Clinical Questions of Combined Liver Kidney Transplantation

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Disclosure

- Merck Co, Abbvie – Advisory Board

Objectives

- Hepato-renal Syndrome
- Epidemiology of Liver Transplant Alone (LTA) and Simultaneous Liver Kidney Transplantation (SLK)
- Eligibility of Simultaneous Liver Kidney Transplantation (SLK)
- Predictors of Kidney Failure in Patients with LTA
- Impact of Post-Transplant Renal Function on Liver Graft Outcome
- Immunological Questions of SLK

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HepatoRenal Syndrome (HRS)

- Hepatorenal syndrome (HRS) is characterized as renal dysfunction secondary to a **reduction in renal blood flow (RBF)** occurring in the setting of underlying cirrhosis and portal hypertension.
- It is classified as either rapidly developing acute kidney injury (AKI), HRS type 1, or slowly progressive chronic kidney disease (CKD), HRS type 2.
- Both types of HRS are associated with a decrease in RBF and glomerular filtration rate (GFR).

Mindikoglu AL, Clin Gastr Hepat, 2018

HepatoRenal Syndrome (HRS)

- The diagnosis conveys a poor prognosis; the median survival for HRS types 1 and 2 is approximately 1 and 6.7 months, respectively.
- Challenges for the study of HRS include establishing when renal dysfunction in patients with cirrhosis occurs, largely related to the limitations of serum creatinine (Cr), evolving criteria for the diagnosis of HRS, the uncertain value of renal biomarkers, and the limited availability of pharmacologic and other therapies to address the fundamental underlying pathophysiology.

Mindikoglu AL, Clin Gastr Hepat, 2018

Diagnosis of Renal Dysfunction in Patients with Cirrhosis

- It is well established that serum Cr is not an accurate marker of renal dysfunction in cirrhosis.
- The production of creatine, the precursor of serum Cr, is impaired in hepatic dysfunction (reduced muscle mass, increased tubular secretion).
- Assessing renal function by measuring GFR (eg, inulin clearance, iothalamate clearance) is the most reliable and accurate method, but it is expensive, time consuming, and labor intensive.
- According to SLKT guidelines, GFR is estimated using the MDRD-6 equation, a Cr-based formula, which shown to underestimate measured GFR when the measured GFR was greater than 30 mL/min/ 1.73 m2 in patients with cirrhosis.

Mindikoglu AL, Clin Gastr Hepat, 2018

Diagnosis of Renal Dysfunction in Patients with Cirrhosis

- Studies have shown that Cr–cystatin C combined GFR equations were more accurate compared with Cr-based GFR equations in estimating measured GFR in patients with cirrhosis.

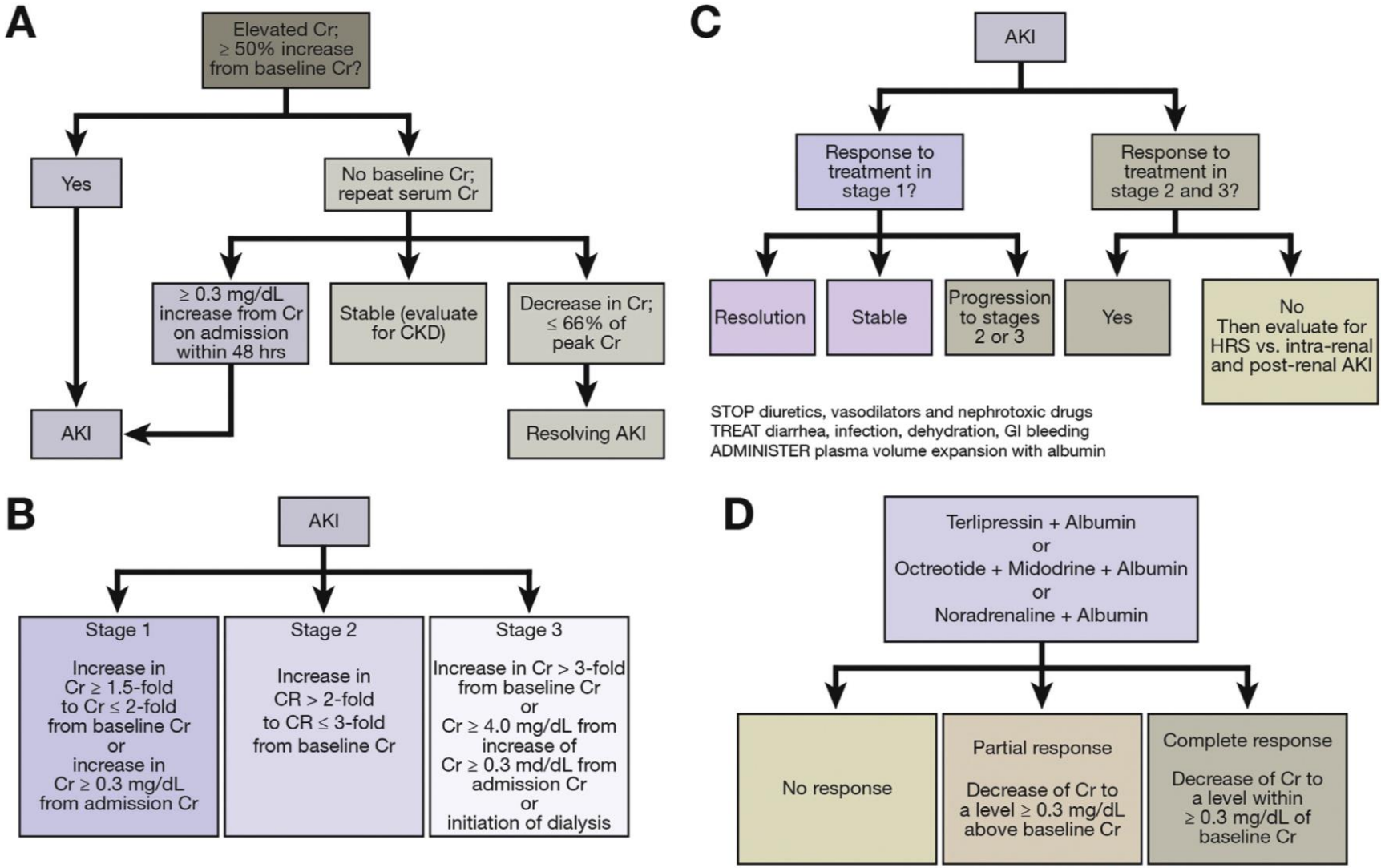

Figure 1. Algorithm in the diagnosis and treatment of AKI–HRS for hepatorenal disorders in cirrhosis.[30,32–35] AKI, acute kidney injury; Cr, serum creatinine; CKD, chronic kidney disease; HRS, hepatorenal syndrome.

Mindikoglu AL, Clin Gastr Hepat, 2018

Prevalence of HRS

- Salerno et al. reported that they **presumed the diagnosis of HRS in 36%** of patients because they **did not meet all the consensus diagnostic criteria** prevailing at that time (Salerno et al., J Hepatol, 2011).
- Planas et al. reported among 263 patients with decompensated cirrhosis and moderate to severe ascites, **8% of patients developed HRS** (3% developed type 1 and 5% developed type 2 HRS) during a mean follow-up period of 41 months (Planas et al., Clin Gastr Hepat, 2006).
- 19% of hospitalized patients with cirrhosis had AKI/acute renal failure, and among those with acute renal failure, approximately 17% had HRS (Garcia-Tsao, Hepatology, 2008).

Mindikoglu AL, Clin Gastr Hepat, 2018

Pathophysiology of HRS

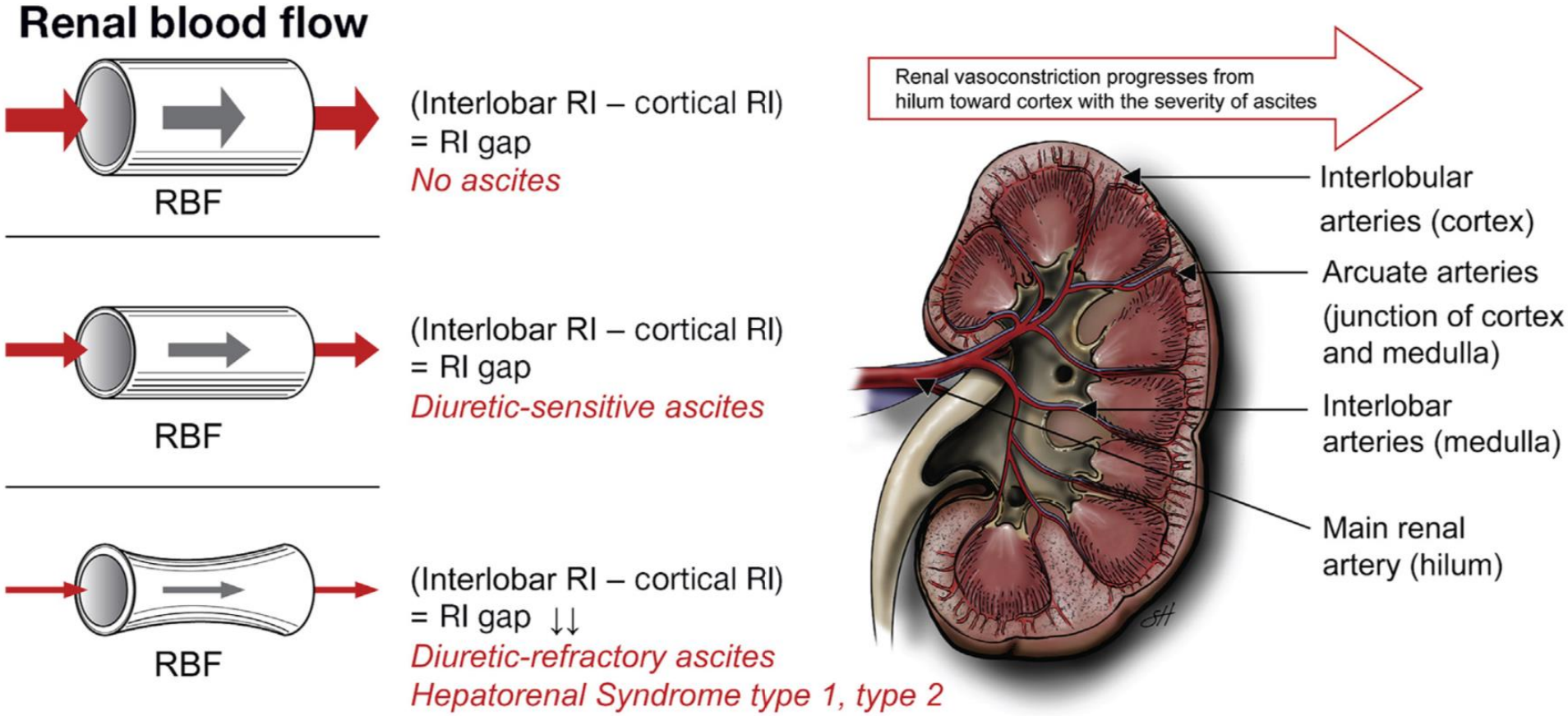

Figure 2. Renal vasoconstriction in cirrhosis progresses from the main renal artery (hilum), toward the interlobar arteries (renal medulla), and finally affects the arcuate (junction of renal medulla and cortex) and interlobular arteries (renal cortex).[40] There is an inverse relationship between RBF and the renal RI.[39,40] When RBF decreases, the renal RI increases.[39,40] Although patients without ascites and with diuretic-sensitive ascites preserve cortical renal blood, patients with diuretic-refractory ascites have a substantial reduction in cortical renal blood flow.[39,40] Therefore, although there is a renal RI gap between interlobar and cortical arteries in patients with cirrhosis without ascites and with diuretic-sensitive ascites, this RI gap disappears owing to an increase in both interlobar and cortical RIs in patients with cirrhosis and diuretic-refractory ascites.[40] Cortical ischemia is considered to be the landmark feature of cirrhosis and diuretic-refractory ascites and HRS.[1,38–41] RI, resistive index. Reprinted with permission from Baylor College of Medicine.

Mindikoglu AL, Clin Gastr Hepat, 2018

Treatment of HRS

Table 2. Meta-Analyses of Randomized Controlled Trials of Vasoactive Drugs for Reversal of HRS

Meta-analysis studies	Studies, n	Drug combinations	OR or RR for HRS reversal (95% CI)	Heterogeneity, I^2	Test for overall effect, *P* value	Studies included in the meta-analysis
Fabrizi et al[96] (2009)	5	Terlipressin vs placebo	OR, 8.09; (3.52–18.59)	41%	.0001	Hadengue et al[106] (1998), Solanki et al[112] (2003), Sanyal et al[109] (2008), Martin-Llahi et al[107] (2008), Neri et al[108] (2008)
Gluud et al[99] (2010)	4	Terlipressin alone or with albumin vs no intervention or albumin	RR, 3.76 (2.21–6.39)	0%	Not reported	Solanki et al[112] (2003), Sanyal et al[109] (2008), Martin-Llahi et al[107] (2008), Neri et al[108] (2008)
Sagi et al[102] (2010)	4	Terlipressin vs placebo	RR, 3.66 (2.15–6.23)	0%	<.00001	Solanki et al[112] (2003), Sanyal et al[109] (2008), Martin-Llahi et al[107] (2008), Neri et al[108] (2008)
Dobre et al[95] (2011)	4	Terlipressin vs placebo	OR, 7.47 (3.17–17.59)	24%	<.00001	Solanki et al[112] (2003), Sanyal et al[109] (2008), Martin-Llahi et al[107] (2008), Neri et al[108] (2008)
	2	Terlipressin vs noradrenaline	OR, 1.23 (0.43–3.54)	0%	.70	Alessandria et al[103] (2007), Sharma et al[110] (2008)
	6	Terlipressin vs placebo/terlipressin vs noradrenaline	OR, 4.49 (1.75–11.56)	56%	.002	Solanki et al[112] (2003), Sanyal et al[109] (2008), Martin-Llahi et al[107] (2008), Neri et al[108] (2008), Alessandria et al[103] (2007), Sharma et al[110] (2008)
Gluud et al[100] (2012)	4	Terlipressin alone or with albumin vs no intervention or albumin	RR, 3.76 (2.21–6.39)	0%	<.00001	Solanki et al[112] (2003), Sanyal et al[109] (2008), Martin-Llahi et al[107] (2008), Neri et al[108] (2008)
Mattos et al[101] (2016)	4	Terlipressin vs noradrenaline	RR, 1.03 (0.81–1.31)	0%	.80	Alessandria et al[103] (2007), Sharma et al[110] (2008), Singh et al[111] (2012), Ghosh et al[105] (2013)
Gifford et al[98] (2017)	5	Terlipressin ± albumin vs no intervention/ placebo ± albumin	RR, 2.54 (1.51–4.26)	52%	.0004	Solanki et al[112] (2003), Sanyal et al[109] (2008), Martin-Llahi et al[107] (2008), Neri et al[108] (2008), Boyer et al[117] (2016)
	1	Terlipressin infusion vs terlipressin bolus	RR, 1.22 (0.77–1.93)	Not applicable	.40	Cavallin et al[92] (2016)
	3	Terlipressin vs noradrenaline	RR, 0.99 (0.67–1.45)	0%	.94	Alessandria et al[103] (2007), Sharma et al[110] (2008), Singh et al[111] (2012)
	1	Terlipressin + albumin vs dopamine + standard care	RR, 2.00 (1.14–3.52)	Not applicable	.02	Silawat et al[114] (2011)
	1	Noradrenaline + albumin vs octreotide + midodrine + albumin	RR, 1.25 (0.70–2.24)	Not applicable	.45	Tavakkoli et al[113] (2012)
Facciorusso et al[97] (2017)	5	Terlipressin vs placebo	OR, 4.48 (1.88–10.67)	60%	.0007	Sanyal et al[109] (2008), Martin-Llahi et al[107] (2008), Neri et al[108] (2008), Zafar et al[116] (2012), Boyer et al[117] (2016)
	4	Terlipressin vs noradrenaline	OR, 0.89 (0.47–1.69)	0%	.72	Alessandria et al[103] (2007), Sharma et al[110] (2008), Singh et al[111] (2012), Indrabi et al[115] (2013)
	1	Terlipressin vs octreotide + midodrine	OR, 26.25 (3.07–224.21)	Not applicable	.003	Cavallin et al[104] (2015)
	1	Noradrenaline vs octreotide + midodrine	OR, 2.50 (0.19–32.19)	Not applicable	.48	Tavakkoli et al[113] (2012)

HRS, hepatorenal syndrome; OR, odds ratio; RR, risk ratio.

Mindikoglu AL, Clin Gastr Hepat, 2018

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Number of LTA and SLK in US

TABLE

Number
2000 and

Year	2011
LTx	5090
SLK Tx (%)	363 (7)
LTx Dial-pr	743
SLK Tx Dia	271 (37)

SLK Tx, simult

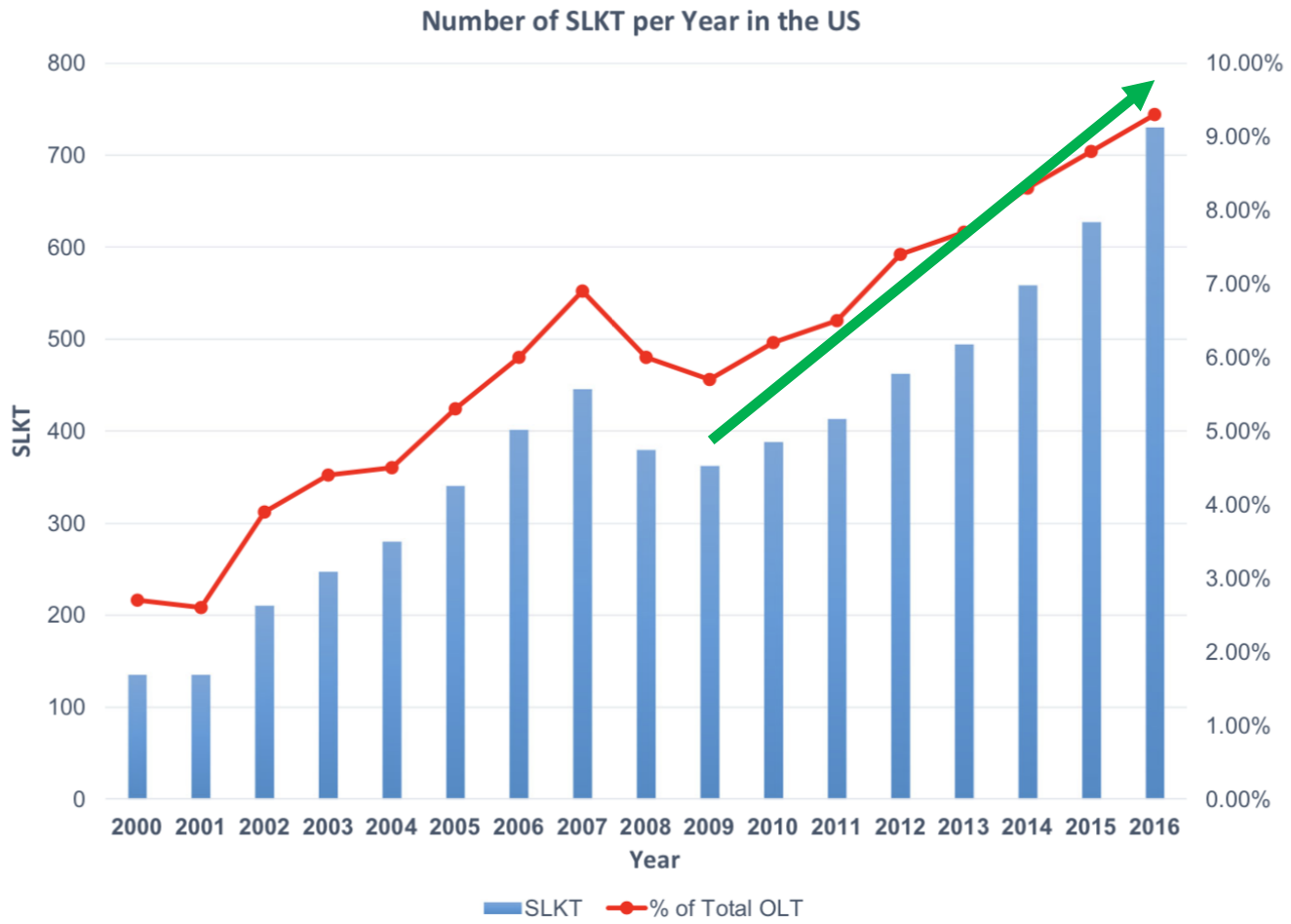

Fig. 1 The number of SLKT performed in the USA has grown from fewer than 150 per year to more than 700 over the past 15 years. The percent of total liver transplants performed as SLKT has also risen four-fold over this time

Miles CD, Current Transpl Rep, 2018

Cantarovich M, Transplantation, 2016

Survival Probability in patients with LTA and SLK

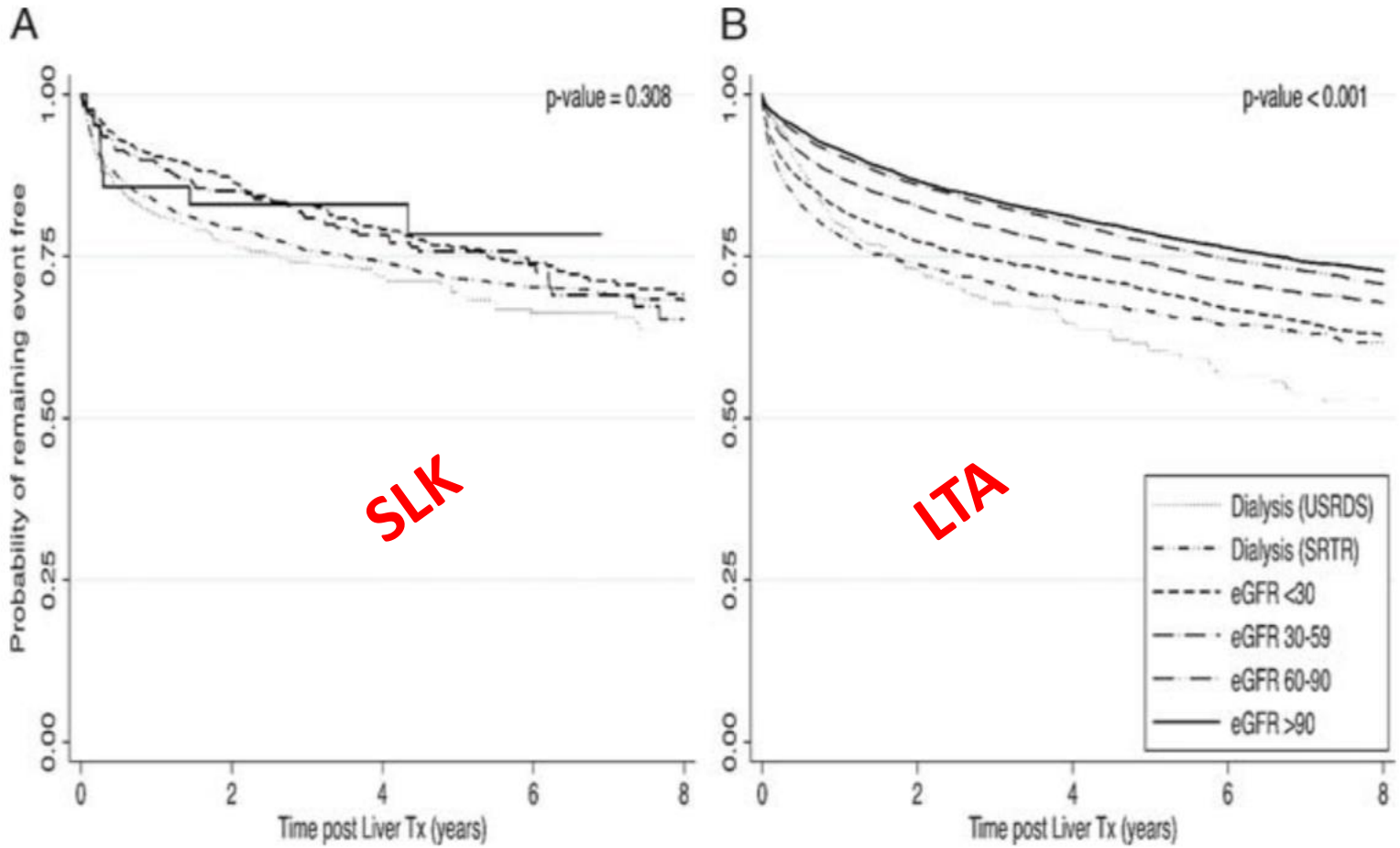

FIGURE 1. Patient survival after liver transplantation by level of kidney function. Two dialysis groups are shown (dialysis, USRDS; dialysis at Tx, UNOS). A, Simultaneous liver-kidney transplantation. B, Liver transplantation alone.

Cantarovich M, Transplantation, 2016

Survival Probability in patients with LTA and SLK

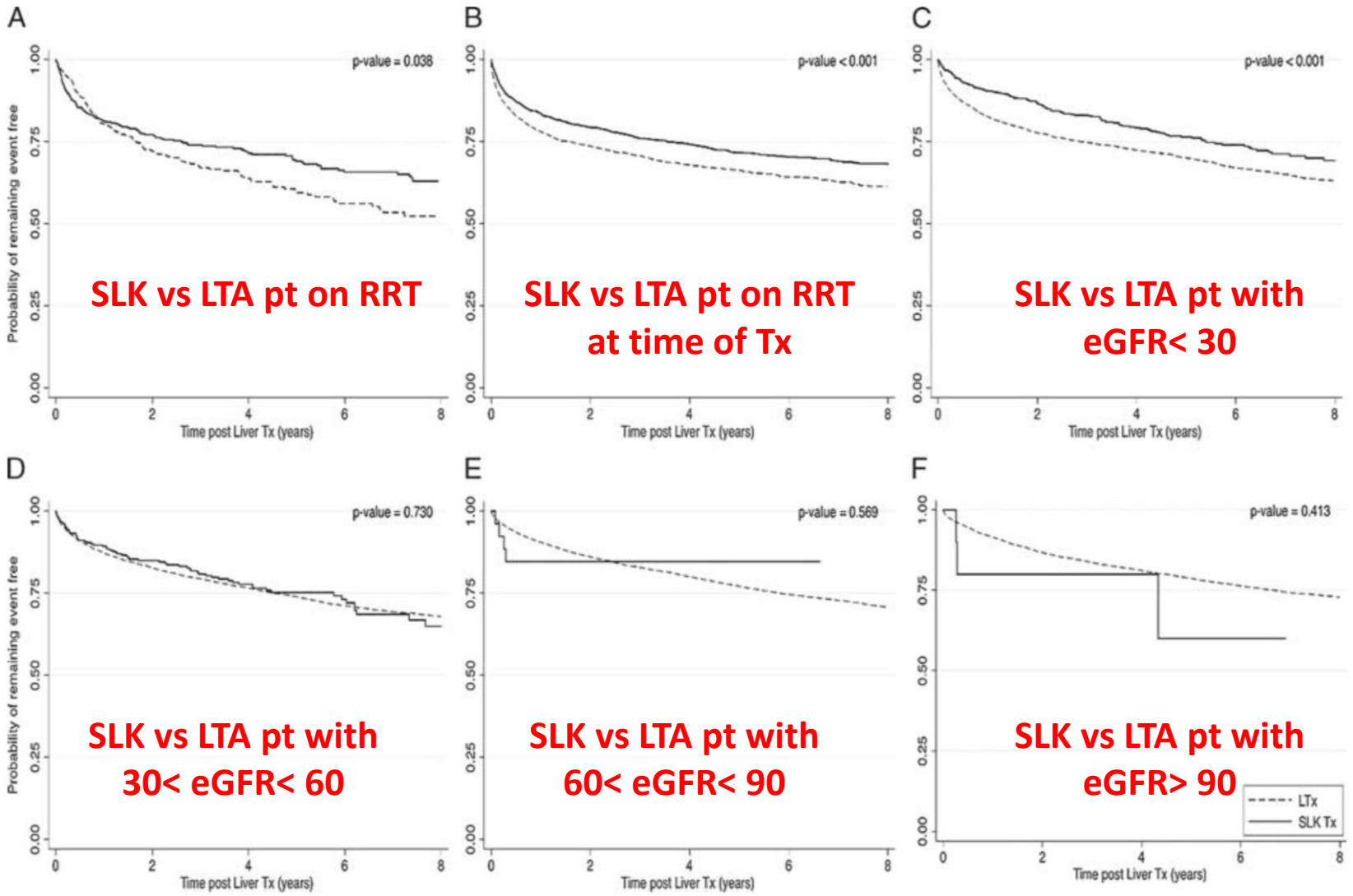

FIGURE 2. Patient survival after liver transplant alone and simultaneous liver-kidney transplant by level of kidney function at time of liver transplantation. Two dialysis groups are shown (Dialysis = USRDS, Dialysis at Tx = UNOS). A, SLK Tx versus LTx alone for patients on dialysis. B, SLK Tx versus LTx alone for patients on dialysis at the time of LTx. C, eGFR <30 mL/min per 1.73 m^2. D, eGFR 30 to 59 mL/min per 1.73 m^2. E, eGFR 60 to 90 mL/min per 1.73 m^2. F, eGFR >90 mL/min per 1.73 m^2.

Cantarovich M, Transplantation, 2016

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Canadian recommendation

TABLE 4.

Recommendations for combined nonrenal and renal transplantation according to renal function

		On dialysis	GFR <30 mL/min not on dialysis	GFR ≥30 mL/min
Time	<1 mo	Possibly eligible[a]	Not currently eligible	Not currently eligible
	1- < 3 mo	Possibly eligible[a]	Possibly eligible[a]	Not currently eligible
	≥3 mo	Eligible	Possibly eligible[a]	Not currently eligible

[a] Possibly eligible requires additional criteria to rule-in eligibility for simultaneous combined listing (see "Documenting the degree of nonreversible kidney injury").

Cantarovich M, Transplantation, 2016

Canadian recommendation for work-up

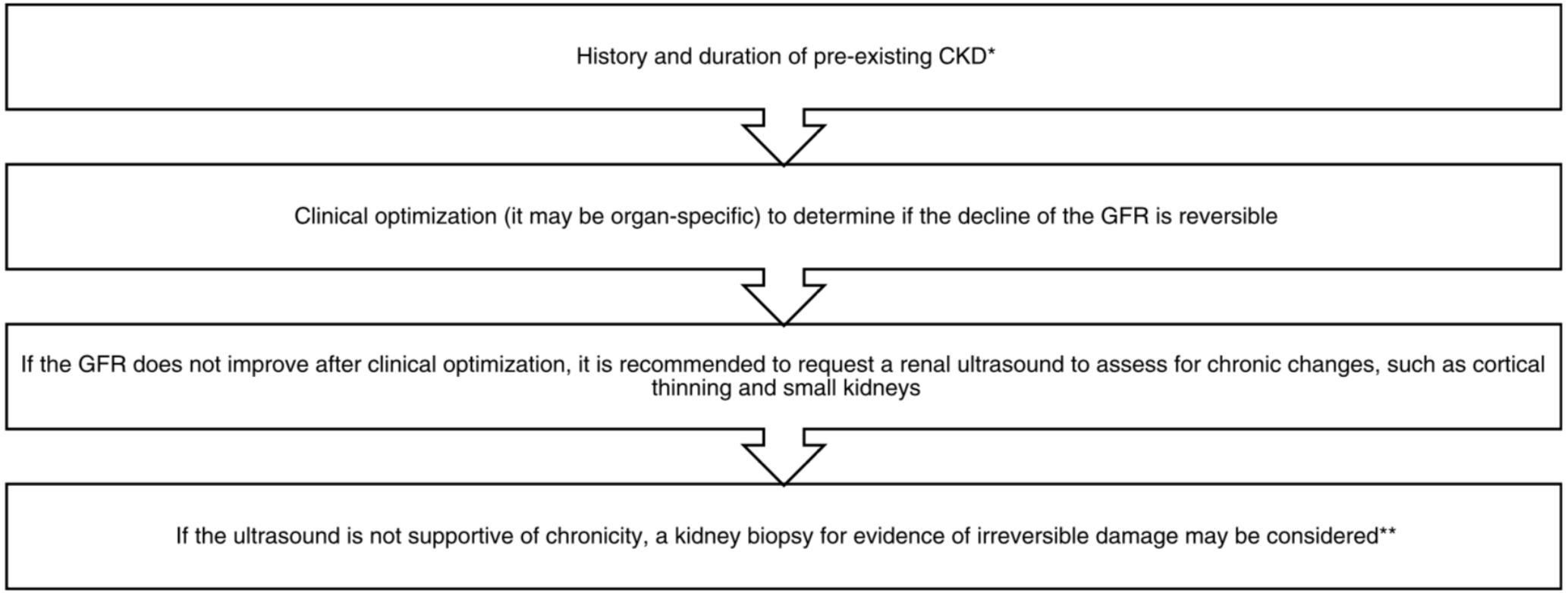

FIGURE 6. Documenting the degree of nonreversible kidney injury in candidates for combined renal/nonrenal transplantation. *Adapted from the National Kidney Foundation Kidney Disease Outcome Quality Initiative definition[19]: kidney damage ≥3 months as defined by structural or functional abnormalities of the kidney with or without decreased GFR, manifested by pathologic abnormalities, or markers of kidney damage, which include abnormalities in the composition of blood or urine or abnormalities in imaging tests; and CKD stages 3 to 5 for at least 3 months before the onset of end-stage liver/heart/lung disease. This establishes a history of CKD and prior progression toward end-stage renal disease. **In the event the kidney biopsy is not possible or results are inconclusive, history of CKD and other tests results may support the diagnosis of chronic kidney damage. CKD indicates chronic kidney disease

Cantarovich M, Transplantation, 2016

What are the goals of US/UNOS proposal?

Main goal: Establish SLK allocation policy that addresses different perspectives within the transplant community

- Establish medical eligibility criteria for SLK
- Ensure a balance of fairness and utility in allocation of kidneys

Kidney community

- Provide clearer liver-kidney allocation policies
- Provide information in UNOS computer system to direct OPO in allocation process

OPO community

- Resolve inconsistency between multi-organ and deceased donor liver allocation policy re: liver Share 35 policy
- Ensure safety net for liver recipients who need a kidney tx soon after liver tx

Liver community

How does the proposal address the problems?

- Requires all adult candidates seeking a liver-kidney transplant to meet medical eligibility criteria

Kidney community

- Establishes rules for OPOs that specify when liver-kidney allocation is required, prohibited, or permissible (at all levels)
- Computer system will guide OPOs

OPO community

- Resolves inconsistency between deceased donor liver and liver-kidney allocation
- Establishes “safety net” for liver recipients with continued dialysis dependency/kidney dysfunction in first year after liver transplant

Liver community

SLK Medical Eligibility Criteria

Transplant nephrologist must confirm candidate has <u>one</u> of the following:	**And tx hospital must report to UNOS and document <u>one</u> of the following in the medical record:**
1. Chronic kidney disease with measured or calculated GFR less than or equal to 60 mL/min for greater than 90 consecutive days	• Dialysis for ESRD • Most recent eGFR/CrCl is at or below **30** mL/min at or after registration on kidney waiting list
2. Sustained acute kidney injury	One or a combination of both of the following **in the past six weeks**: • Dialysis for six consecutive weeks • eGFR/CrCl at or below 25 mL/min for six consecutive weeks. The program must confirm criteria continues to be met **at least once every seven days**.
3. Metabolic disease	Diagnosis of: • Hyperoxaluria • Atypical HUS from mutations in factor H or factor I • Familial non-neuropathic systemic amyloid • Methylmalonic aciduria

Justification and Concerns regarding UNOS policy

- SLK recipient candidates are sicker, and therefore, it is ethically appropriate to prioritize them for transplantation over KA patients waiting longer.
- The more liberal cutoff eGFR of 30 ml/min for SLK compared with the cutoff of 20 ml/min required for a kidney candidate to start accruing time on the KA waiting list may seem unfair.
- Single- center study using post–SLK radionuclide renal scans, it was calculated that **nearly one third of UNOS criteria recipients recovered a native GFR exceeding 20 ml/min** (Levitsky et al., AJT, 2012).
- **Fewer than 10% of LA recipients requiring dialysis in the first year.**
- 19% of SLK recipients in the past 10 years would not have met the eligibility criteria currently being proposed.

SLK Recipients, Jan 2005 – Jun 2015

Would SLK recipient have met proposed SLK eligibility criteria?		Total	
		N	%
Chronic kidney disease	On Dialysis for ESRD at Time of Transplant	1,874	41.6
	Not on Dialysis for ESRD, eGFR <21	1,081	24.0
	Not on Dialysis for ESRD, eGFR 21-25	328	7.3
	Not on Dialysis for ESRD, eGFR 26-30	267	5.9
Sustained acute kidney injury	On dialysis for 6+ weeks before transplant #	101	2.2
Would not have qualified for SLK	No Dialysis for ESRD or temporary dialysis for 6+ weeks, eGFR 31-35	213	4.7
	No Dialysis for ESRD or temporary dialysis for 6+ weeks, eGFR > 35	636	14.1
Total		4,543	100.0

Approximately 19% of previous SLK recipients would not have qualified under proposed eligible criteria.

Proposed “Safety Net” Eligibility

- Candidates who are on the kidney waiting list and have eGFR/CrCl at or below 20 mL/min or are on dialysis in the 60-365 days after liver transplant will be eligible to appear in this new kidney allocation match classification.
- To continue to be eligible, the transplant program must report at least once every 30 days that this medical criteria continues to be met. Once this has been confirmed for three consecutive periods, the candidate will be eligible indefinitely*

*the three consecutive 30-day period rule will still apply if the candidate’s first report of eligibility is in month 10, 11, or 12 after the liver transplant.

Sequence A
KDPI <=20%

Highly Sensitized
0-ABDRmm
Prior living donor
Local pediatrics
Local top 20% EPTS
0-ABDRmm (all)
Local (all)
Regional pediatrics
Regional (top 20%)
Regional (all)
National pediatrics
National (top 20%)
National (all)

Sequence B
KDPI >20% but <35%

Highly Sensitized
0-ABDRmm
Prior living donor
Local pediatrics
Local safety net
Local adults
Regional pediatrics
Regional adults
National pediatrics
National adults

Sequence C
KDPI >=35% but <=85%

Highly Sensitized
0-ABDRmm
Prior living donor
Local safety net
Local
Regional
National

Sequence D
KDPI>85%

Highly Sensitized
0-ABDRmm
Local safety net
Local + Regional
National

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Predictors of AKI after Liver Transplantation

- High MELD score of the recipient (O'Riordan A. et al., AJT, 2007).
- Ischemia reperfusion injury (age, steatosis, longer warm and cold ischemic time).
- DCD liver.
- Hypoperfusion during OR.
- Piggy back technique to avoid complete clamp of IVC.
- Post-operative factors: sepsis, CNI, bleeding, re-operation.

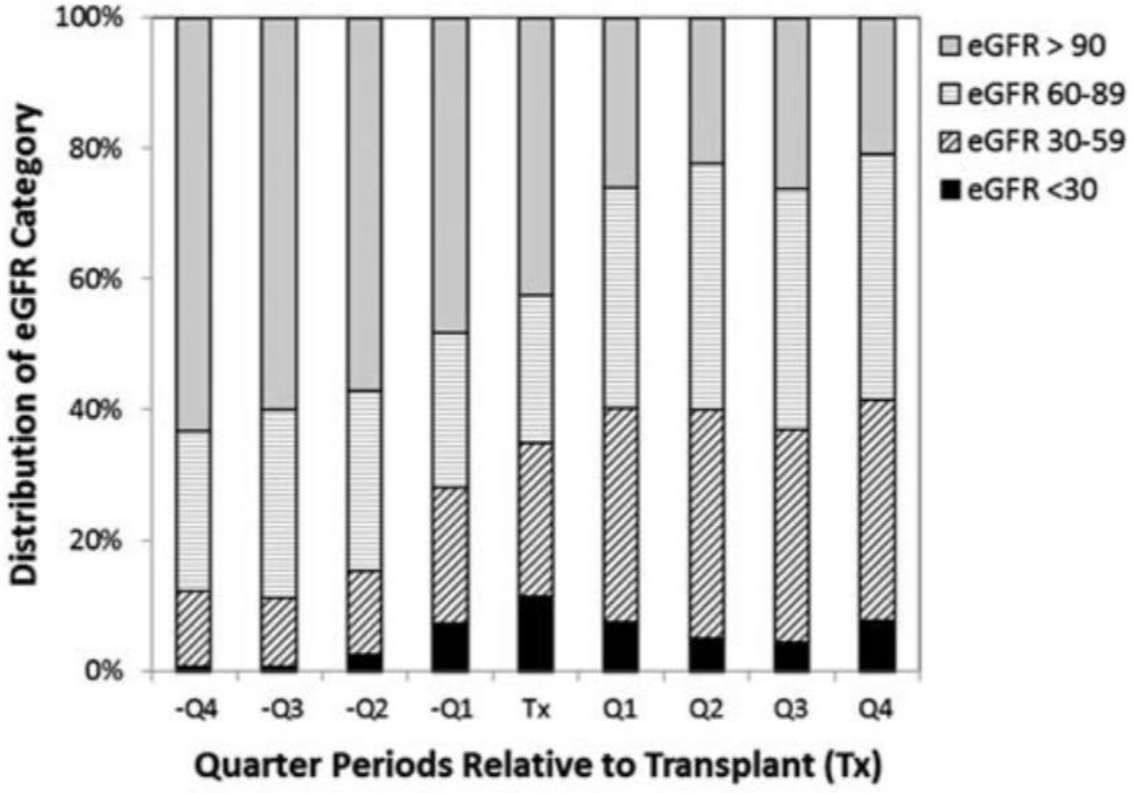
Durand F, Transplantation, 2018

Patterns of Kidney Function Perioperatively

- 416 patients from John Hopkins between 1996-2009.
- Excluded: age < 18years, multi-organ transplant, liver re-transplantation.
- CKD-EPI has been used to calculate eGFR with median 59 values.
- Time before and after transplant has been divided to quarters.
- Data was merged with USRDS.

Longenecker JC, Transplantation, 2015

eGFR in peri-operative period of 416 LTA patients



Tx, 14 to 0 days prior to transplant; –Q1, 91 to 15 days prior to transplant; all other quarters represent successive 3-month periods before and after transplant.

FIGURE 1. Change in the distribution of eGFR Category, according to quarter periods relative to liver transplantation (n = 369). Tx, 14 to 0 days before transplantation; –Q1, 91 to 15 days before transplantation; all other quarters represent successive 3-month periods before and after transplantation. The eGFR distribution at the time of transplant is statistically different from the distribution at all other quarter time points.

Longenecker JC, Transplantation, 2015

eGFR in peri-operative period of 416 LTA patients

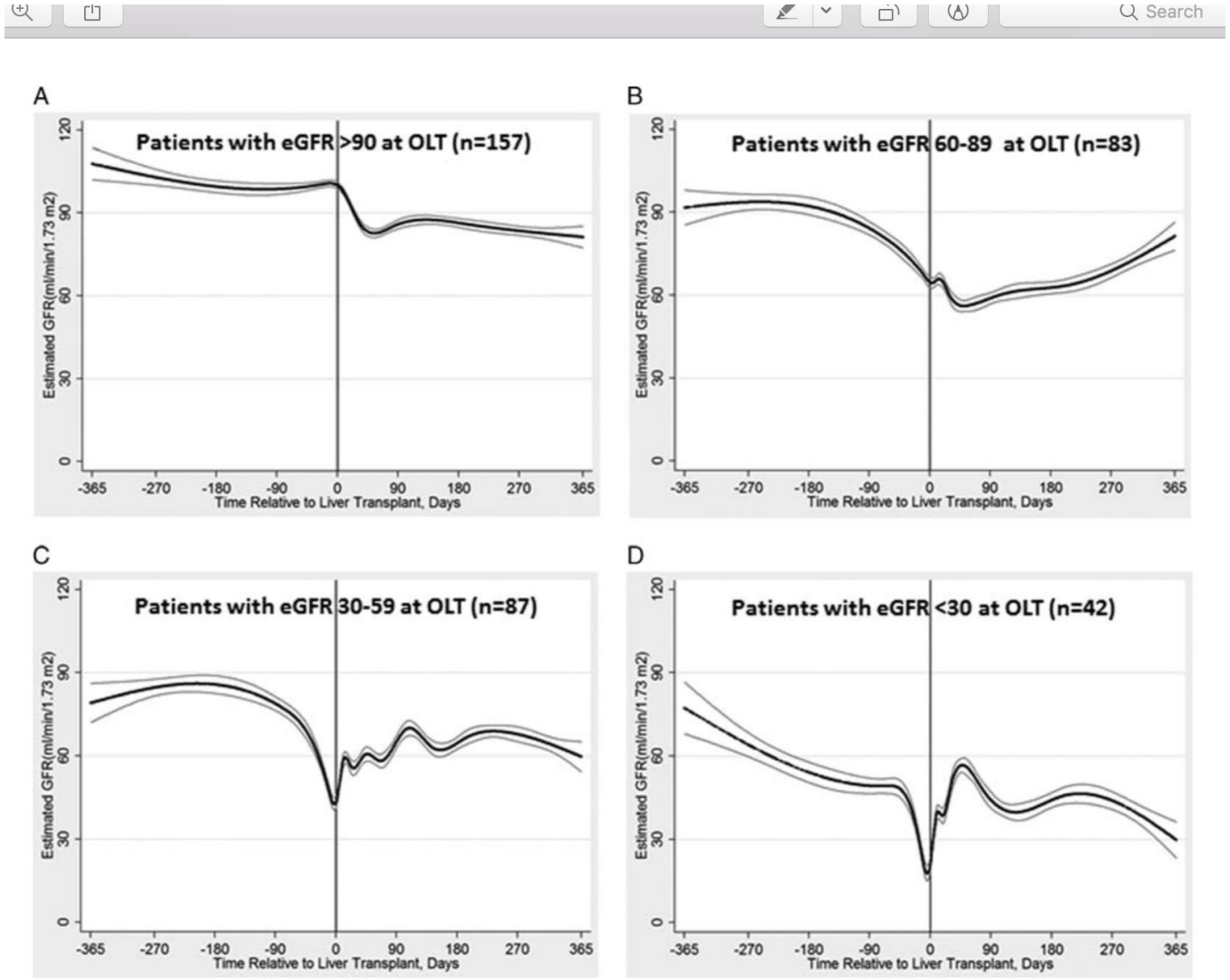


FIGURE 2. Change in estimated GFR (mg/mL per 1.73 m^2) over time among 369 liver transplant patients, stratified by eGFR level at time of OLT. Cubic regression spline models were used to generate change in eGFR and serum creatinine over time. Error bars represent 95% confidence intervals around the cubic spline function. The 3 regression splines for eGFR and the 3 for serum creatinine are statistically significantly different from each other. Included in this analysis are the 369 patients who had serum creatinine values in all 3 time periods (A, B, and C).

Longenecker JC, Transplantation, 2015

Factors Associated with ESRD in 416 LTA patients

TABLE 3.

Characteristics Associated With Progression to End-Stage Renal Disease With USRDS Registration During 15 years of Follow-Up After Liver Transplantation (n = 411)[a]

	Crude Incidence of ESRD		Adjusted[b] Hazard Ratio of ESRD		
Characteristic	**(per 1000 p-y)**	***P***	**HR**	**[95% CI]**	***P***
eGFR category at OLT					
≥90	7.6	—	1.0	Reference	
60-89	14.6	0.06	1.8	[0.8, 4.0]	0.11
30-59	25.3	0.007	3.1	[1.5, 6.6]	0.001
<30	34.8	<0.001	4.4	[1.9, 10.0]	<0.001
P trend	<0.001		<0.001		
eGFR category at OLT					
≥60	10.0	—	1.0	Reference	
<60	28.2	0.001	2.7	[1.6, 4.7]	<0.001
MELD score category at OLT					
<20	11.8	—	1.0	Reference	
20-29	18.2	0.09	1.6	[1.6, 4.8]	0.16
≥30	29.0	0.009	2.5	[1.2, 4.9]	0.01
Diabetes					
No	11.7	—	1.0	Reference	
Yes	31.5	0.002	2.6	[1.5, 4.5]	<0.001
Diabetes/eGFR Category at OLT[c]					
No diabetes/eGFR ≥60	8.5	—	1.0	Reference	
Diabetes/eGFR ≥ 60	19.0	0.03	2.2	[1.0, 5.1]	0.06
No diabetes/eGFR < 60	20.6	0.01	2.4	[1.1, 5.0]	0.02
Diabetes/eGFR < 60	49.8	<0.0001	5.5	[2.7, 11.4]	<0.001

[a] Five individuals already enrolled in USRDS ESRD program were excluded from this analysis.
[b] All models include age and gender as covariates.
[c] *P* value for interaction = 0.94.

Longenecker JC, Transplantation, 2015

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Henry Ford Hospital 2009-2015

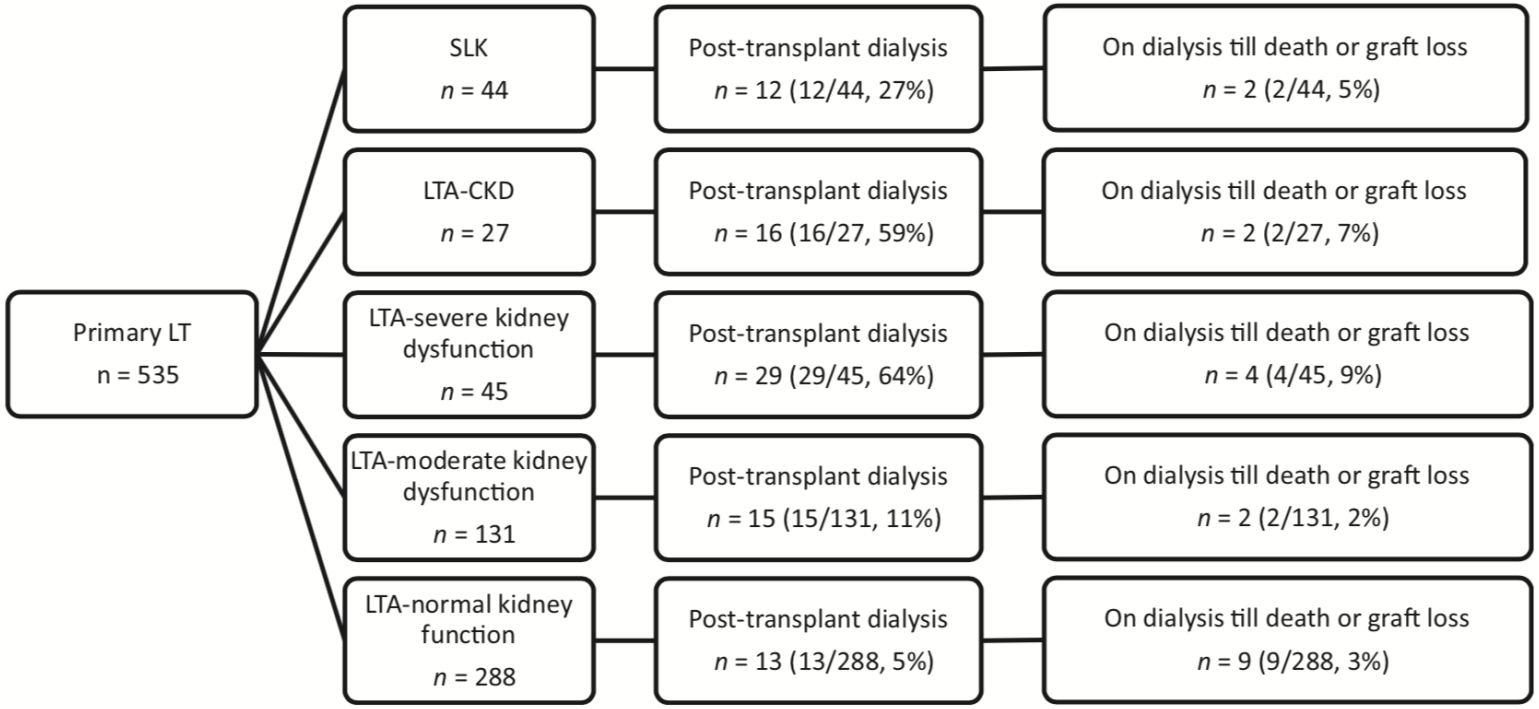

Figure 1 Requirement of post-transplant dialysis and graft loss associated with persistent renal failure. Simultaneous liver–kidney transplant (SLK) and liver transplant alone (LTA) patients classification as follows: (i) SLK group (n = 44), (ii) LTA-chronic kidney disease (CKD) group: patients who met the CKD criteria but did not have SLK (n = 27), (iii) LTA-severe kidney dysfunction group: LTA patients with an eGFR ≤30 ml/min who did not meet the CKD criteria (n = 45), (iv) LTA-moderate kidney dysfunction group: LTA patients with an eGFR 31–60 ml/min (n = 131), and (v) LTA-normal kidney function group: LTA patients with an eGFR >60 ml/min (n = 288). The LTA-CKD and LTA-severe kidney dysfunction groups showed significantly higher rates of post-transplant dialysis than the SLK group (59% [16/27], 64% [29/45] vs. 27% [12/44], P = 0.01 and <0.001, respectively). LTA-moderate kidney dysfunction and LTA-normal kidney function groups showed significantly lower rates of post-transplant dialysis than the SLK group (11% [15/131] and 5% [13/288] vs. 27% [12/44], P < 0.001 and <0.001, respectively)

Nagai S, Transpl Int, 2018

Henry Ford Hospital 2009-2015

Table 2. Logistic regression analysis of possible risk factors for post-transplant dialysis after liver transplant alone without pretransplant dialysis (n = 448).

	No. of patients (%)	Odds ratio (95% CI)	Univariate P*	Adjusted odds ratio (95% CI)	Multivariate P*
Recipient age					
≥ 60 yo (Ref. <60 yo)	162 (36)	1.19 (0.59–2.42)	0.62		
Recipient sex					
Female (Ref. male)	162 (36)	2.24 (1.12–4.49)	0.02	1.61 (0.69–3.8)	0.27
Recipient race (Ref. Caucasian)					
African-American	70 (16)	1.7 (0.73–3.94)	0.22		
Hispanic	17 (4)	1.75 (0.38–8.11)	0.47		
Middle East	7 (2)	–	–		
Others	15 (3)	2.11 (0.45–9.94)	0.34		
MELD score					
≥30 (Ref. <30)	57 (13)	2.16 (0.93–5.02)	0.07	0.78 (0.24–2.64)	0.7
Primary liver disease					
HCV (Ref. non-HCV)	178 (44)	0.96 (0.48–1.93)	0.9		
Donor age					
≥40 yo (Ref. <40 yo)	253 (57)	1.52 (0.74–3.15)	0.25		
DCD donor (Ref. DBD)	54 (12)	0.23 (0.03–1.78)	0.16	0.59 (0.07–4.71)	0.62
Pretransplant kidney function (Ref. LTA-normal kidney function)					
LTA-CKD	15 (3)	7.69 (2.16–27.5)	0.001	5.59 (1.27–24.7)	0.02
LTA-severe kidney dysfunction	17 (4)	8.81 (2.7–28.8)	<0.001	7.77 (1.54–39.2)	0.01
LTA-moderate kidney dysfunction	128 (29)	2.39 (1.08–5.32)	0.03	1.74 (0.64–4.78)	0.28
CIT					
≥350 min (Ref. <350 min)	154 (43)	2.35 (1.07–5.13)	0.03	1.93 (0.8–4.66)	0.14
WIT					
≥33 min (Ref. <33 min)	269 (70)	4.09 (1.22–13.8)	0.02	3.45 (0.93–12.8)	0.06
Intra-operative PRBC + autologous transfusion					
>10 units (Ref. ≤10 units)	80 (21)	4.35 (2.03–9.35)	<0.001	2.85 (1.21–6.7)	0.02

CI, confidence interval; CIT, cold ischemia time; CKD, chronic kidney disease; DBD, donation after brain death; DCD, donation after cardiac death; LTA, liver transplant alone; MELD score, model for end-stage liver disease–sodium score; PRBC, packed red blood cell transfusion; WIT, warm ischemia time.

*Logistic regression model.

Only four independent predictors:

- LTA-CKD
- LTA severe dysfunction
- WIT
- >10 U PRBC

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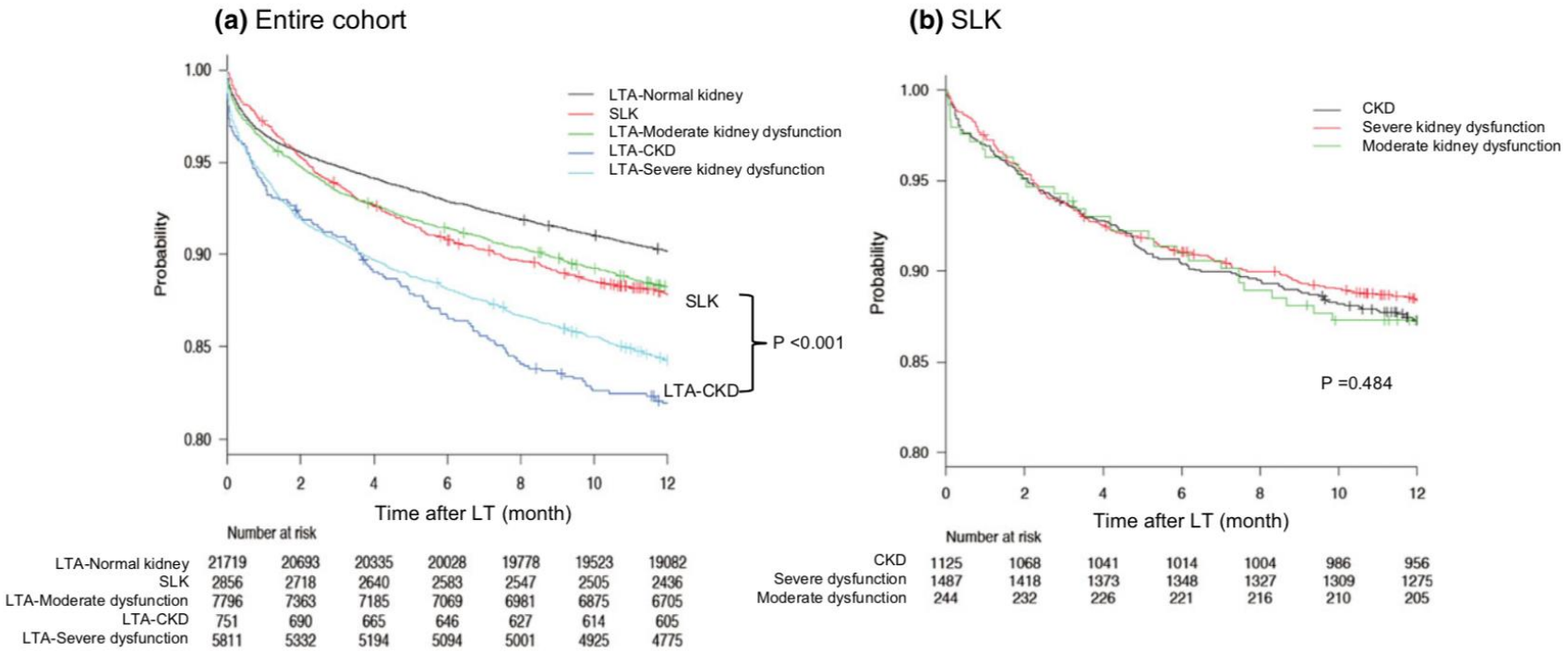

Figure 3 (a) Graft survival up to 1 year according to graft type and pretransplant kidney function Organ Procurement and Transplant Network/United Organ Sharing Network (OPTN/UNOS registry). Patients were categorized in the same way. (i) liver transplant alone (LTA)-normal kidney function group, (ii) simultaneous liver–kidney transplant (SLK) group, (iii) LTA-moderate kidney dysfunction group, (iv) and LTA-chronic kidney disease (CKD) group, (v) LTA-severe kidney dysfunction group. The LTA-CKD group showed significantly worse 1-year graft survival rate (82.0%), compared with the SLK group (87.8%) ($P < 0.001$) and among all groups (90.2%, 88.2%, and 84.3% in LTA-normal kidney, LTA-moderate dysfunction, and LTA-severe kidney dysfunction groups, respectively, $P < 0.001$). (b) Graft survival up to 1 year according to pretransplant kidney function in the SLK group (OPTN/UNOS registry). SLK patients were categorized according to pretransplant kidney function as follows. CKD: SLK patients who met the CKD criteria, Severe kidney dysfunction: SLK patients who showed eGFR ≤30 ml/min at transplant but not meeting the CKD criteria, Moderate kidney dysfunction: SLK patients who showed eGFR 30–60 ml/min. Pretransplant kidney function was not associated with 1-year graft survival rates (87.3%, 88.3%, and 87.3% in the CKD, severe dysfunction, and moderate dysfunction groups, respectively, $P = 0.484$).

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Table 4. Cox's regression analysis of possible risk factors for graft loss in the first year (validation analysis based on the Organ Procurement and Transplant Network/United Organ Sharing Network registry).

	No. of patients (%)	Adjusted hazard ratio (95% CI)	*P* value*
Recipient age			
≥60 yo (Ref. <60 yo)	14 568 (37.4)	1.152 (1.103–1.203)	<0.001
Recipient sex			
Female (Ref. male)	12 956 (33.3)	0.976 (0.932–1.022)	0.295
Recipient race (Ref. Caucasian)	27 608 (70.9)		
African-American	3835 (9.9)	1.241 (1.161–1.327)	<0.001
Hispanic	5248 (13.5)	0.931 (0.873–0.993)	0.03
Asian	1714 (4.4)	0.860 (0.769–0.962)	0.008
Others	528 (1.4)	0.955 (0.792–1.152)	0.631
MELD score			
≥30 (Ref. <30)	10 467 (26.9)	0.992 (0.931–1.056)	0.796
Primary liver disease			
HCV (Ref. non-HCV)	15 813 (40.6)	1.225 (1.173–1.280)	<0.001
Donor age			
≥40 yo (Ref. <40 yo)	21 027 (54.0)	1.349 (1.291–1.490)	<0.001
DCD donor (Ref. DBD)	2098 (5.4)	1.368 (1.256–1.491)	<0.001
Pretransplant dialysis w/o SLK (Ref. no pretransplant dialysis)	3383 (8.7)	1.191 (1.083–1.310)	<0.001
SLK (Ref.)	2856 (7.3)		
LTA-CKD	751 (1.9)	1.348 (1.157–1.572)	<0.001
LTA-severe kidney dysfunction	5811 (14.9)	1.087 (0.976–1.212)	0.129
LTA-moderate kidney dysfunction	7796 (20.0)	0.963 (0.879–1.054)	0.413
LTA-normal kidney function	21 719 (55.8)	0.881 (0.809–0.960)	0.004
CIT (per hour)	–	1.023 (1.017–1.03)	<0.001

CIT, cold ischemia time; CKD, chronic kidney disease; DBD, donation after brain death; DCD, donation after cardiac death; HCV, hepatitis C virus infection; LTA, liver transplant alone; MELD score, model for end-stage liver disease–sodium score; SLK, simultaneous liver and kidney transplant.

*Cox's proportional hazards model.

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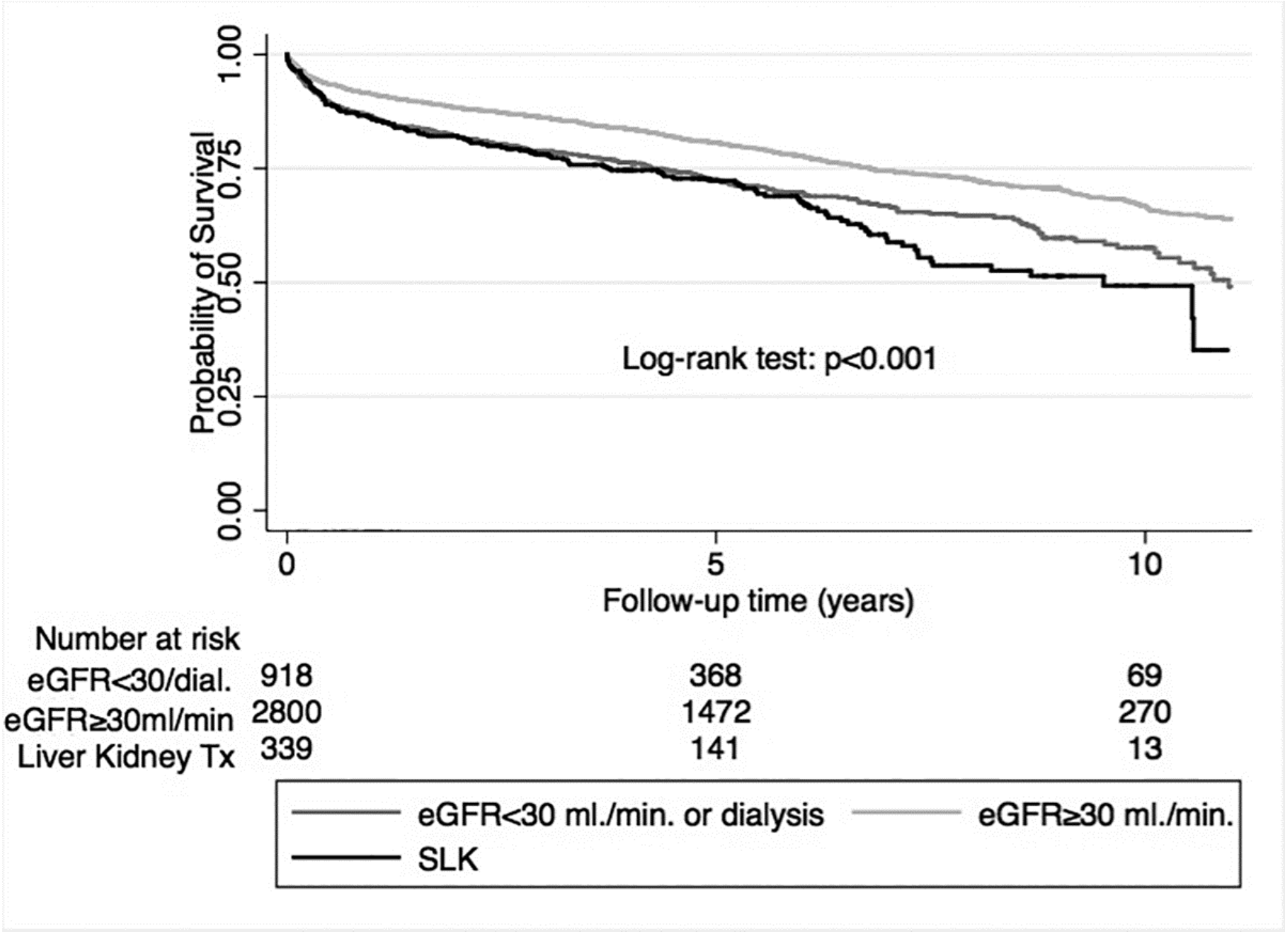
Survival in NASH Liver Transplant Recipients



Molnar MZ, under review

Molnar MZ, under review

Survival in NASH Liver Transplant Recipients

Reference: Recipients who had eGFR< 30 ml/min./1.73m^2 and/or received dialysis	Sub-Hazard Ratios (SHRs)	95% Confidence Interval of SHRs	p-value
Model 1 (n=4,057):			
eGFR ≥ 30 ml/min./1.73m^2	0.67	0.58-0.77	<0.001
Simultaneous liver kidney transplantation	1.18	0.96-1.46	0.123
Model 2 (n=4,057):			
eGFR ≥ 30 ml/min./1.73m^2	0.66	0.57-0.76	<0.001
Simultaneous liver kidney transplantation	1.11	0.90-1.38	0.326
Model 3 (n=3,793):			
eGFR ≥ 30 ml/min./1.73m^2	0.75	0.60-0.93	0.010
Simultaneous liver kidney transplantation	1.14	0.91-1.43	0.252
Model 4 (n=3,323):			
eGFR ≥ 30 ml/min./1.73m^2	0.81	0.64-1.02	0.079
Simultaneous liver kidney transplantation	1.23	0.96-1.57	0.109
Multiple imputation model (n=4,057):			
eGFR ≥ 30 ml/min./1.73m^2	0.76	0.62-0.93	0.009
Simultaneous liver kidney transplantation	1.21	0.97-1.50	0.096

Objectives

- Hepato-renal Syndrome
- Epidemiology of Liver Transplant Alone (LTA) and Simultaneous Liver Kidney Transplantation (SLK)
- Eligibility of Simultaneous Liver Kidney Transplantation (SLK)
- Predictors of Kidney Failure in Patients with LTA
- Impact of Post-Transplant Renal Function on Liver Graft Outcome
- **Immunological Questions of SLK**

Immunology of Liver Transplant

- Until recently, preformed DSA were generally considered to be clinically irrelevant to liver allograft outcomes based on the perceived absence of hyperacute rejection and the rarity of early allograft loss from rejection (Starzl TE, Clin Transpl, 1989).
- However, adequately powered studies since the early 1990s have shown that liver transplant recipients with a positive crossmatch have an increased risk of early allograft damage and failure (Takaya S., Trans Proc, 1991).
- Recent studies have confirmed inferior clinical outcomes in some but not all DSA-positive patients (O`Leary JG, Liver Transpl, 2013).

O`Leary JG, AJT, 2014 – Meeting Report

Pathophysiological explanations why liver can absorb antibodies

- Soluble Classes I and II antigen secretion is increased during injury
- Increased area of distribution (capillary surface: liver: 21 m^2 vs kidney 0.21 m^2)
- Dual blood supply of the liver
- Hepatocyte regenerative capacity is tremendous
- Hypocomplementemia in liver patients
- Role of Kupffer cells (remove activated complements and immune complexes)
- Antigen location and density and DSA concentration and characteristics

O`Leary JG, AJT, 2014 – Meeting Report

Table 1: Patient and donor characteristics

Age	Recipient	51
	Donor	22
Cold ischemia time		8.7 h
MELD		23
Male		67%
Race	Black	13%
	White	56%
	Other	31%
Liver diagnosis	Hepatitis C	36%
	Alcoholic liver disease	15%
	NASH/CC/metabolic	15%
	Retransplant	10%
	Hepatitis B	5%
	PSC/AIH/PBC	4%
	Other	15%
Hepatocellular carcinoma		12%
Immunosupression 3 months	Tacrolimus	59%
	Cyclosporine	37%
	Steroids	96%
Renal indications for transplant	Diabetic or hypertensive nephropathy	26%
	Polycystic kidney disease	12%
	Glomerulonephritis	14%
	HRS/ATN	11%
	Retransplant	7%
	CNI toxicity	6%
	Oxalosis	5%
	Amyloid/IN/reflux	5%
	IgA nephropathy	2%
	Other	12%

MELD = Model for End-Stage Liver Disease; NASH = nonalcoholic steatohepatitis; CC = cryptogenic cirrhosis; PSC, primary sclerosing cholangitis; AIH, autoimmune hepatitis; PBC = primary biliary cirrhosis; HRS = hepatorenal syndrome; ATN = acute tubular necrosis; IN = interstitial nephritis.

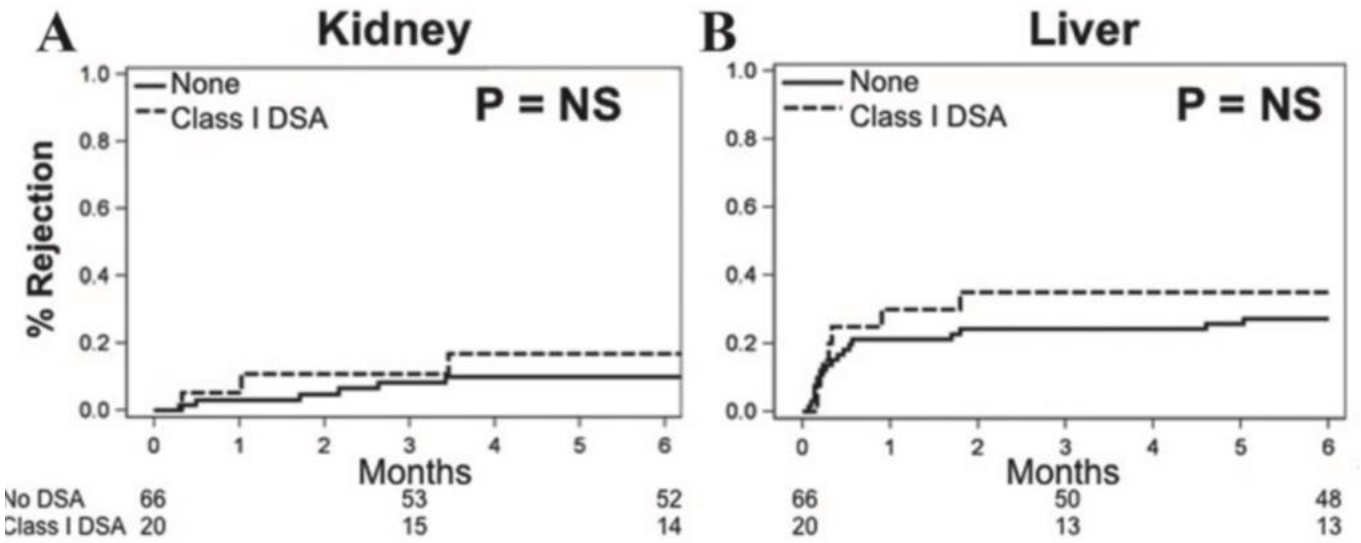
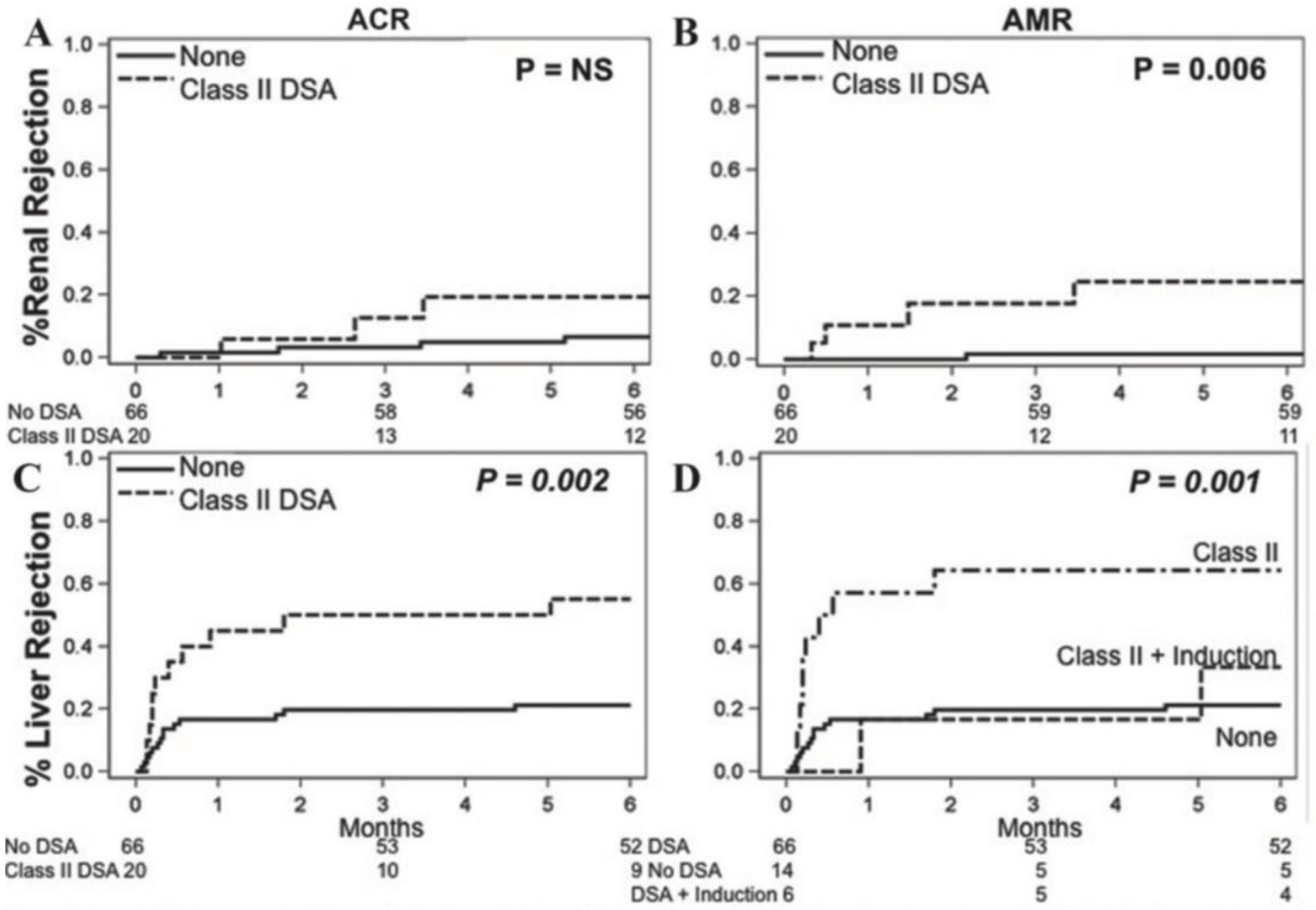


Figure 1: Risk of (A) all types of renal and (B) liver allograft rejection in patients with preformed class I DSA with MFI > 2000. All rejections are biopsy proven. There was no difference in ACR or AMR of the kidney (data not shown).

O`Leary JG, AJT, 2014

Class II DSA and liver / kidney rejection



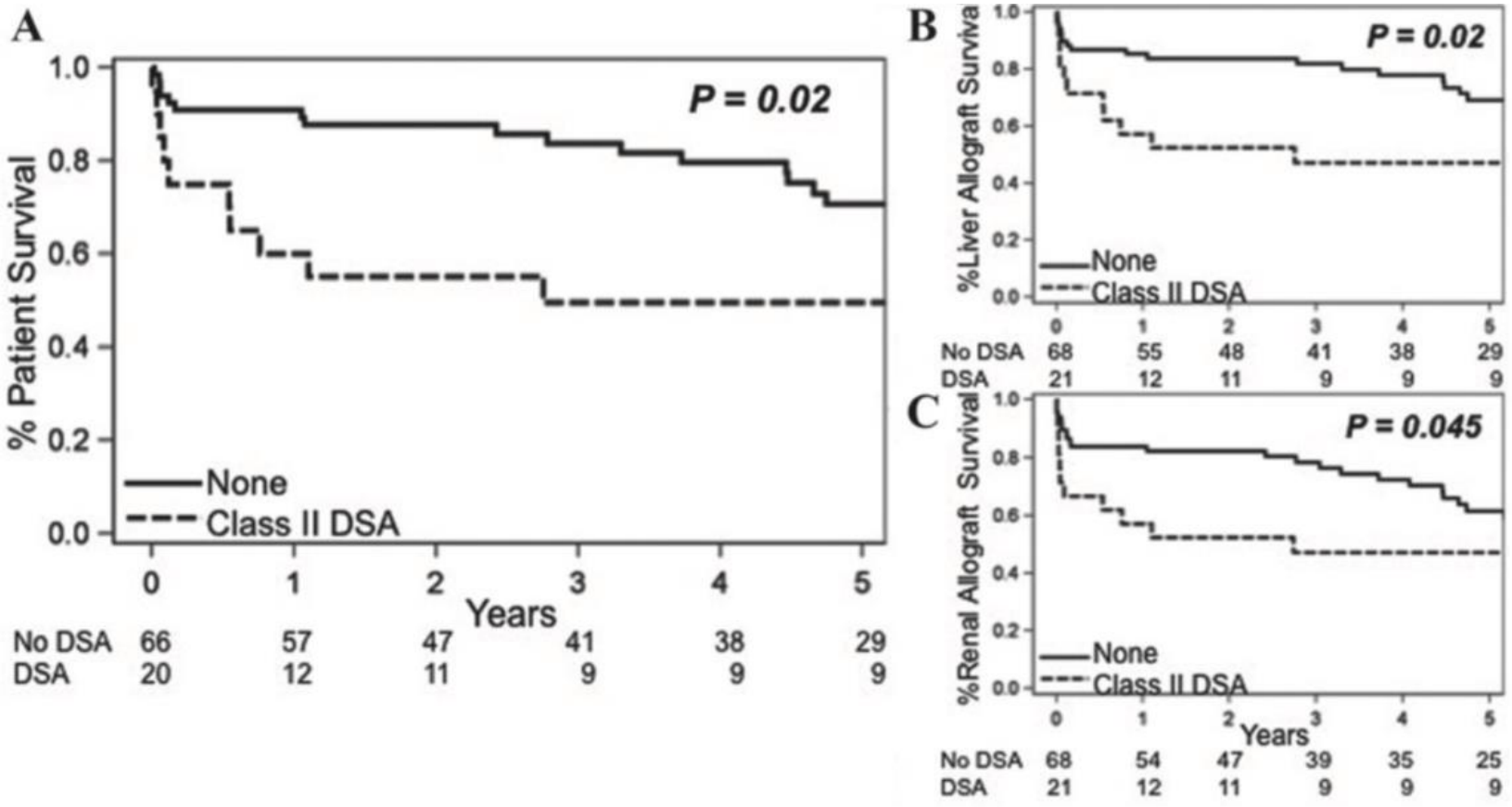
Pre-formed Class II DSA

Figure 2: Risk of (A) renal ACR, (B) renal AMR and (C) liver allograft rejection in patients with preformed class II DSA with MFI > 2000. (D) Induction decreased the risk of rejection but did not change the overall survival impairment. Induction used was Daclizumab in 16 patients, Daclizumab plus Thymoglobulin in three patients, and OKT3 in two patients. All rejections are biopsy proven.

How about C1q biding and IgG class II or IV subclass?

O`Leary JG, AJT, 2014

Class II DSA and liver / kidney rejection



De-novo Class II DSA

Figure 3: Preformed class II DSA (MFI > 2000) decreases (A) patient, (B) liver allograft and (C) renal allograft survival.

How about C1q biding and IgG class II or IV subclass?

O`Leary JG, AJT, 2014

Class II DSA and patient's and graft survival

Table 4: Univariate analysis was undertaken and all factors with $p < 0.2$ (all the factors shown) were entered into a stepwise multivariable model. The final multivariable model shows that only three factors remained significantly associated ($p < 0.05$) with patient and liver allograft survival. Class II DSA for this analysis was defined as either preformed or *de novo*.

	Patient		Liver graft		Renal graft	
	HR	p-Value	HR	p-Value	HR	p-Value
Class II DSA	2.2	0.043	2.2	0.044	2.0	0.066
Steroids 1 month	0.03	0.004	0.03	0.004	0.07	0.022
Recipient age >50	6.4	<0.001	6.3	<0.001	2.8	0.024
Cytomegalovirus		NS		NS		NS
Acute cellular rejection		NS		NS		NS
Hepatocellular carcinoma		NS		NS		NS
MELD >15		NS		NS		NS
Induction		NS		NS		

MELD = Model for End-Stage Liver Disease.

O`Leary JG, AJT, 2014

Thank you very much for your attention!

Questions?