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ORIGINAL ARTICLE

Excessive immunosuppression as a potential cause of poor survival in simultaneous liver/kidney transplantation for hepatitis C

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Summary

Appropriate recipient selection of simultaneous liver/kidney transplantation (SLKT) remains controversial. In particular, data on liver graft survival in hepatitis C virus-infected (HCV+) SLKT recipients are lacking. We conducted a single-center, retrospective study of HCV+ SLKT recipients ($N = 25$) in comparison with HCV− SLKT ($N = 26$) and HCV+ liver transplantation alone (LTA, $N = 296$). Despite backgrounds of HCV+ and HCV− SLKT being similar, HCV+ SLKT demonstrated significantly impaired 5-year liver graft survival of 35% (HCV− SLKT, 79%, $P = 0.004$). Compared with HCV+ LTA, induction immunosuppression was more frequently used in HCV+ SLKT. Five-year liver graft survival rate for HCV+ SLKT was significantly lower than that for LTA (35% vs. 74%, respectively, $P < 0.001$). Adjusted hazard ratio of liver graft loss in HCV+ SLKT was 4.9 (95% confidence interval 2.0–12.1, $P = 0.001$). HCV+ SLKT recipients were more likely to succumb to recurrent HCV and sepsis compared with LTA (32% vs. 8.8%, $P < 0.001$ and 24% vs. 8.8%, $P = 0.030$, respectively). Ten HCV+ SLKT recipients underwent anti-HCV therapy for recurrent HCV; only 1 achieved sustained virological response. HCV+ SLKT is associated with significantly decreased long-term prognosis compared with HCV− SLKT and HCV+ LTA.

Introduction

Since the implementation of the Model for End-stage Liver Disease (MELD) scoring system in 2002, the number of simultaneous liver/kidney transplantations (SLKT) in the United States substantially increased to 413 cases in 2011, which is nearly a twofold increase from 2002 [1, http://optn.transplant.hrsa.gov]. Although a consensus meeting in 2008 proposed the SLKT selection criteria with recent modifications [2,3], there is a significant regional variation in SLKT practices [4] and lack of data to identify predictive factors of survival. Upon retrospective analysis, we found that hepatitis C viral (HCV) infection was an independent risk factor affecting both patient and death-censored kidney

graft survivals in SLKT [5]. The clinical evidence of patient and liver graft survival in HCV+ SLKT recipients is scarce [6–10], with only two reports contrasting the results of SLKT and liver transplantation alone (LTA) [9,10].

To clarify the HCV+ impact on SLKT in the MELD era, we retrospectively compared the long-term outcomes of HCV+ SLKT with those of HCV− SLKT and then with those of LTA for patients exclusively with HCV infection at our institution since 2002.

Patients and methods

We retrospectively reviewed all consecutive adult patients who underwent primary SLKT (both HCV+ and HCV−) and HCV+ LTA from February 2002 to December 2010 at the University of Miami/Jackson Memorial Hospital. This study conformed to the ethical guidelines of Declaration of Helsinki (1975) and was approved by the Institutional Review Board of University of Miami. The indication for SLKT was end-stage liver disease with evidence of irreversible chronic kidney disease. Each patient was discussed and approved by a multidisciplinary selection committee of the transplant program. All transplant candidates were screened serologically for anti-HCV antibody using enzyme immunoassay before 2003 and chemiluminescence assay thereafter. Patients with detectable serum anti-HCV antibodies underwent HCV-RNA PCR testing to confirm HCV infection (HCV+). Patients were excluded from the study whether they had a live donor or donation after cardiac death, coinfection with hepatitis B virus or human immunodeficiency virus, coexisting inborn metabolic disorders or autoimmune disease, or any malignancy (including, but not limited to, hepatocellular carcinoma) confirmed histopathologically in the explanted native liver.

Data collected and analyzed included recipient/donor demographics, causes of graft loss, survival rates, recurrent HCV, and anti-HCV treatment. As a rule, liver biopsies were performed in response to liver enzyme elevations and protocol biopsies were not obtained. Recurrent HCV was defined by histological criteria [11]. Kidney biopsy was performed when renal allograft dysfunction occurred. Biopsy-proven acute liver or kidney rejection requiring a steroid pulse was recorded as rejection. From 2005, we strengthened our steroid avoidance policy for HCV+ recipients and steroid pulses were used less frequently. Cholestatic HCV was diagnosed in patients who underwent transplantation more than 1 month ago and who met the following criteria: (i) histological features (ballooning of hepatocytes, cholestasis, fibrosis, and cholangiolar proliferation); (ii) laboratory data (serum bilirubin >6 mg/dl and HCV-RNA $\geq 1 \times 10^6$ IU/ml); and (iii) the absence of biliary obstruction and hepatic artery thrombosis [12,13]. Induction immunotherapy was administered at the discretion of the transplant team, which comprised lymphocyte depleting agents and/or interleukin-2 receptor antagonists. SLKT recipients were maintained on a triple drug immunosuppressive regimen comprising tacrolimus, mycophenolate mofetil, and prednisone. Immunosuppression for LTA recipients comprised tacrolimus with prednisone. Prednisone was tapered off over 3–6 months in both groups. Tacrolimus was switched to cyclosporine A or sirolimus when toxicity was encountered. Mycophenolate mofetil was used occasionally in LTA recipients with kidney dysfunction to lower the dose of tacrolimus. In both groups, post-transplant antiviral therapy was primarily recurrence-based and was given to stable patients with a progressive rise in liver enzymes and histologic evidence of recurrent HCV. A combination of pegylated interferon alpha and ribavirin was used in the vast majority of patients. Conversion to cyclosporine A from tacrolimus was not undertaken. This principal strategy was consistent over the study period.

Statistical analysis

Patients were censored if they were alive at the time of last follow-up. A liver graft was deemed "lost" when a patient died or underwent retransplantation. When an SLKT recipient returned to permanent dialysis, underwent graft nephrectomy, or received kidney retransplantation, the kidney graft was defined as "lost." If an LTA recipient required chronic dialysis, the native kidney was categorized as "kidney failure." Survival time was calculated as the interval between the time of transplantation and recipient death or graft loss. Unadjusted survival rates were estimated using the Kaplan–Meier method, and survival distributions were compared using the log–rank test.

To identify baseline recipient/donor characteristics associated with decreased patient and liver graft survival in HCV+ SLKT and HCV+ LTA, univariate Cox regression analyses were performed. The variables included were the type of transplantation; recipient factors, that is, age/gender/race/duration of dialysis prior to transplantation/MELD score/pretransplant HCV-RNA PCR/induction immunotherapy using a lymphocyte depleting agent, interleukin-2 receptor antagonist, or both/era (the first era from 2002 to 2005 and the second era from 2006 to 2010); and donor factors, i.e., age/D-MELD [14]/gender/cold ischemia time of the liver allograft. Factors that emerged in the entire cohort with a P value <0.20 were considered as the significant baseline covariates for survival. They were adjusted for comparison between SLKT and LTA by multivariate Cox regression analyses using the forced entry method. To check for consistency, Cox proportional hazard models were also generated using the stepwise backward elimination method and the log-likelihood ratio was applied to determine the goodness of fit.

The Mann–Whitney U-test was used to compare continuous variables and the χ^2 test or Fisher's exact probability test for categorical variables. Data were shown as median (interquartile range) or number (%). Statistical significance was defined as a P value <0.05. All statistical analyses were performed using IBM SPSS STATISTICS 20 (SPSS, Inc., Chicago, IL, USA).

Results

A total of 25 patients underwent HCV+ SLKT, 26 patients underwent HCV− SLKT, and 217 patients underwent HCV+ LTA from February 2002 to December 2010. For reference, six malignant tumors (five hepatocellular carcinomas and one neuroendocrine tumor) were found in SLKT recipients, and 204 tumors (202 hepatocellular carcinomas and two intrahepatic cholangiocarcinomas) were found in HCV+ LTA recipients during the same period, and these cases were excluded from the study.

Comparison between HCV+ SLKT and HCV− SLKT

Regarding HCV+ SLKT ($N = 25$) and HCV− SLKT ($N = 26$) recipients, the pretransplant information, immunosuppression regimen, and major clinical outcomes are summarized in Table 1. Uncommon indications for kidney transplantation in HCV+ SLKT included renal agenesis in two (8%) patients and bilateral renovascular disease in one (4%). In HCV− SLKT, four (15%) patients had polycystic kidney disease, two (8%) had Caroli's disease, and one (4%) had sickle cell disease as the cause of kidney failure. Contrarily, backgrounds including panel reactive antibody and cross match were comparable between the groups and the majority of patients received induction immunotherapy. Lymphocyte-depleting agents were more frequently used in HCV− SLKT. A total of four episodes of liver rejection were successfully treated with steroid pulse therapy except in one HCV− SLKT recipient who subsequently required anti-CD3 monoclonal antibody for reversal. Over a median follow-up of 48 months, HCV+ SLKT demonstrated significantly impaired 5-year overall patient and liver graft survivals of 35 ± 10% and 35 ± 10%, respectively, compared with HCV− SLKT (79 ± 8%, $P = 0.005$ and 79 ± 8%, $P = 0.004$, respectively). Detailed features and outcomes of HCV+ SLKT recipients are reported in Table 2. A total of 15 deaths in HCV+ SLKT, 13 (87%) deaths occurred within two years post-transplant. Recurrent HCV (cases 1–8) and sepsis (cases 9–14 in Table 2) were the two leading causes of death: 1 HCV+ SLKT recipient died after valve replacement surgery for severe aortic stenosis (case 15 in Table 2). In HCV− SLKT, five recipients died of sepsis ($N = 3$), stroke ($N = 1$), and delayed hemoperitoneum after paracentesis ($N = 1$).

Table 1. Comparison between HCV+ SLKT ($N = 25$) and HCV− SLKT ($N = 26$).

Factors	HCV+ SLKT	HCV− SLKT	*P* value
Age, year	56 (47–62)	56 (51–61)	0.82
Female gender	9 (36)	10 (39)	0.86
African–American	3 (12)	2 (8)	0.67
Model for end-stage liver disease	23 (21–28)	23 (22–29)	0.64
Duration of pretransplant dialysis ≥8 week	17 (68)	12 (46)	0.12
Etiology for liver failure			
Chronic HCV infection	25 (100)	–	–
Alcoholic liver disease	–	8 (31)	
Chronic hepatitis B infection	–	4 (15)	
Polycystic liver disease	–	4 (15)	
Non-alcoholic steatohepatitis	–	3 (12)	
Cryptogenic disease	–	3 (12)	
Caroli's disease	–	2 (8)	
Primary sclerosing cholangitis	–	1 (4)	
Sickle cell disease	–	1 (4)	
Etiology for kidney failure			
Diabetes mellitus/ hypertension	10 (40)	6 (23)	0.34
Glomerulonephritis	8 (32)	6 (23)	
Hepatorenal syndrome	4 (16)	7 (27)	
Others	3 (12)	7 (27)	
Previous kidney transplantation	5 (20)	2 (8)	0.25
Panel reactive antibody, %	10 (0–42)	4 (0–14)	0.48
Donor age, year	34 (19–46)	35 (19–42)	0.90
Donor female gender	9 (36)	10 (39)	0.86
Human leukocyte antigen mismatch	5 (4–5)	5 (4–5)	0.97
Liver cold ischemia time, min	460 (385–536)	446 (389–502)	0.85
Induction immunotherapy, total	19 (76)	25 (96)	0.050
Anti-interleukin-2 receptor antibodies	17 (68)	11 (42)	0.065
Lymphocyte depleting agents	9 (36)	20 (77)	**0.003**
Maintenance immunosuppression			
Tacrolimus	20 (80)	25 (96)	0.13
Cyclosporine	0 (0)	3 (12)	
Sirolimus	1 (4)	2 (8)	
With mycophenolate mofetil	14 (56)	12 (46)	0.48
With prednisone	6 (24)	7 (27)	0.81
Liver rejection	1 (4)	3 (12)	0.61
Sepsis as the cause of death	6 (24)	3 (12)	0.29
Liver graft loss	15 (60)	5 (19)	**0.003**

Data presented as median (interquartile range) or number (%). HCV, hepatitis C virus; SLKT, simultaneous liver/kidney transplantation. Bold values are statistically significant.

Table 2. Clinical details of HCV+ SLKT recipients (N = 25).

Case	Age/Sex	Pretransplant dialysis, days	HCV-RNA, IU/ml	Immunosuppression		Re-HCV	PEGIFN + RIB	OS, mo	Status	Cause of death
				Induction	Maintenance					
1	32/F	42	2 830 000	–	TAC/MMF/PRED	Yes	Yes	4	Dead	Re-HCV
2	54/M	30	22 100 000	DAC	CYA	Yes	No	6	Dead	Re-HCV
3	39/M	1825	8 980 000	ATG/DAC	TAC	Yes	Yes	9	Dead	Re-HCV
4	58/M	44	25 100	DAC	TAC	Yes	Yes	12	Dead	Re-HCV
5	76/M	180	6 500 000	ATG/DAC	TAC/MMF	Yes	No	16	Dead	Re-HCV
6	54/M	536	102 000	ATG/BAS	TAC/MMF	Yes	Yes	16	Dead	Re-HCV
7	69/M	121	623 000	–	TAC/MMF	Yes	Yes	19	Dead	Re-HCV
8	73/F	–	691 000	DAC	TAC/MMF	Yes	Yes	40	Dead	Re-HCV
9	42/F	–	1 260 000	ALEM	TAC/MMF/PRED	No	No	1	Dead	Sepsis
10	51/M	56	96 300	–	CYA/MMF/PRED	Yes	Yes	2	Dead	Sepsis
11	57/M	576	Detected	DAC	TAC/MMF/PRED	No	No	2	Dead	Sepsis
12	54/F	38	1010	DAC	TAC	Yes	Yes	2	Dead	Sepsis
13	58/M	643	251 000	DAC	CYA/PRED	No	No	5	Dead	Sepsis
14	58/F	895	11 100 000	ATG	SRL/MMF	Yes	No	17	Dead	Sepsis
15	63/M	136	11 100 000	DAC	TAC	Yes	No	26	Dead	Cardiac
16	56/M	242	1 040 000	ATG/BAS	TAC/MMF	No	No	12	Alive	–
17	62/M	548	2 580 000	ATG/BAS	TAC	No	No	13	Alive	–
18	62/F	247	2 060 000	ATG/BAS	TAC	Yes	No	17	Alive	–
19	53/F	730	14 600 000	ATG/DAC	SRL	No	No	33	Alive	–
20	61/F	30	53 900	–	TAC/MMF	Yes	No	49	Alive	–
21	47/M	140	6 110 000	–	TAC/MMF	No	No	59	Alive	–
22	62/M	665	22 300 000	DAC	TAC/MMF/PRED	No	No	65	Alive	–
23	46/M	14	Detected	–	TAC	Yes	Yes	83	Alive	–
24	47/F	68	406 000	DAC	TAC/MMF	Yes	Yes	102	Alive	–
25	27/M	1460	850 000	DAC	TAC	No	No	108	Alive	–

HCV, hepatitis C virus; SLKT, simultaneous liver-kidney transplantation; Re-HCV, recurrent hepatitis C; PEGIFN, pegylated interferon; RIB, ribavirin; OS, overall survival; TAC, tacrolimus; MMF, mycophenolate mofetil; PRED, prednisone; DAC, Daclizumab; CYA, cyclosporine A; ATG, anti-thymocyte globulin; BAS, basiliximab; ALEM, alemtuzumab; SRL, sirolimus.

Patient demographics of HCV+ SLKT and HCV+ LTA

Recipient and donor demographics of HCV+ SLKT and HCV+ LTA are outlined in Table 3. The HCV+ SLKT cohort had a higher MELD score and a longer time on dialysis (median, 6 months) before transplantation compared with the HCV+ LTA cohort. In the HCV+ SLKT group, 5/25 (20%) patients underwent an isolated kidney transplantation previously (median interval from first transplantation, 18 years). Of these patients, three were completely off immunosuppressants (cases 1, 19, and 25), one was on methylprednisolone at 4 mg and azathioprine at 25 mg daily (case 9), and one was on methylprednisolone at 2 mg daily (case 12 in Table 2) at the time of HCV+ SLKT. HCV-RNA titers before transplantation were higher and the donor age was younger in HCV+ SLKT recipients compared with HCV+ LTA recipients.

Liver and kidney allografts for an HCV+ SLKT patient were universally procured from the same deceased donor. Liver allografts for SLKT had longer cold ischemia time than those for HCV+ LTA. Four (16%) HCV+ SLKT recipients received kidneys from expanded criteria donors (cases 4, 6, 9, and 22 in Table 2). Median cold ischemia time for kidneys in HCV+ SLKT was 13.7 (11.9–18.9) hours.

Patient and liver graft survival

In-hospital mortality was comparable between both groups [HCV+ SLKT, 1/25 (4%) versus HCV+ LTA, 7/296 (2.4%)]. The incidence of recurrent HCV (cases 1–8) and

Table 3. Patient demographics of HCV+ SLKT ($N = 25$) and HCV+ LTA ($N = 217$).

Factors	HCV+ SLKT	HCV+ LTA	*P* value
Age, year	56 (47–62)	53 (49–58)	0.27
Female gender	9 (36)	71 (32.7)	0.74
Race/Ethnicity			
Caucasian	15 (60)	135 (62.2)	0.38
Hispanic	7 (28)	70 (32.3)	
African American	3 (12)	9 (4.1)	
Others	0 (0)	3 (1.4)	
Model for end-stage liver disease	23 (21–28)	20 (16–24)	**0.016**
Total bilirubin, mg/dl	1.4 (1.1–2.2)	3.9 (2.2–6.9)	**<0.001**
Creatinine, mg/dl	6.6 (4.0–8.9)	1.1 (0.8–1.5)	**<0.001**
Pretransplant dialysis	23 (92)	10 (4.6)	**<0.001**
Duration, days	180 (44–643)	9 (4–35)	**<0.001**
Pretransplant HCV-RNA ($\times 10^6$ IU/ml)	1.3 (0.3–9.0)	0.3 (0.1–0.9)	**0.002**
Donor age, year	34 (19–46)	42 (26–53)	0.051
Donor female gender	9 (36)	77 (35.5)	0.96
D-MELD	767 (474–1073)	767 (566–1061)	0.50
Liver cold ischemia time, min	460 (385–536)	422 (347–469)	**0.041**
Era, 2002–2005:2006–2010	10:15	112:105	0.27

Data presented as median (interquartile range) or number (%).
HCV, hepatitis C virus; SLKT, simultaneous liver/kidney transplantation; LTA, liver transplant alone; D-MELD, donor age × calculated model for end-stage liver disease score. Bold values are statistically significant.

sepsis (cases 9–14 in Table 2) as the cause of death was significantly higher in HCV+ SLKT than in HCV+ LTA [HCV+ SLKT, 8/25 (32%) versus HCV+ LTA, 19/217 (8.8%), $P < 0.001$ and HCV+ SLKT, 6/25 (24%) versus HCV+ LTA, 19/217 (8.8%), $P = 0.030$, respectively]. Of note, mortality from cholestatic HCV occurred more frequently in HCV+ SLKT [HCV+ SLKT, 5/25 (20%, cases 1–4 and 6 in Table 2) versus HCV+ LTA, 6/217 (2.8%), $P < 0.001$].

With a median follow-up of 60 months, 5-year overall patient and liver graft survivals for HCV+ SLKT were 35 ± 10% and 35 ± 10%, respectively, which were significantly lower than those for HCV+ LTA (75 ± 3% and 74 ± 3%, respectively; both $P < 0.001$: Fig. 1a and b). Univariate analysis of the entire cohort revealed SLKT, recipient age, race (African–American versus others), duration of pretransplant dialysis, induction immunotherapy, and donor female gender as potential risk factors for decreased overall patient survival. With adjustments for these baseline characteristics, the risk (hazard ratio) of patient death in HCV+ SLKT was 5.7 (95% confidence interval 2.3–14.6, $P < 0.001$) compared with HCV+ LTA. For liver graft survival, SLKT, recipient race, duration of pretransplant dialysis, induction immunotherapy, and donor female gender were the significant baseline covariates of graft loss. The adjusted hazard ratio of liver graft loss in HCV+ SLKT was 4.9 (95% confidence interval 2.0–12.1, $P = 0.001$). Even when the subgroup of HCV+ SLKT recipients with a previous history of isolated kidney transplantation ($N = 5$) were excluded, the results of univariate (Table 4) and multivariate analyses were essentially the same; the adjusted risks were 3.6 (95% confidence interval 1.9–6.8, $P < 0.001$) for patient death and 3.2 (95% confidence interval 1.7–6.0, $P < 0.001$) for liver graft loss in HCV+ SLKT compared with HCV+ LTA as the reference. It is worth mentioning that donor female gender also emerged as an independent predictive factor of diminished overall patient (hazard ratio, 2.0; 95% confidence interval 1.3–3.3, $P = 0.004$) and liver graft survivals (hazard ratio, 2.0; 95% confidence interval 1.2–3.2, $P = 0.005$) in the entire cohort. Analogous results were obtained after exclusion of kidney retransplantation recipients in HCV+ SLKT.

Immunosuppression regimens and clinical outcomes

For induction immunotherapy, 19/25 (76%) HCV+ SLKT patients received interleukin-2 receptor antagonists (daclizumab, $N = 13$; basiliximab, $N = 4$) and/or lymphocyte depleting agents (anti-thymocyte globulin, $N = 8$; alemtuzumab, $N = 1$; Table 5). Dual regimens were administered to seven recipients (28%) in the HCV+ SLKT group (cases 3, 5, 6, and 16–19 in Table 2). In contrast, only 7.8% (17/217) in the HCV+ LTA group underwent induction with daclizumab ($P < 0.001$), although higher doses were administered in HCV+ LTA than in HCV+ SLKT. There was no difference in the use of calcineurin inhibitors, but HCV+ SLKT recipients were more often maintained on mycophenolate mofetil and prednisone.

The incidence of recurrent HCV and post-transplant diabetes mellitus was equivalent in both groups. Liver allograft rejection occurred more frequently in HCV+ LTA than in HCV+ SLKT. Death-censored kidney graft loss occurred in 11 (44%) HCV+ SLKT recipients (cases 1–3, 5, 9, 10, 12, 14, 18, 19, and 22 in Table 2), whereas 18 (8.3%) HCV+ LTA recipients developed native kidney failure postoperatively. Five (1.7%) HCV+ LTA and no HCV+ SLKT recipients underwent subsequent kidney transplantation. One HCV+ SLKT recipient who suffered acute cellular rejection of the kidney was successfully treated with steroids and anti-thymocyte globulin (case 22 in Table 2).

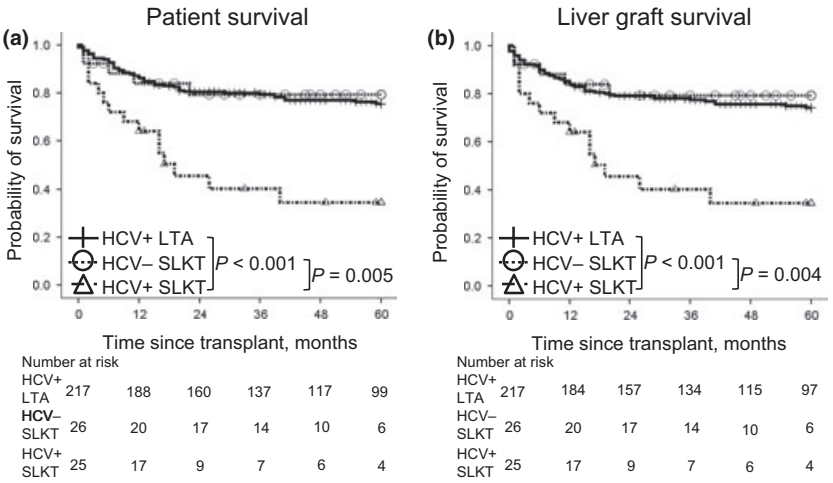

Figure 1 Comparison of cumulative overall (a) patient and (b) liver graft survivals of HCV+ liver transplantation alone recipients (LTA) and HCV−/+ simultaneous liver/kidney transplantation (SLKT). Five-year overall patient and liver graft survivals of HCV+ SLKT ($N = 25$: dot-dashed line) were 35 ± 10% and 35 ± 10%, respectively, significantly lower than those of HCV+ LTA ($N = 217$; 75 ± 3% and 74 ± 3%, respectively; both $P < 0.001$: solid line) and HCV− SLKT ($N = 26$; 79 ± 8%, $P = 0.005$ and 79 ± 8%, $P = 0.004$, respectively: dotted line). Differences in patient and liver graft survivals of HCV+ LTA and HCV− SLKT were not statistically significant (both $P > 0.05$). HCV, hepatitis C virus.

Table 4. Factors affecting survival of HCV+ SLKT ($N = 25$) and HCV+ LTA ($N = 217$) using univariate Cox regression analysis.

	Overall patient survival at 5 years				Liver graft survival at 5 years			
	Entire cohort		No kidney retransplants		Entire cohort		No kidney retransplants	
Factors	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
SLKT	3.6 (2.0–6.4)	<0.001	3.4 (1.8–6.4)	<0.001	3.2 (1.8–5.7)	<0.001	3.1 (1.6–5.8)	<0.001
Recipient age, year	1.0 (1.0–1.1)	0.14	1.0 (1.0–1.1)	0.059	1.0 (1.0–1.0)	0.28	1.0 (1.0–1.1)	0.15
Female gender	1.4 (0.8–2.2)	0.24	1.2 (0.7–2.0)	0.47	1.2 (0.8–2.0)	0.39	1.1 (0.7–1.9)	0.68
African–American	2.3 (1.0–5.3)	0.055	2.4 (1.0–5.6)	0.042	2.1 (0.9–4.8)	0.089	2.2 (0.9–5.1)	0.072
Duration of dialysis ≥8 week	2.2 (1.0–4.6)	0.040	2.7 (1.3–5.8)	0.008	2.0 (1.0–4.2)	0.065	2.5 (1.2–5.3)	0.016
MELD	1.0 (1.0–1.0)	0.49	1.0 (1.0–1.0)	0.51	1.0 (1.0–1.0)	0.78	1.0 (1.0–1.0)	0.81
HCV-RNA ≥800 000 IU/ml	1.2 (0.7–2.1)	0.50	1.2 (0.7–2.0)	0.59	1.1 (0.7–1.9)	0.71	1.1 (0.6–1.9)	0.80
Induction immunotherapy	2.0 (1.1–3.5)	0.023	1.9 (1.0–3.5)	0.044	2.0 (1.1–3.4)	0.019	1.9 (1.1–3.4)	0.033
Donor age, year	1.0 (1.0–1.0)	0.55	1.0 (1.0–1.0)	0.53	1.0 (1.0–1.0)	0.53	1.0 (1.0–1.0)	0.52
D-MELD	1.0 (1.0–1.0)	0.25	1.0 (1.0–1.0)	0.21	1.0 (1.0–1.0)	0.41	1.0 (1.0–1.0)	0.36
Donor female gender	2.0 (1.2–3.3)	0.004	2.1 (1.3–3.5)	0.003	2.0 (1.2–3.2)	0.005	2.1 (1.3–3.3)	0.004
Liver cold ischemia time >8 h	0.8 (0.4–1.5)	0.55	0.8 (0.4–1.5)	0.50	0.8 (0.4–1.5)	0.43	0.8 (0.4–1.4)	0.39
Era, year 2002–2005	1.3 (0.8–2.1)	0.32	1.3 (0.8–2.1)	0.37	1.3 (0.8–2.2)	0.25	1.3 (0.8–2.2)	0.29

HR, hazard ratio; CI, confidence interval; SLKT, simultaneous liver-kidney transplantation; MELD, Model for End-stage Liver Disease; HCV, hepatitis C virus; D-MELD, donor age × MELD.

Antiviral therapy

Overall, 10/25 (40%) in HCV+ SLKT (cases 1, 3, 4, 6–8, 10, 12, 23, and 24 in Table 2) and 119/217 (54.8%) in HCV+ LTA received antiviral therapy for recurrent HCV using a combination of pegylated interferon alpha and ribavirin (Table 6). More recipients in HCV+ SLKT (9/10, 90%) were treatment-naïve than in HCV+ LTA (65/119, 54.6%, $P = 0.043$). The number of recipients with METAVIR activity grade ≥2 and/or fibrosis score ≥2 was similar in both groups (HCV+SLKT, 6/8 (75%) versus HCV+ LTA, 40/80 (50%), $P = 0.27$). Median doses of medications were higher, and the duration of therapy was longer in HCV+ LTA than in HCV+ SLKT. HCV genotype, response rate, and toxicity were analogous between both groups.

In HCV+ SLKT, only one (10%) recipient achieved sustained virological response (case 23), 4 (40%) discontinued medications because of adverse events (acute kidney injury, cases 3 and 12; pancytopenia, case 7; anemia and psychosis, case 6), and 8 (80%) were nonresponders (cases 1, 3, 4, 7,

Table 5. Immunosuppression regimens and clinical outcomes of HCV+ SLKT ($N = 25$) and HCV+ LTA ($N = 217$).

Factors	HCV+ SLKT	HCV+ LTA	*P* value
Induction immunotherapy, total	19 (76)	17 (7.8)	**<0.001**
Anti-interleukin-2 receptor antibodies	17 (68)	17 (7.8)	**<0.001**
Daclizumab, mg/kg	4.0 (1.0–4.0)	8.0 (5.5–8.0)	**<0.001**
Basiliximab, mg	40.0 (25.0–40.0)	–	–
Lymphocyte depleting agents	9 (36)	0 (0)	**<0.001**
Anti-thymocyte globulin, mg/kg	1.5 (1.0–2.8)	–	–
Alemtuzumab, mg	30 (–)	–	–
Maintenance immunosuppression			
Tacrolimus	20 (80)	188 (87.0)	0.28
Cyclosporine	3 (12)	10 (4.6)	
Sirolimus	2 (8)	18 (8.3)	
With mycophenolate mofetil	14 (56)	70 (32.4)	**0.019**
With prednisone	6 (24)	21 (9.7)	**0.032**
Recurrent hepatitis C	16 (64)	108 (49.8)	0.18
Liver rejection	1 (4)	49 (22.6)	**0.034**
Kidney graft loss* or native kidney failure	11 (44)	18 (8.3)	**<0.001**
Kidney rejection	1 (4)	–	–
Post-transplant diabetes mellitus	5/13 (39)	48/186 (25.8)	0.32

Data presented as median (interquartile range) or number (%).
HCV, hepatitis C virus; SLKT, simultaneous liver/kidney transplantation; LTA, liver transplant alone. Bold values are statistically significant.
*Death-censored.

Table 6. Post-transplant antiviral therapy in HCV+ SLKT ($N = 10$) and HCV+ LTA ($N = 119$).

Factors	HCV+ SLKT	HCV+ LTA	*P* value
HCV genotype			
1	9 (90)	96 (80.7)	1.00
2	0 (0)	7 (5.9)	
3	0 (0)	2 (1.7)	
4	0 (0)	2 (1.7)	
Unknown	1 (10)	12 (10.1)	
HCV-RNA prior to therapy ($\times 10^6$ IU/ml)	13.9 (1.0–47.3)	2.7 (0.5–12.8)	0.22
Interval after transplant, mo	3.0 (1.0–6.8)	4.0 (2.0–7.0)	0.30
Pegylated interferon alpha, mcg/wk	90 (86–101)	135 (90–180)	**0.011**
Ribavirin, mg/d	200 (175–400)	400 (300–800)	**0.001**
Duration, mo	5 (2–12)	24 (12–51)	**0.002**
Virological response			
Sustained virological response	1 (10)	28 (23.5)	0.71
End-of-treatment response	0 (0)	2 (1.7)	
Early virological response	0 (0)	4 (3.4)	
Partial responder	0 (0)	3 (2.5)	
Relapse	1 (10)	22 (18.5)	
Nonresponder	8 (80)	60 (50.4)	
Treatment discontinued	4 (40)	58 (48.7)	0.63

Data presented as median (interquartile range) or number (%).
HCV, hepatitis C virus; SLKT, simultaneous liver/kidney transplantation; LTA, liver transplant alone. Bold values are statistically significant.

8, 10, 12, and 24 in Table 2). None of the interferon-treated HCV+ SLKT recipients experienced acute rejection of the kidney. In this subgroup, there were four death-censored kidney graft losses (HCV-related glomerulonephritis in cases 1, 10, and 12; lupus nephritis in case 3 in Table 2) during the study period. Ultimately, there were eight mortalities (liver graft failure due to recurrent HCV in patients 1, 3, 4, 12, and 6–8; sepsis in case 10 in Table 2), of which 7/8 (88%) occurred within two years after transplantation. The remaining two patients are currently alive at 83 and 102 months (cases 23 and 24 in Table 2).

Discussion

This is the first study describing significantly lower patient and liver graft survival rates of primary HCV+ SLKT compared with those of HCV− SLKT and HCV+ LTA in the MELD era. Our previous study primarily focused on kidney graft survival in SLKT and included cases of liver retransplantation and malignancies; moreover, head-to-head comparisons between HCV+ and HCV− SLKT were not conducted [5]. In the present study, we found that the predominant causes of patient death in our HCV+ SLKT recipients were recurrent HCV and sepsis. Two major factors were implicated in the poorer outcomes in HCV+ SLKT recipients: (i) Induction immunotherapy in the HCV+ SLKT cohort was equivalent to HCV− SLKT and was more potent than HCV+ LTA, thus bringing the negative consequences of possible over-immunosuppression to light in a subset of SLKT recipients with HCV infection, and (ii) Anti-HCV therapy for recurrent HCV was ineffective in SLKT, reflecting not only inadequate dosage and shorter duration of treatment but also a potentially more aggressive course of disease, which was supported by a higher incidence of death from cholestatic HCV. The discrepancy from earlier reports [9,10] may be attributed in part to our study inclusion criteria and the use of induction agents. The etiology of kidney failure and the duration of pretransplant dialysis were also different, implying a variation in SLKT indications. It is noteworthy that a previous history of isolated kidney transplantation affected neither

the overall patient nor liver graft survivals among HCV+ SLKT recipients. A combination of primary liver transplantation and kidney retransplantation may be justified in carefully selected cases when patients are maintained at a low-immunosuppressive level.

In the 2009 Organ Procurement and Transplantation Network/Scientific Registry of Transplant Recipients Annual Report: Transplant Data 1999–2008 (http://www.ustransplant.org/annual_reports/current/), HCV+ SLKT patients ($N = 954$) were associated with lower 5-year unadjusted patient survival in the 60% range compared with that of HCV− SLKT patients ($N = 1431$) exceeding 75%. These data call for serious attention; however, precise patient information are not provided in this report, and we do not know whether the potential contributing factors of poor survival for HCV+ SLKT recipients in our series match those of the national database. There is no doubt that SLKT is a life-saving procedure for many recipients with end-stage liver and kidney disease, and most recipients enjoy prolonged survival [5]. Nonetheless, our results necessitated a reappraisal of SLKT in HCV+ individuals. We recently reported that isolated kidney transplantation for HCV+ patients with end-stage renal disease confers a long-term survival benefit over those on the waitlist [15]. Chronic dialysis is poorly tolerated in liver transplant recipients than in patients with kidney failure alone [16]. The deleterious effect of sequential transplantation on survival has also been recognized [17,18]. SLKT is still justified for HCV+ patients with end-stage liver and kidney disease; cautious immunosuppression, strict donor/recipient selection [5], and refinements in anti-HCV treatment will play pivotal roles in improving outcomes.

Optimal immunosuppression after liver transplantation in HCV+ recipients remains controversial. A recent consensus report concluded that the use of a specific calcineurin inhibitor has shown no impact on long-term outcomes in HCV+ recipients [19]. A multicenter trial lately described that steroid-free immunosuppression has no clear advantage over other regimens incorporating steroids [20], which was in accordance with our preceding studies [21,22]. Most of our SLKT recipients received an interleukin-2 receptor antagonist and/or lymphocyte-depleting agent for induction, for which their use in HCV+ patients is yet to be determined [23–26]. The influence of mycophenolate mofetil on recurrent HCV has also been the subject of conflicting results [27,28]. In recipients receiving sirolimus, one group observed a lower rate of fibrosis over time [29]. An analysis of the United Network for Organ Sharing registry data reported contradictory outcomes with an increased risk of death and graft loss [30]. HCV+ SLKT recipients require individually tailored immunosuppression; particularly, the induction regimen needs to be carefully chosen because SLKT is associated with increased mortality from infection [5,6,9]. The results of this study led us to reduce the induction dose of antithymocyte globulin by half to one-third of what is currently given for isolated kidney transplantation at our center or to use other regimens with less immunosuppressive potency.

In the present investigation, donor female gender had a detrimental effect on long-term survival. Gender should be one of the critical determinants when a potential donor is being evaluated for HCV+ SLKT [5,31]. Meanwhile, we failed to demonstrate the widely accepted negative prognostic impact of donor age [32,33]. Donor age tended to be younger in HCV+ SLKT than in LTA in our study, entailing a more favorable allocation reserved to the SLKT cohort. We are extremely cautious about the degree of liver steatosis and arterial conditions at the time of organ procurement, which is in line with a recent publication reporting satisfactory results with the use of carefully selected donors 60 years or older [34]. Furthermore, there was a lack of correlation between survival and MELD or D-MELD. The limited number of cases and the adopted statistical approach in our study being different from their original description may be the underlying reasons. Numerous variables that may affect outcomes such as recipient age/gender/race, donor gender/race/liver steatosis, cold ischemia time, multiorgan transplantation, and pretransplant conditions are all excluded from MELD score calculation [35–38]. For D-MELD, an Italian study and further international correspondence appear to have clarified some of the drawbacks of the original study, such as its short follow-up period [39–45]. Therefore, the importance of appropriate donor and recipient matching cannot be overstated.

Management of recurrent HCV remains a major challenge in liver transplantation [46–48] and it may be exceedingly difficult in SLKT [5]. In our series, only 1 SLKT recipient achieved sustained virological response to anti-HCV therapy and 80% (8/10) of the treated SLKT recipients eventually succumbed to sepsis or liver graft failure due to recurrent HCV. On the contrary, a recent French study reported better outcomes: differences in the timing, duration, and dosage of therapy may explain the discrepancy [49]. Novel approaches in antiviral therapy for HCV are on the verge of a breakthrough [50,51]. Recently, the successful use of new direct-acting antiviral agents in LTA recipients has been reported, indicating a paradigm shift in the treatment of HCV+ transplant candidates [52,53]. Given our disappointing results, a deliberate strategy for HCV infection is imperative in SLKT.

Whether SLKT provides an immunologic advantage for kidney allografts has been controversial. Several mechanisms, such as absorption of anti-HLA antibodies by the liver, have been proposed [54,55], with a beneficial clinical application to positive lymphocytotoxic cross-match SLKT

recipients [56]. We and other authors reported that pre-SLKT sensitization or class II donor-specific antibody has a negative impact on patient and kidney graft survival [5,57,58].

There are several limitations of our study: (i) the retrospective design, (ii) selection bias on which patient underwent SLKT, (iii) era bias with patient data collected over a 9-year period, (iv) potential confounders such as recipient/donor age, sex, and race, (v) heterogeneity in immunosuppression, and (vi) a limited number of SLKT recipients. To solve the shortcomings from (i) to (v), we focused on primary transplantations with no coexisting liver disorders or malignancies and performed multivariate analyses to control for multiple factors that may affect survival outcomes. Consequently, although the sample size issue still remains, we believe our results unveiled detrimental effects of HCV infection on prognosis in SLKT.

In conclusion, patient and graft survival rates of HCV+ SLKT are significantly lower than those of HCV− SLKT and HCV+ LTA. Main causes of patient death in HCV+ SLKT are recurrent HCV and sepsis, which necessitate immunosuppression to be individually tailored according to the patients' condition. Response to anti-HCV therapy after SLKT is limited; therefore, novel approaches for HCV infection are critical for improving outcomes.

Authorship

HT, NS, SJ and TAG: concept and design. HT, NS, SJ, LDM, RP, RD, MP, BGW, CG and TAG: data collection. HT, NS, SJ, MP, OK and TA: data analysis. HT: drafting article. NS, SJ, MP and OK: critical revision of article. HT, NS, SJ, LDM, RP, RD, MP, OK, BGW, CG and TAG: approval of article.

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References

1. Papafragkakis H, Martin P, Akalin E. Combined liver and kidney transplantation. *Curr Opin Organ Transplant* 2010; **15**: 263.
2. Eason JD, Gonwa TA, Davis CL, Sung RS, Gerber D, Bloom RD. Proceedings of consensus conference on simultaneous liver kidney transplantation (SLK). *Am J Transplant* 2008; **8**: 2243.
3. Nadim MK, Sung RS, Davis CL, *et al.* Simultaneous liver-kidney transplantation summit: current state and future directions. *Am J Transplant* 2012; **12**: 2901.
4. 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.
5. Hibi T, Sageshima J, Molina E, *et al.* Predisposing factors of diminished survival in simultaneous liver/kidney transplantation. *Am J Transplant* 2012; **12**: 2966.
6. 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.
7. Ruiz R, Jennings LW, Kim P, *et al.* Indications for combined liver and kidney transplantation: propositions after a 23-yr experience. *Clin Transplant* 2010; **24**: 807.
8. 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.
9. Van Wagner LB, Baker T, Ahya SN, Norvell JP, Wang E, Levitsky J. Outcomes of patients with hepatitis C undergoing simultaneous liver-kidney transplantation. *J Hepatol* 2009; **51**: 874.
10. del Pozo AC, Martín JD, Rodriguez-Laiz G, *et al.* Outcome of combined liver and kidney transplantation in hepatitis C: a single-center long-term follow-up experience. *Transplant Proc* 2009; **41**: 1713.
11. Intraovserver and interobserver variations in liver biopsy interpretation in patients with chronic hepatitis C. The French METAVIR Cooperative Study Group. *Hepatology* 1994; **20**: 15.
12. Wiesner RH, Sorrell M, Villamil F, International Liver Transplantation Society Expert Panel. Report of the first International Liver Transplantation Society expert panel consensus conference on liver transplantation and hepatitis C. *Liver Transpl* 2003; **9**: S1.
13. Verna EC, Abdelmessih R, Salomao MA, Lefkowitch J, Moreira RK, Brown RS Jr. Cholestatic hepatitis C following liver transplantation: an outcome-based histological definition, clinical predictors and prognosis. *Liver Transpl* 2013; **19**: 78.
14. Halldorson JB, Bakthavatsalam R, Fix O, Reyes JD, Perkins JD. D-MELD, a simple predictor of post liver transplant mortality for optimization of donor/recipient matching. *Am J Transplant* 2009; **9**: 318.
15. Roth D, Gaynor JJ, Reddy KR, *et al.* Effect of kidney transplantation on outcomes among patients with hepatitis C. *J Am Soc Nephrol* 2011; **22**: 1152.
16. Al Riyami D, Alam A, Badovinac K, Ivis F, Trpeski L, Cantarovich M. Decreased survival in liver transplant patients requiring chronic dialysis: a Canadian experience. *Transplantation* 2008; **85**: 1277.

17. Martin EF, Huang J, Xiang Q, Klein JP, Bajaj J, Saeian K. Recipient and graft survival are not diminished by simultaneous liver-kidney transplantation: an analysis of the united network for organ sharing database. *Liver Transpl* 2012; **18**: 914.
18. Simpson N, Cho YW, Cicciarelli JC, Selby RR, Fong TL. 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.
19. Berenguer M, Charco R, Manuel Pascasio J, Ignacio Herrero J. Spanish society of liver transplantation (SETH) consensus recommendations on hepatitis C virus and liver transplantation. *Liver Int* 2012; **32**: 712.
20. Klintmalm GB, Davis GL, Teperman L, *et al.* A randomized, multicenter study comparing steroid-free immunosuppression and standard immunosuppression for liver transplant recipients with chronic hepatitis C. *Liver Transpl* 2011; **17**: 1394.
21. Zervos XA, Weppler D, Fragulidis GP, *et al.* Comparison of tacrolimus with microemulsion cyclosporine as primary immunosuppression in hepatitis C patients after liver transplantation. *Transplantation* 1998; **65**: 1044.
22. Kato T, Gaynor JJ, Yoshida H, *et al.* Randomized trial of steroid-free induction versus corticosteroid maintenance among orthotopic liver transplant recipients with hepatitis C virus: impact on hepatic fibrosis progression at one year. *Transplantation* 2007; **84**: 829.
23. Goralczyk AD, Hauke N, Bari N, Tsui TY, Lorf T, Obed A. Interleukin 2 receptor antagonists for liver transplant recipients: a systematic review and meta-analysis of controlled studies. *Hepatology* 2011; **54**: 541.
24. Samonakis DN, Germani G, Burroughs AK. Immunosuppression and HCV recurrence after liver transplantation. *J Hepatol* 2012; **56**: 973.
25. Uemura T, Schaefer E, Hollenbeak CS, Khan A, Kadry Z. Outcome of induction immunosuppression for liver transplantation comparing anti-thymocyte globulin, daclizumab, and corticosteroid. *Transpl Int* 2011; **24**: 640.
26. Mangus RS, Fridell JA, Vianna RM, Kwo PY, Chen J, Tector AJ. Immunosuppression induction with rabbit antithymocyte globulin with or without rituximab in 1000 liver transplant patients with long-term follow-up. *Liver Transpl* 2012; **18**: 786.
27. Germani G, Pleguezuelo M, Villamil F, *et al.* Azathioprine in liver transplantation: a reevaluation of its use and a comparison with mycophenolate mofetil. *Am J Transplant* 2009; **9**: 1725.
28. Manzia TM, Angelico R, Toti L, *et al.* Long-term, maintenance MMF monotherapy improves the fibrosis progression in liver transplant recipients with recurrent hepatitis C. *Transpl Int* 2011; **24**: 461.
29. McKenna GJ, Trotter JF, Klintmalm E, *et al.* Limiting hepatitis C virus progression in liver transplant recipients using sirolimus-based immunosuppression. *Am J Transplant* 2011; **11**: 2379.
30. Watt K, Dierkhising R, Heimbach J, Charlton M. Impact of sirolimus and tacrolimus on mortality & graft loss in liver transplant recipients with and without HCV – an analysis of the SRTR database. *Liver Transpl* 2012; **18**: 1029.
31. Lai JC, Verna EC, Brown RS Jr, *et al.* Hepatitis C virus-infected women have a higher risk of advanced fibrosis and graft loss after liver transplantation than men. *Hepatology* 2011; **54**: 418.
32. Mutimer DJ, Gunson B, Chen J, *et al.* Impact of donor age and year of transplantation on graft and patient survival following liver transplantation for hepatitis C virus. *Transplantation* 2006; **81**: 7.
33. Belli LS, Burroughs AK, Burra P, *et al.* Liver transplantation for HCV cirrhosis: improved survival in recent years and increased severity of recurrent disease in female recipients: results of a long term retrospective study. *Liver Transpl* 2007; **13**: 733.
34. Doyle MB, Anderson CD, Vachharajani N, *et al.* Liver transplant for hepatitis C virus: effect of using older donor grafts on short- and medium-term survival. *Arch Surg* 2008; **143**: 679.
35. Cholongitas E, Marelli L, Shusang V, *et al.* A systematic review of the performance of the model for end-stage liver disease (MELD) in the setting of liver transplantation. *Liver Transpl* 2006; **12**: 1049.
36. Silberhumer GR, Hetz H, Rasoul-Rockenschaub S, *et al.* Is MELD score sufficient to predict not only death on waiting list, but also post-transplant survival? *Transpl Int* 2006; **19**: 275.
37. Bernardi M, Gitto S, Biselli M. The MELD score in patients awaiting liver transplant: strengths and weaknesses. *J Hepatol* 2011; **54**: 1297.
38. Weismüller TJ, Fikatas P, Schmidt J, *et al.* Multicentric evaluation of model for end-stage liver disease-based allocation and survival after liver transplantation in Germany–limitations of the 'sickest first'-concept. *Transpl Int* 2011; **24**: 91.
39. Avolio AW, Cillo U, Salizzoni M, *et al.* Balancing donor and recipient risk factors in liver transplantation: the value of D-MELD with particular reference to HCV recipients. *Am J Transplant* 2011; **11**: 2724.
40. Braat AE, Blok JJ, Putter H, *et al.* The Eurotransplant donor risk index in liver transplantation: ET-DRI. *Am J Transplant* 2012; **12**: 2789.
41. Avolio AW, Halldorson JB, Burra P, Dutkowski P, Agnes S, Clavien PA. Balancing utility and need by means of donor-to-recipient matching: a challenging problem. *Am J Transplant* 2013; **13**: 522.
42. Braat AE, Blok JJ, Rahmel AO, *et al.* Incorporation of donor risk into liver allocation algorithms. *Am J Transplant* 2013; **13**: 524.
43. Avolio AW, Agnes S, Cillo U, *et al.* http://www.D-MELD.com, the Italian survival calculator to optimize donor to

recipient matching and to identify the unsustainable matches in liver transplantation. *Transpl Int* 2012; **25**: 294.
44. Schrem H, Reichert B, Frühauf N, *et al.* The Donor-Risk-Index, ECD-Score and D-MELD-Score all fail to predict short-term outcome after liver transplantation with acceptable sensitivity and specificity. *Ann Transplant* 2012; **17**: 5.
45. Avolio AW, Halldorson JB, Lirosi MC, Lupo L, Nicolotti N, Agnes S. D-MELD, a strong and accurate tool to guide donor-2-recipient matching. *Ann Transplant* 2013; **18**: 161.
46. Berenguer M, Aguilera V, Rubín A, Ortíz C, Jimenez M, Prieto M. Comparison of two non-contemporaneous HCV-liver transplant cohorts: strategies to improve the efficacy of antiviral therapy. *J Hepatol* 2012; **56**: 1310.
47. Bzowej N, Nelson DR, Terrault NA, *et al.* PHOENIX: a randomized controlled trial of peginterferon alfa-2a plus ribavirin as a prophylactic treatment after liver transplantation for hepatitis C virus. *Liver Transpl* 2011; **17**: 528.
48. Veldt BJ, Poterucha JJ, Watt KD, *et al.* Impact of pegylated interferon and ribavirin treatment on graft survival in liver transplant patients with recurrent hepatitis C infection. *Am J Transplant* 2008; **8**: 2426.
49. Hassan Q, Roche B, Buffet C, *et al.* Liver-kidney recipients with chronic viral hepatitis C treated with interferon-alpha. *Transpl Int* 2012; **25**: 941.
50. Charlton MR, Thompson A, Veldt BJ, *et al.* Interleukin-28B polymorphisms are associated with histological recurrence and treatment response following liver transplantation in patients with hepatitis C virus infection. *Hepatology* 2011; **53**: 317.
51. Ghany MG, Nelson DR, Strader DB, Thomas DL, Seeff LB, American Association for Study of Liver Diseases. An update on treatment of genotype 1 chronic hepatitis C virus infection: 2011 practice guideline by the American Association for the Study of Liver Diseases. *Hepatology* 2011; **54**: 1433.
52. Kwo PY, Tector AJ. Oral direct-acting antiviral therapy to prevent reinfection of the liver graft after liver transplantation for hepatitis C virus-related cirrhosis. *Liver Transpl* 2013; **19**: 780.
53. Coilly A, Roche B, Duclos-Vallée JC, Samuel D. Management of HCV transplant patients with triple therapy. *Liver Int* 2014; **34**(Suppl. 1): 46.
54. Davis CL, Gonwa TA, Wilkinson AH. Identification of patients best suited for combined liver-kidney transplantation: part II. *Liver Transpl* 2002; **8**: 193.
55. Dar W, Agarwal A, Watkins C, *et al.* Donor-directed MHC class I antibody is preferentially cleared from sensitized recipients of combined liver/kidney transplants. *Am J Transplant* 2011; **11**: 841.
56. Olausson M, Mjörnstedt L, Nordén G, *et al.* Successful combined partial auxiliary liver and kidney transplantation in highly sensitized cross-match positive recipients. *Am J Transplant* 2007; **7**: 130.
57. Askar M, Schold JD, Eghtesad B, *et al.* Combined liver-kidney transplants: allosensitization and recipient outcomes. *Transplantation* 2011; **91**: 1286.
58. O'Leary JG, Gebel HM, Ruiz R, *et al.* Class II alloantibody and mortality in simultaneous liver-kidney transplantation. *Am J Transplant* 2013; **13**: 954.