups (SLT, -11.5 (29.2) %; FSLT, -13.7 (31.3) %, mean (SD), $P = 0.599$). The cumulative incidence of stage 3–5 chronic kidney disease by 3 years post-transplant was 32.5% and 28.7% for SLT and FSLT patients, respectively (log rank $P = 0.534$, Fig. 2). No SLT or FSLT patient fulfilled the criteria for severe chronic kidney (stage 4–5) during the follow-up period. On multivariate analysis, there was no association between SLT and CKD (HR 1.18; 95% CI 0.59–2.36, $P = 0.649$, Table 6).

Discussion

In this large contemporary single-centre study, we have examined in detail the renal consequences of SLT for the adult recipient. We have shown that SLT patients had a lower incidence of peri-operative AKI than FSLT patients transplanted in the same time period. Importantly, when compared with a well-matched FSLT cohort, demonstrating a similar rate of graft-related complications, the SLT group had at least equivalent renal outcomes. SLT recipients had a comparable frequency of AKI to PRS-matched FSLT controls, but were less likely to require renal replacement therapy.

AKI after liver transplantation is multifactorial in origin. Pretransplant neuro-humoral and circulatory derangement, and intrinsic chronic kidney disease, predisposes patients with end-stage liver failure to acute renal dysfunction [35]. Intra-operatively, hemodynamic insults including surgical technique and haemorrhage culminate in renal ischaemia, inflammation and injury [11,12,36]. Thereafter, the administration of a calcineurin inhibitor further compromises renal perfusion and function [37].

The role of the graft in the pathogenesis of AKI after liver transplantation is less well recognised. Hepatic ischaemia–reperfusion injury is accompanied by a systemic inflammatory response, which may cause AKI through hemodynamic mechanisms and direct tubular cell death [38–42]. Liver transplant recipients with ischaemia–reperfusion injury are more likely to develop peri-operative renal dysfunction and to require haemodialysis [43,44]. Moreover, the added donor warm ischaemic time and greater injury of DCD liver transplantation is associated with an increased frequency of AKI [14]. It follows that graft injury, by driving a

systemic inflammatory response, is a contributing factor in post-transplant AKI.

In SLT, the *ex situ* dissection prolongs the cold ischaemic time and potentially exposes the graft to additional warm ischaemia via manipulation [45]. Therefore, it might be anticipated that SLT grafts display greater ischaemia–reperfusion injury. On the other hand, SLT uses ideal quality organs sourced from optimal donors [5,46,47]. Younger age and lack of steatosis are known to have a favourable effect on hepatic ischaemia–reperfusion injury [48,49]. Other factors that may influence renal outcomes in SLT include the reported increased rate of hepatic artery thrombosis, biliary complications and sepsis, and small for size syndrome [6,19,50–52].

In this study, we have shown that when SLT recipients were compared with well-matched FSLT controls the immediate postoperative course was similar, including the frequency of graft-related complications. In this setting, the SLT group did not demonstrate an increased rate of AKI. Indeed, there was a suggestion of reduced renal injury considering the patient numbers, with a lower rate of renal replacement therapy. Where SLT and matched FSLT patients differed was in donor selection. SLT donors were younger and had a lower DRI if the split status was excluded. AKI was more frequent in recipients of grafts from older donors and with a higher DRI. Moreover, when patients were stratified into subgroups according to these donor quality indices, SLT was no longer associated with a reduced risk of renal replacement therapy. Such observations support the postulation that the optimal donor status of SLT may result in less graft injury with renal sparing effects.

It is noteworthy that the definition of AKI applied here has not been used previously in assessing renal injury after liver transplantation and may have influenced the results. We defined AKI as recommended by the recently issued guidelines by KDIGO and the Acute Dialysis Quality Initiative-International Ascites Club Working Party [28,29]. The frequency of acute renal injury and failure in our FSLT recipients when defined according to the RIFLE criteria was comparable to other reports [11,12].

Increasing severity of AKI is associated with increasing risk of chronic kidney disease, whilst AKI patients who require renal replacement therapy and then recover are at particularly high risk of progression to chronic renal impairment [53]. It is therefore perhaps surprising that, despite the reduced frequency of renal replacement therapy in SLT recipients, we did not observe any difference in the incidence of chronic kidney disease. We believe the relatively short duration of follow-up explains the failure to observe a beneficial effect on long-term renal function.

The study has some additional potential limitations that should be mentioned. Firstly, the retrospective nature of the study meant that the frequency of peri-operative creatinine measurement was variable. All patients had blood sampling immediately on arrival to the Intensive Care Unit

and, in most cases, 12 hourly for the first 24 to 48 h. It is possible, for example, that the peak creatinine underestimated the severity of renal injury. Secondly, nephrotoxic medication could have influenced the severity of AKI and development of chronic kidney disease. Our unit avoids nephrotoxic drugs during the peri-operative period but this does not preclude exposure after discharge. All patients were under regular outpatient review, and there were no documented drug-induced adverse renal events. Thirdly, the lack of pretransplant renal impairment may raise some concerns about the generalizability of the results for some populations of liver transplant recipients. Nevertheless, the study cohort is typical of those who undergo single organ liver transplantation in many countries.

Our findings have important implications for patient care. SLT recipients should not be considered a high risk group for developing AKI during the immediate postoperative period. Consequently, renal sparing immunosuppression should be reserved for select individuals only. The at least comparable renal outcomes to FSLT controls add further weight to the argument that SLT is a valuable resource to expand the donor pool.

In conclusion, in this large single-centre case-controlled study, we have shown that SLT is not associated with an increased frequency of AKI. Our observations support the postulation that the optimal donor status of SLT may result in less graft injury with renal sparing effects.

Authorship

JAL: designed research study, performed research study, collected data, analysed data and wrote paper. MJA, CC, MA, CK and BKG: collected data. DM, PM and JWF: wrote paper.

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