Dual organ allocation implications: Older NASH patients, More CKD

Richard Formica
Professor of Medicine and Surgery
Yale University

CEOT CUTTING EDGE OF TRANSPLANTATION

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RESOLVING THE ORGAN SHORTAGE

PRACTICE | POLICY | POLITICS

FEBRUARY 25-27, 2016 • PHOENIX, ARIZONA

Simultaneous liver-kidney allocation policy: The problem, policy proposal rationale and future directions.

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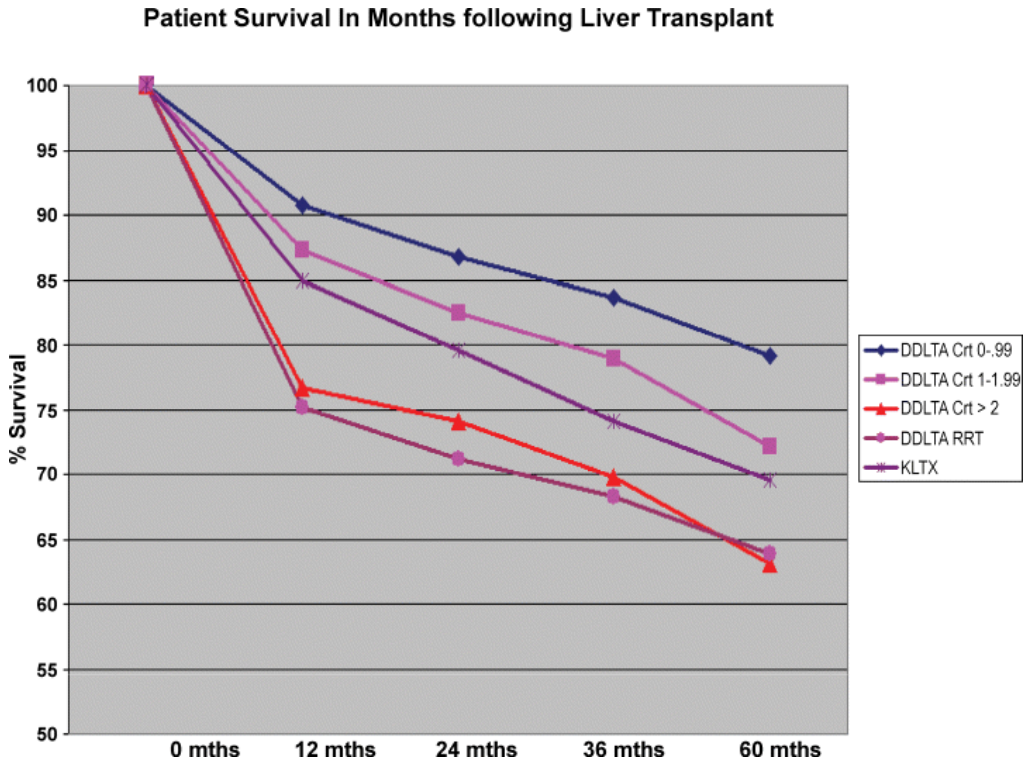
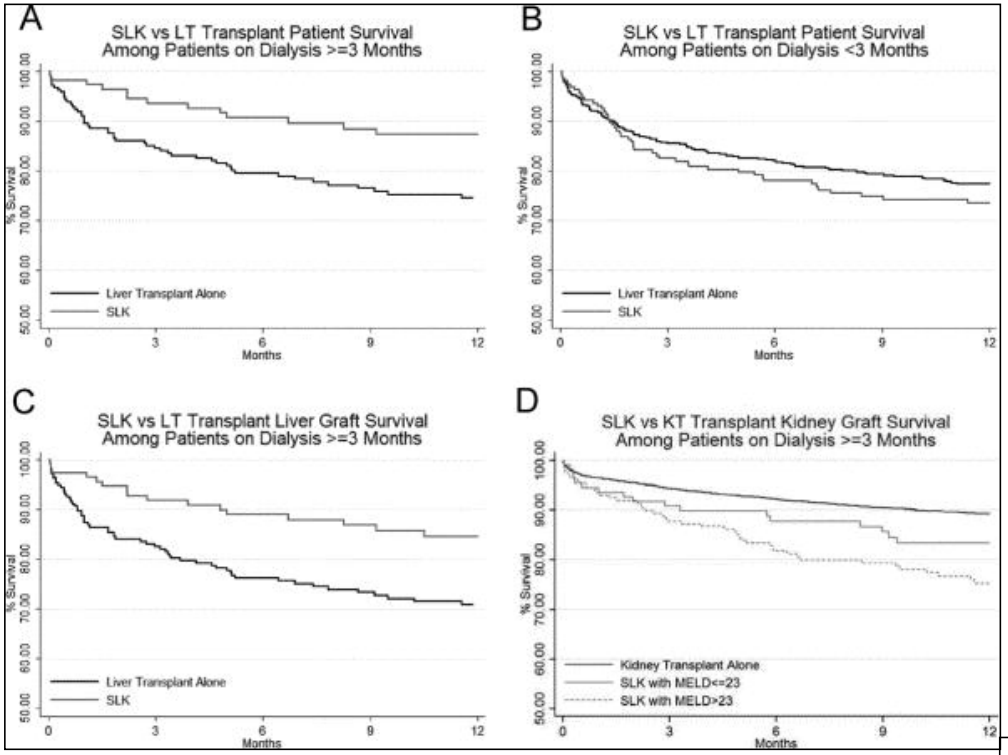
Conflict of Interest Disclosure

- I have no relevant financial relationships to disclose.
- I am Chairman of the Simultaneous Liver-Kidney working group.

Continued Influence of Preoperative Renal Function on Outcome of Orthotopic Liver Transplant (OLTX) in the US: Where Will MELD Lead Us?



Gonwa TA et a.American Journal of Transplantation
Volume 6, Issue 11, pages 2651-2659, 29 AUG 2006 DOI: 10.1111/j.1600-6143.2006.01526.x
http://onlinelibrary.wiley.com/doi/10.1111/j.1600-6143.2006.01526.x/full#f1

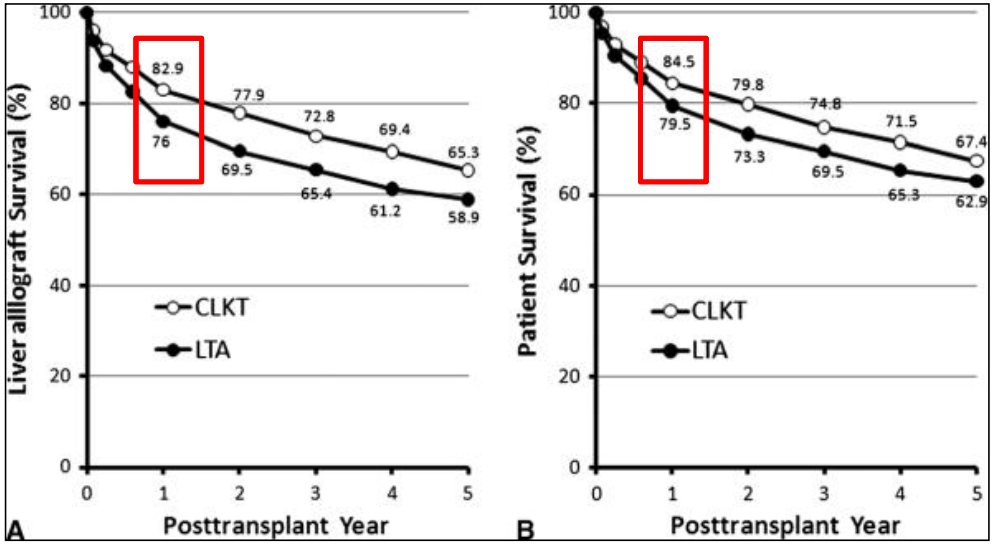


Declining Outcomes in Simultaneous Liver-Kidney Transplantation in the MELD Era: Ineffective Usage of Renal Allografts.

Locke, Jayme; Warren, Daniel; Singer, Andrew; Segev, Dorry; Simpkins, Christopher; Maley, Warren; Montgomery, Robert; Danovitch, Gabriel; Cameron, Andrew

Transplantation. 85(7):935-942, April 15, 2008.
DOI: 10.1097/TP.0b013e318168476d

Liver allograft survival and patient survival after combined liver-kidney transplantation or liver transplant alone.



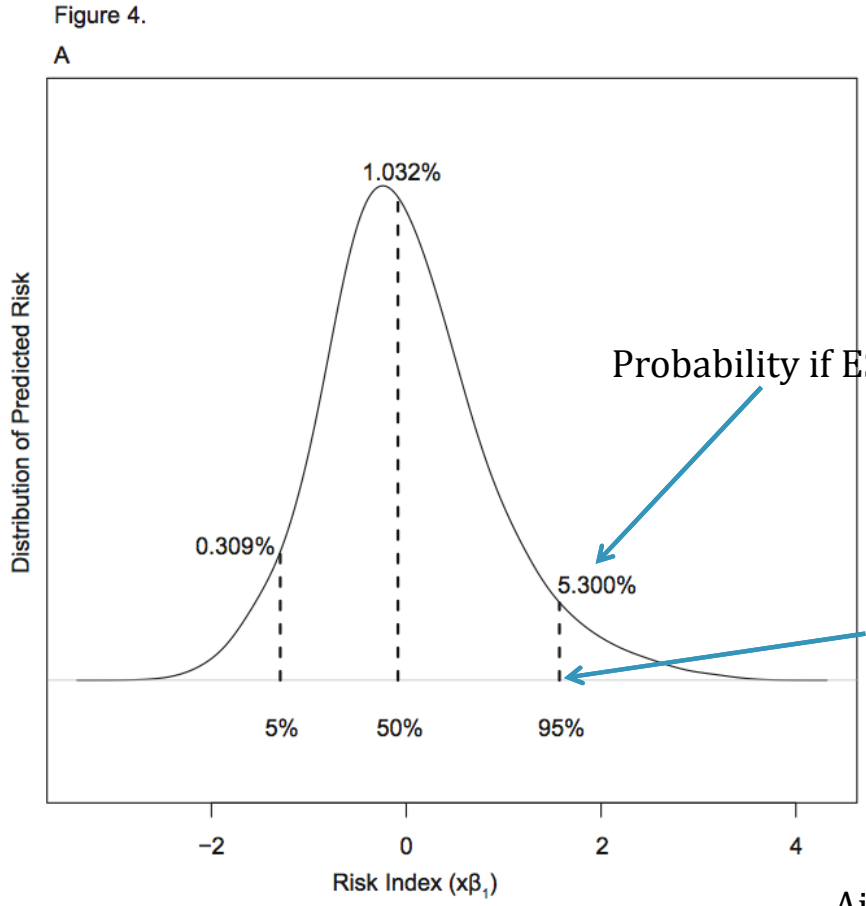
However in this study CLKT patients:

1. Had lower MELD scores
2. Had less severe liver disease
3. Received organs from younger donors
4. Had shorter cold and warm ischemia time

Combined Liver-Kidney Transplantation Is Preferable to Liver Transplant Alone for Cirrhotic Patients With Renal Failure.
Fong, Tse-Ling; Khemichian, Saro; Shah, Tariq; Hutchinson, Ian; Cho, Yong

Transplantation. 94(4):411-416, August 27, 2012.
DOI: 10.1097/TP.0b013e3182590d6b

Early onset of ESRD 0-6 months after liver transplantation

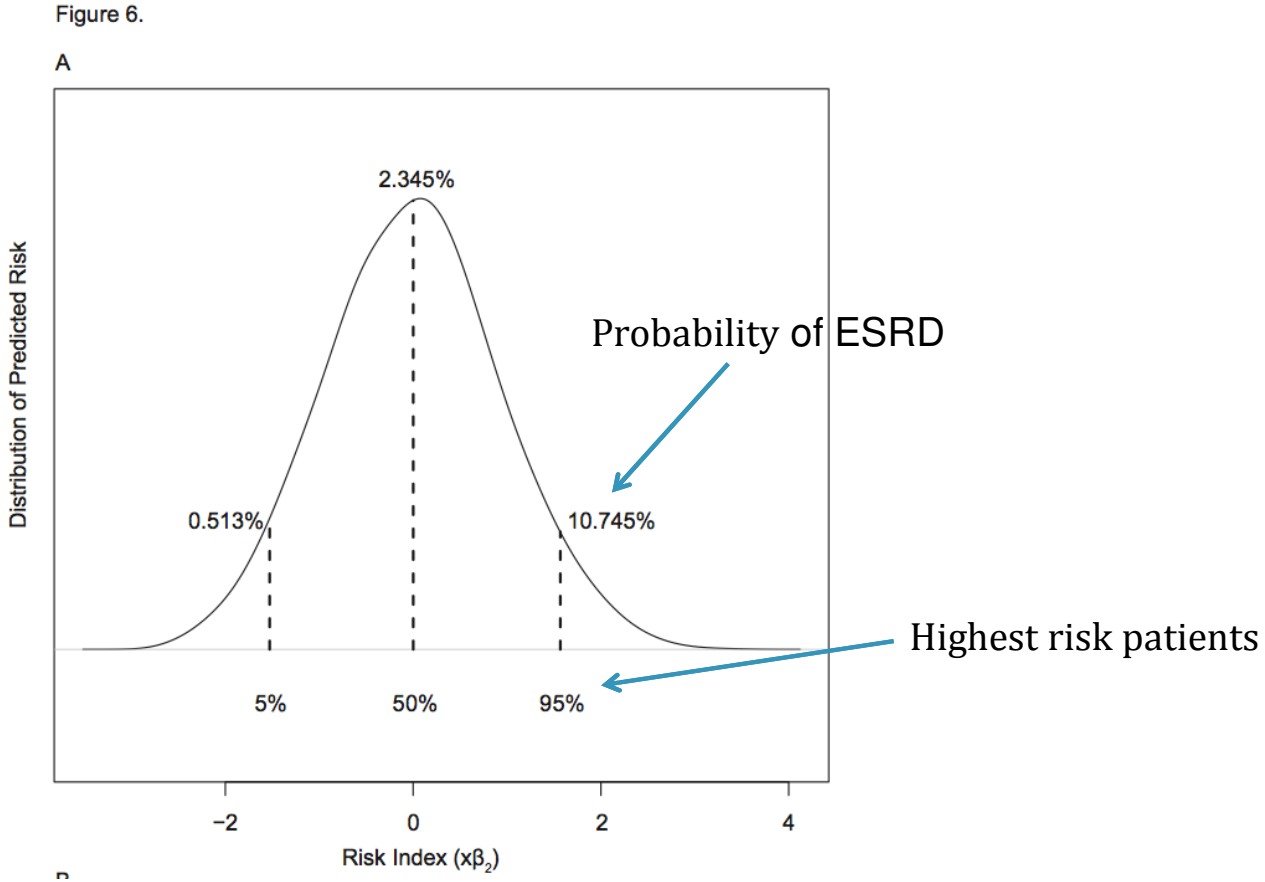


Probability if ESRD

Highest risk patients

Ajay Israni *AJT* – 2013

Late on onset of ESRD > 6 months after liver transplantation

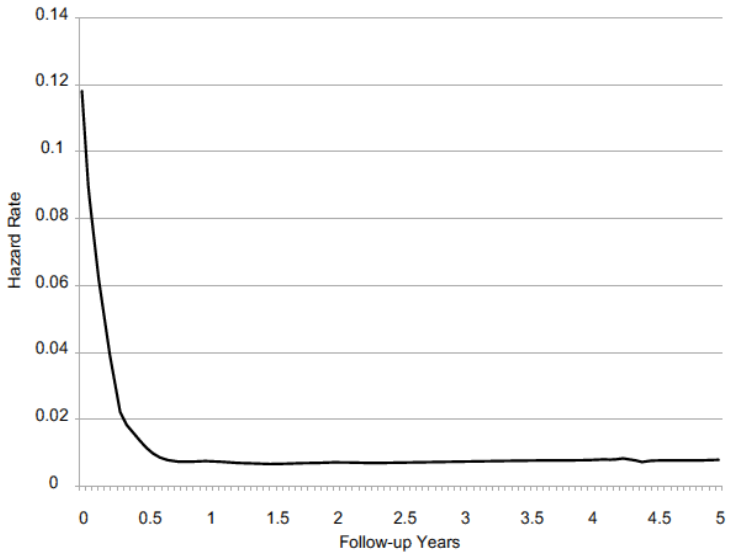


Ajay Israni *AJT* – 2013

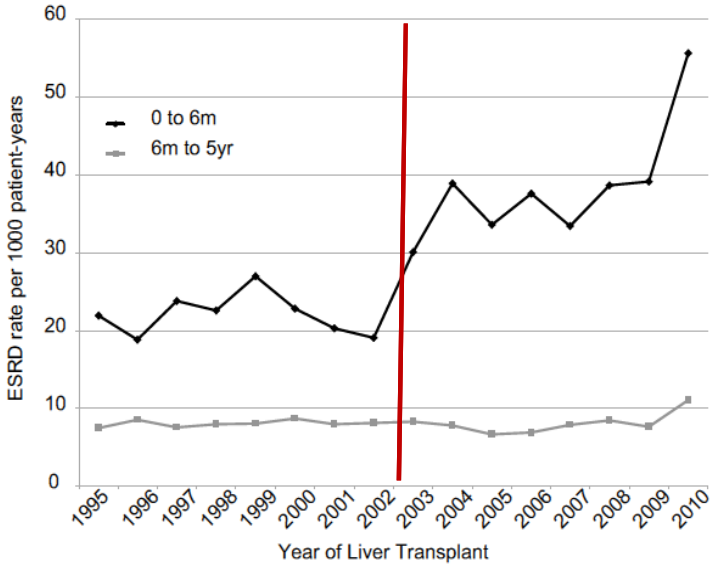
Predicting ESRD* after LI tx

Israni, at al *Am J Transplant* 2013; *13: 1782–1792*

Hazard function for ESRD (post MELD)



Incidence of ESRD



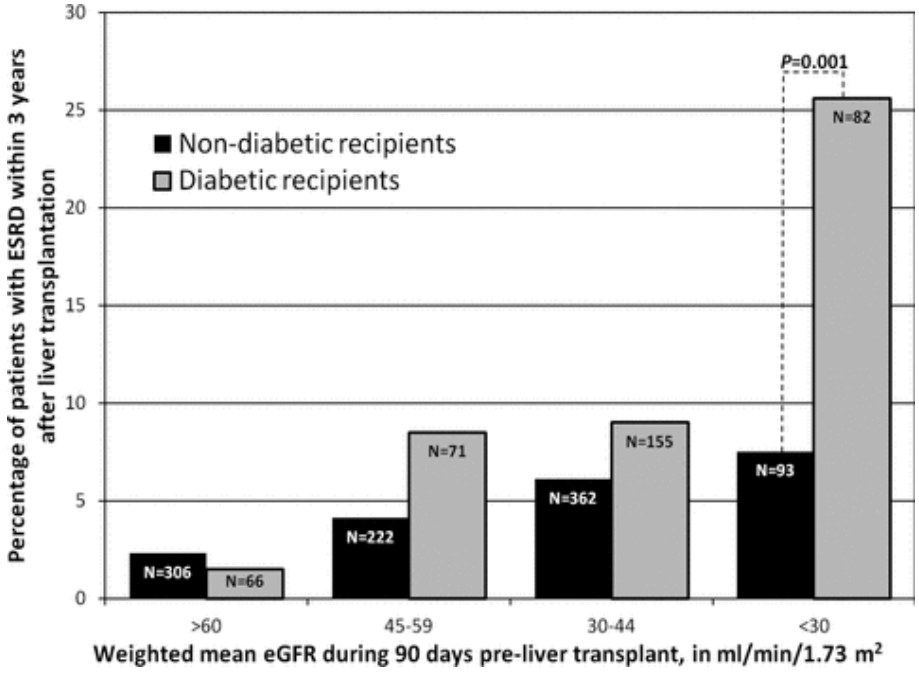
Post MELD:
risk of ESRD is highest in the first 6m

Incidence of ESRD in post MELD vs pre:
- 6m – increased
- 6m to 5 yrs – stable

Post MELD:
cumulative incidence of ESRD is 5.1% during 5 years post tx

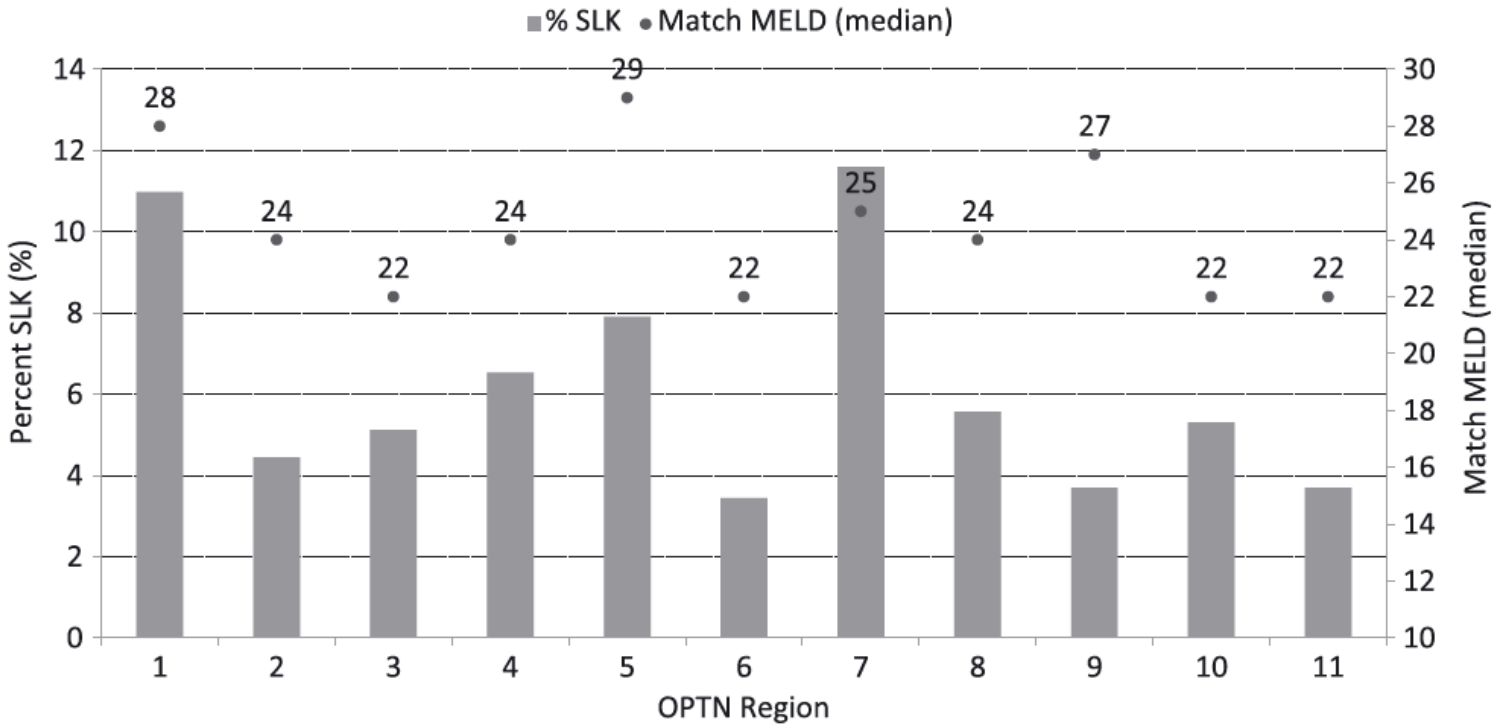
* Initiation of maintenance dialysis therapy, KI tx or listing for KI tx

Risk of End-Stage Renal Disease Among Liver Transplant Recipients With Pretransplant Renal Dysfunction



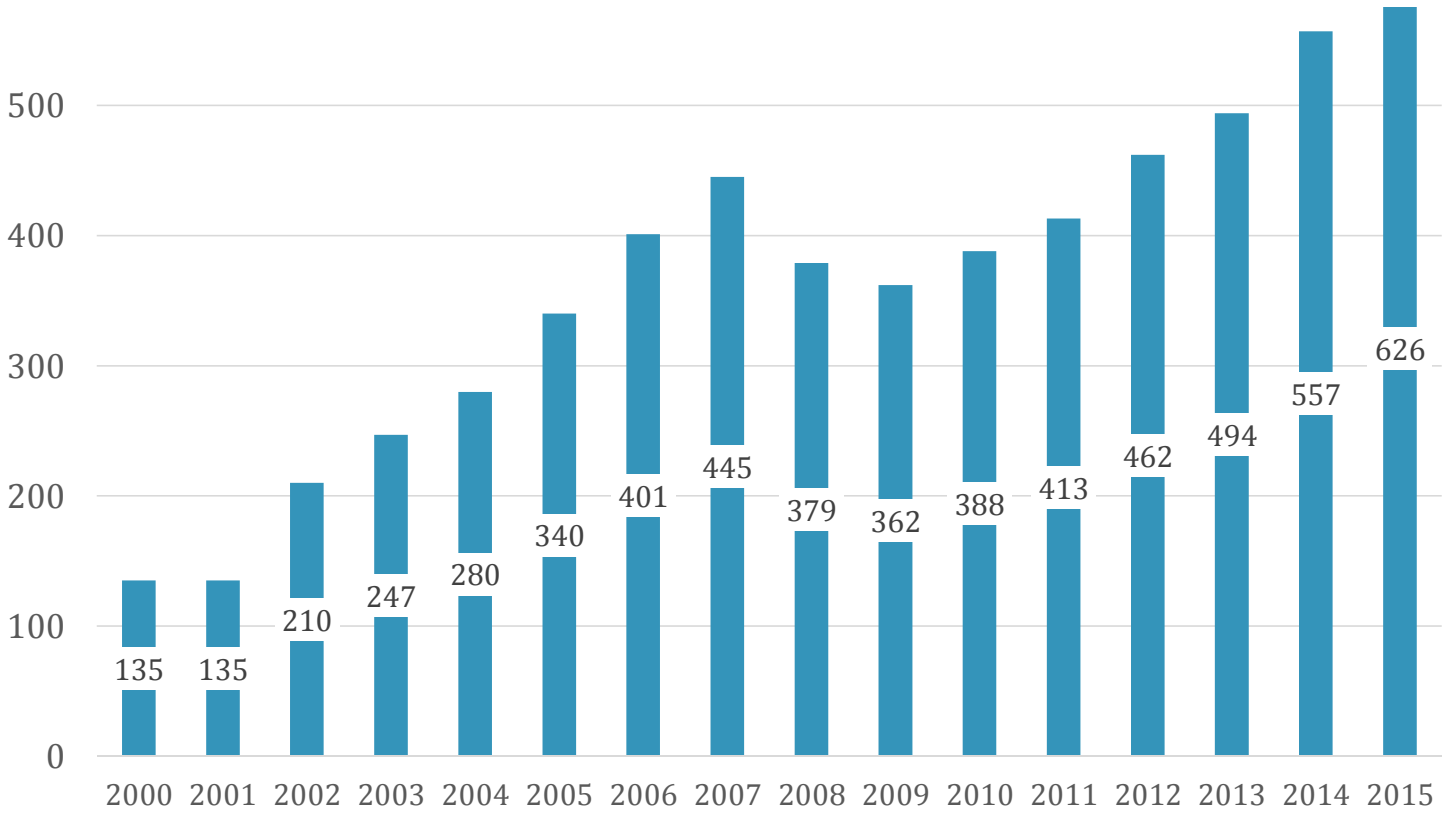
American Journal of Transplantation
Volume 12, Issue 11, pages 2958-2965, 3 JUL 2012 DOI: 10.1111/j.1600-6143.2012.04177.x
http://onlinelibrary.wiley.com/doi/10.1111/j.1600-6143.2012.04177.x/full#f2

% of SLK of all DD adult LI txs, 2002-2010



MK Nadim, et al. *Am J Transplant* 2012; 12: 2901

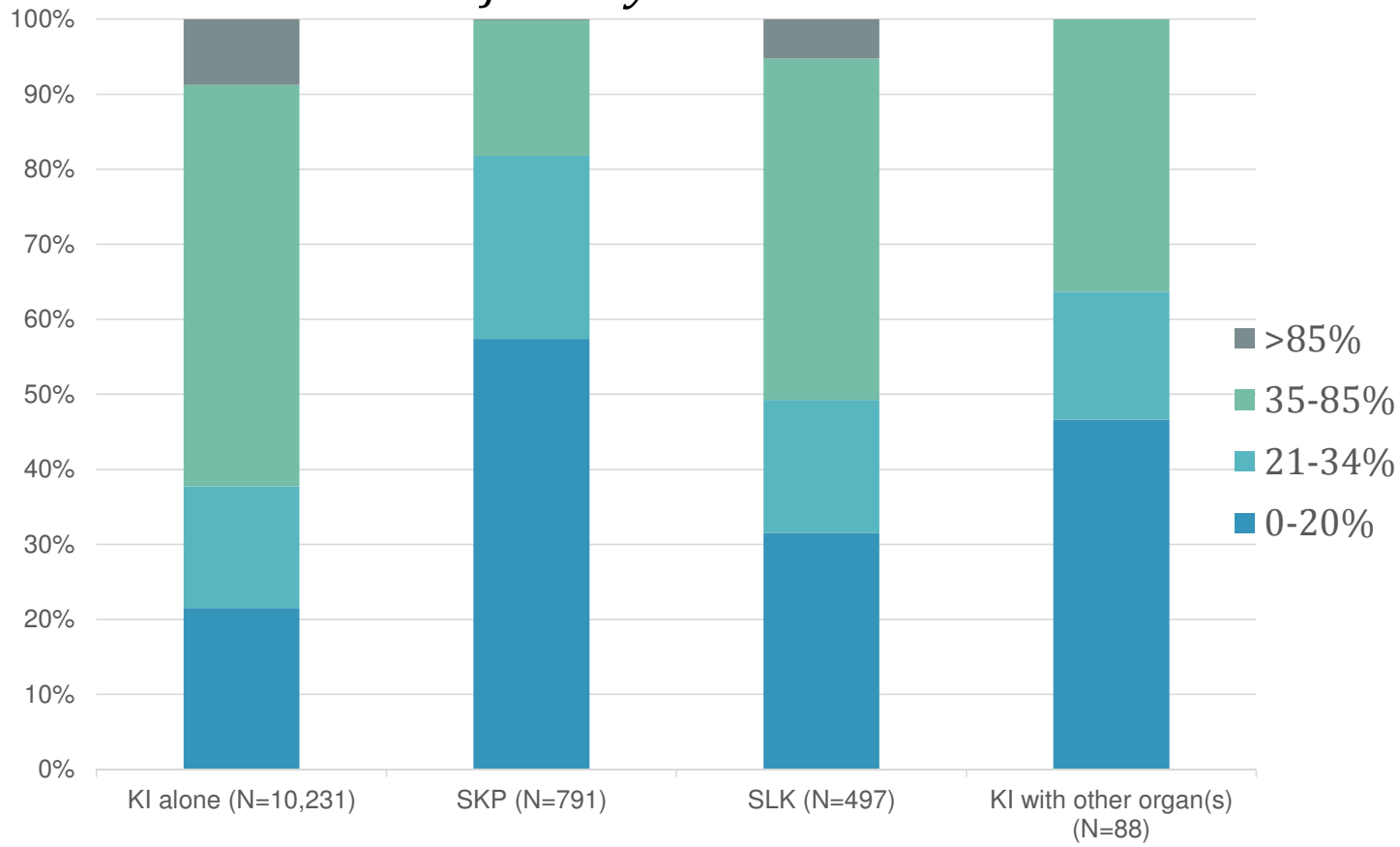
Number of SLK transplants by year



SLK transplants with other organs were excluded from the tabulation.

KDPI distribution among multi-organ transplants

January-December 2012



Excludes less than 1% of transplants with missing KDPI values

48.3% of Kidneys allocated to SLK have a KDPI < .35

Medical Eligibility Criteria

Veil of ignorance

"Original position"

American Journal of Transplantation 2016; 16: 758–766
Wiley Periodicals Inc.

doi: 10.1111/ajt.13631

Special Article

Simultaneous Liver–Kidney Allocation Policy: A Proposal to Optimize Appropriate Utilization of Scarce Resources

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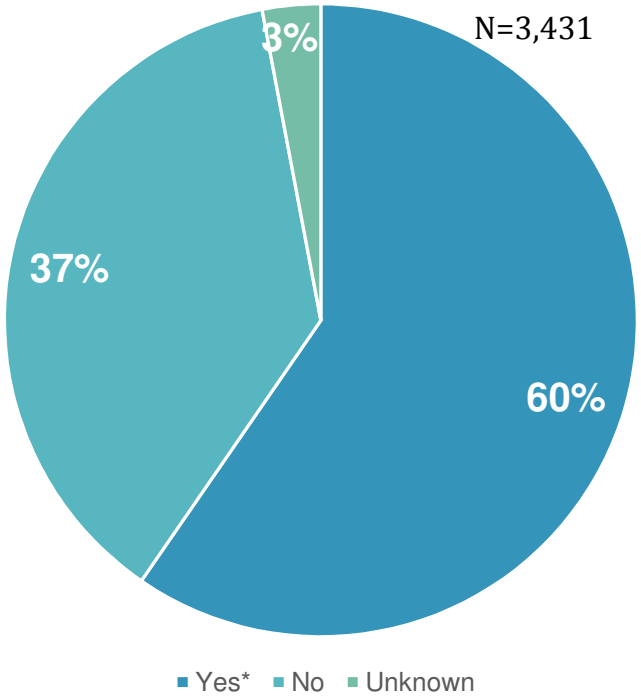
[2]*University Hospitals Case Medical Center, CWRU, Cleveland, OH*
[3]*United Network of Organ Sharing, Richmond, VA*
[4]*University of California, San Francisco, San Francisco, CA*
**Corresponding author: Richard N. Formica, richard.formica@yale.edu*

Introduction

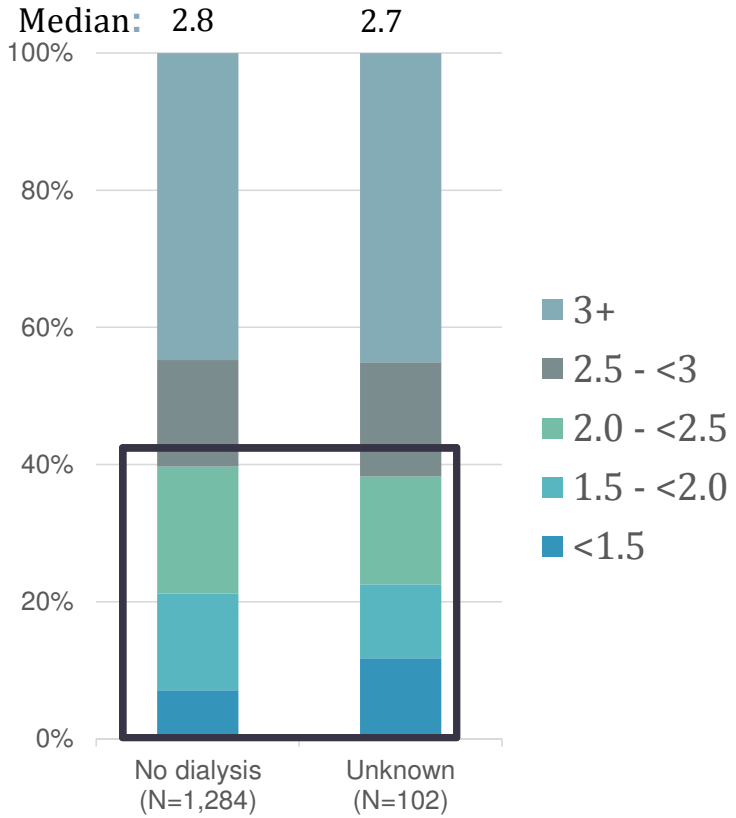
The introduction of the Mayo End-Stage Liver Disease (MELD) score into the Organ Procurement and Transplantation Network (OPTN) deceased donor liver allocation policy in 2002 (1) has led to a significant increase in the number of simultaneous liver–kidney (SLK) transplants in the United States (2) (Figure 1). Also contributing to the increasing trend is the fact that there are no medical criteria on which allocation of the kidney with a liver is based. This has resulted in heterogeneity in both numbers of SLK transplants performed in the different

SLK recipients (2005-6/2013)

*Pre-transplant dialysis**



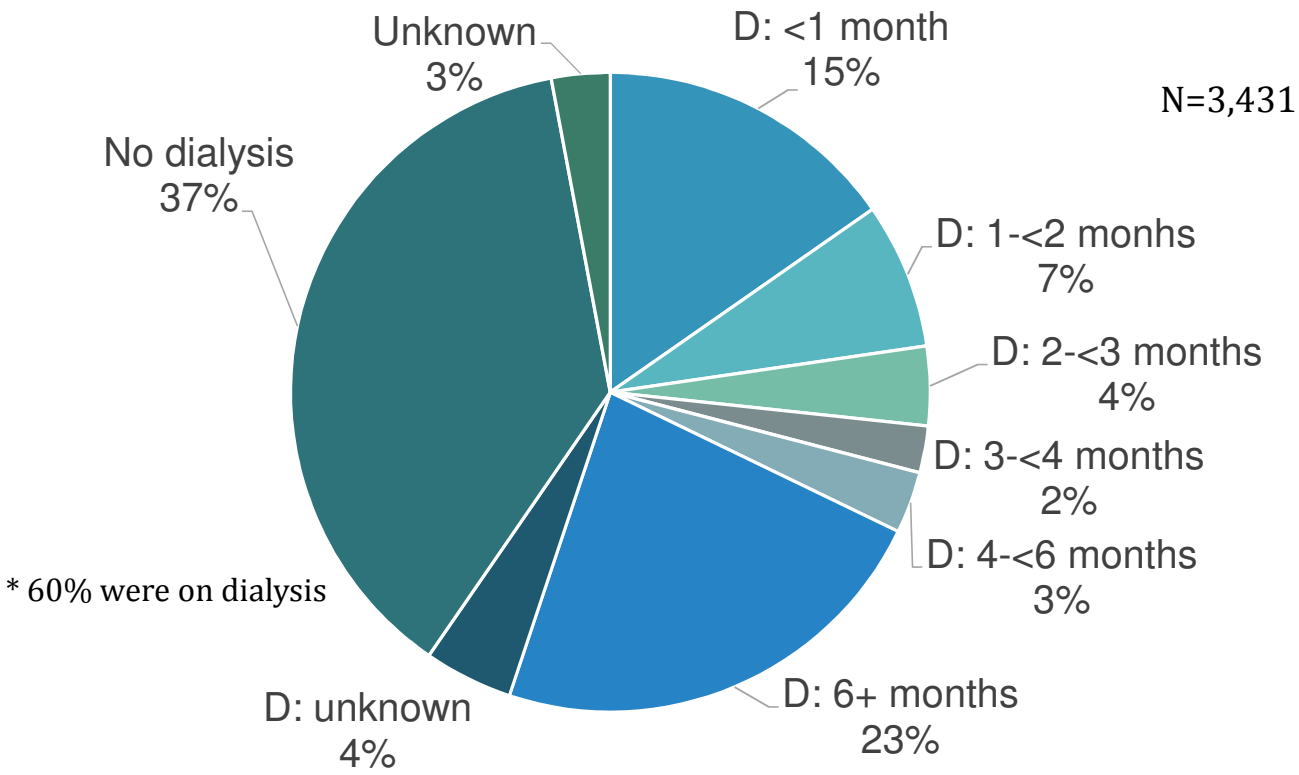
Serum creatinine values (mg/dl)



Analyses are based on deceased donor SLK transplants performed during 2005-6/2013. SLK transplants with other organs were excluded from the tabulation.

SLK recipients (2005-6/2013)

*Pre-transplant dialysis**

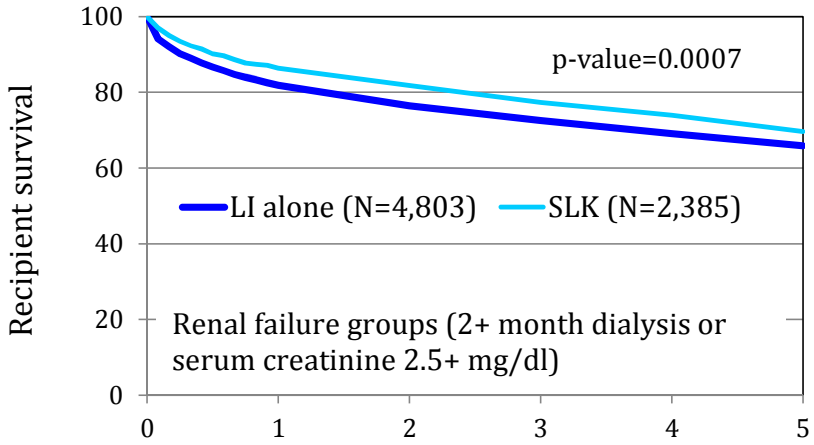


Analyses are based on deceased donor SLK transplants performed during 2005-6/2013. SLK transplants with other organs were excluded from the tabulation.

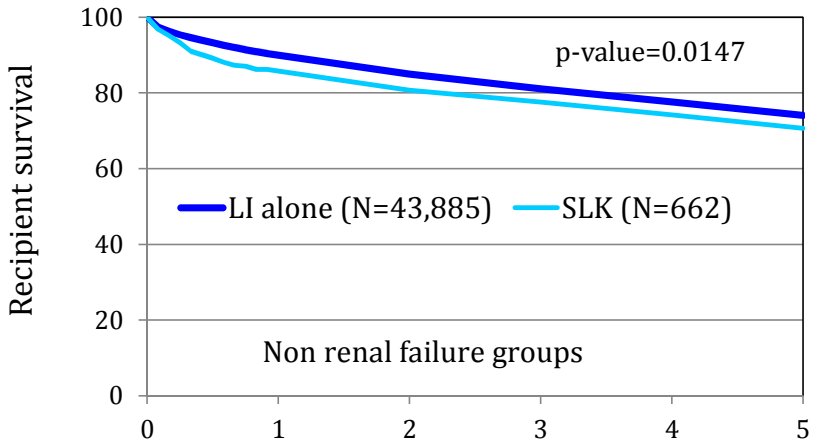
Renal failure:

1. Serum creatinine greater than 2.5 mg/dl
2. More than eight weeks on dialysis

Crude survival advantage of receiving an SLK vs. liver alone



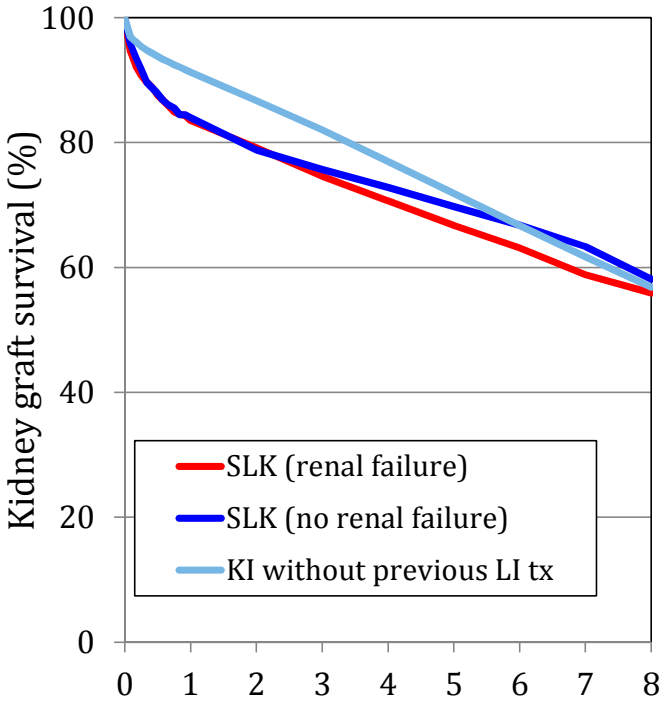
	LI Alone	SLK
White	70%	62%
Diabetes	27%	41%
MELD*	36	27
KDPI%	50	40
Age*	55	56
LI CIT*	6.9	6.4



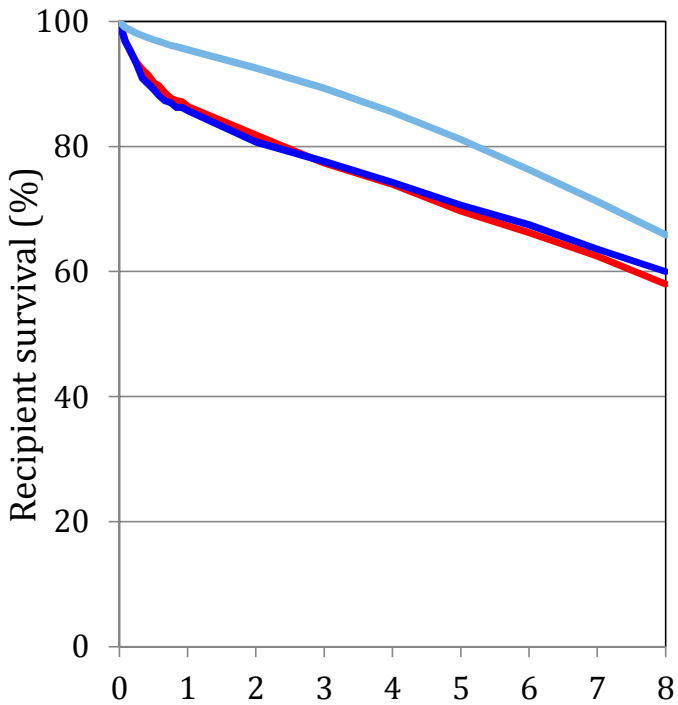
	LI Alone	SLK
White	73%	65%
Diabetes	23%	38%
MELD*	17	28
KDPI%	50	40
Age*	55	57
LI CIT*	6.7	6.5

* Medians are shown

Kidney graft survival



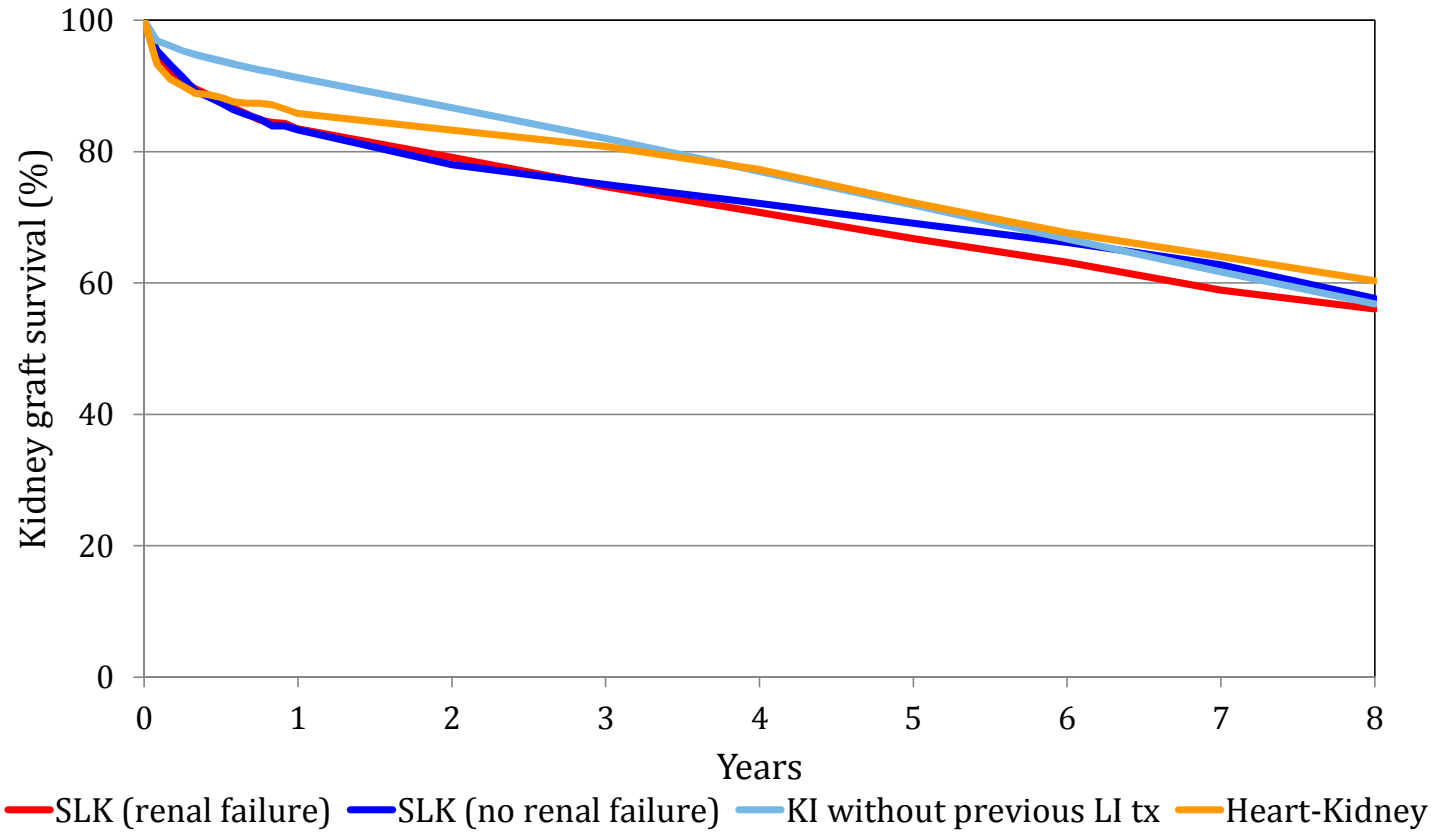
Recipient survival



	SLK (ren. failure)	SLK (no ren. failure)	KI
White	62%	65%	45%
Age (median)	56	57	54

Cohort: recipients Mar 31, 2002 – Dec 21, 2012

Kidney graft survival



Cohort: recipients Mar 31, 2002 – Dec 21, 2012

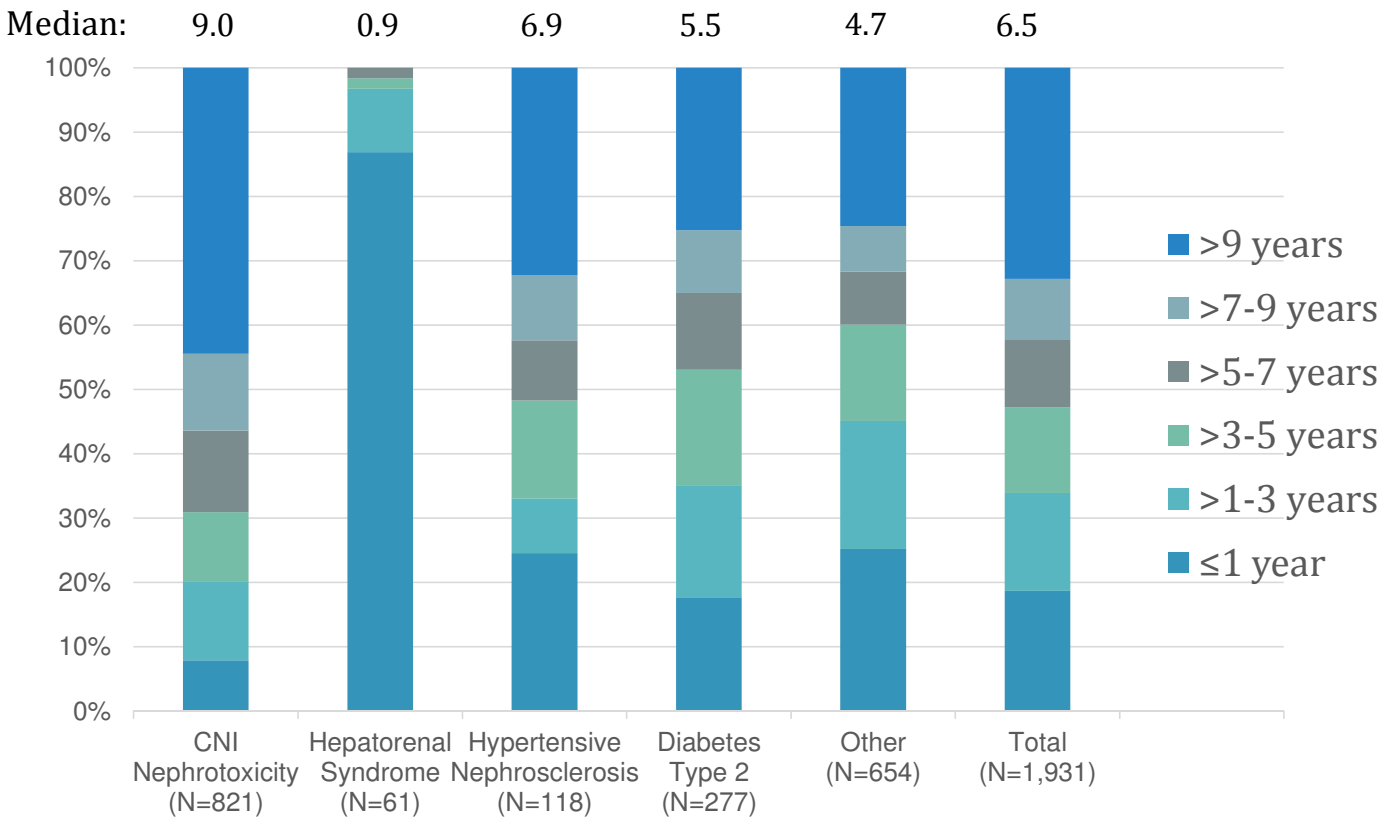
SLK Medical Eligibility Criteria

Transplant nephrologist must confirm candidate has <u>one</u> of the following:	And transplant 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

Safety Net

Kidney listings after liver transplants (2005-6/2013)

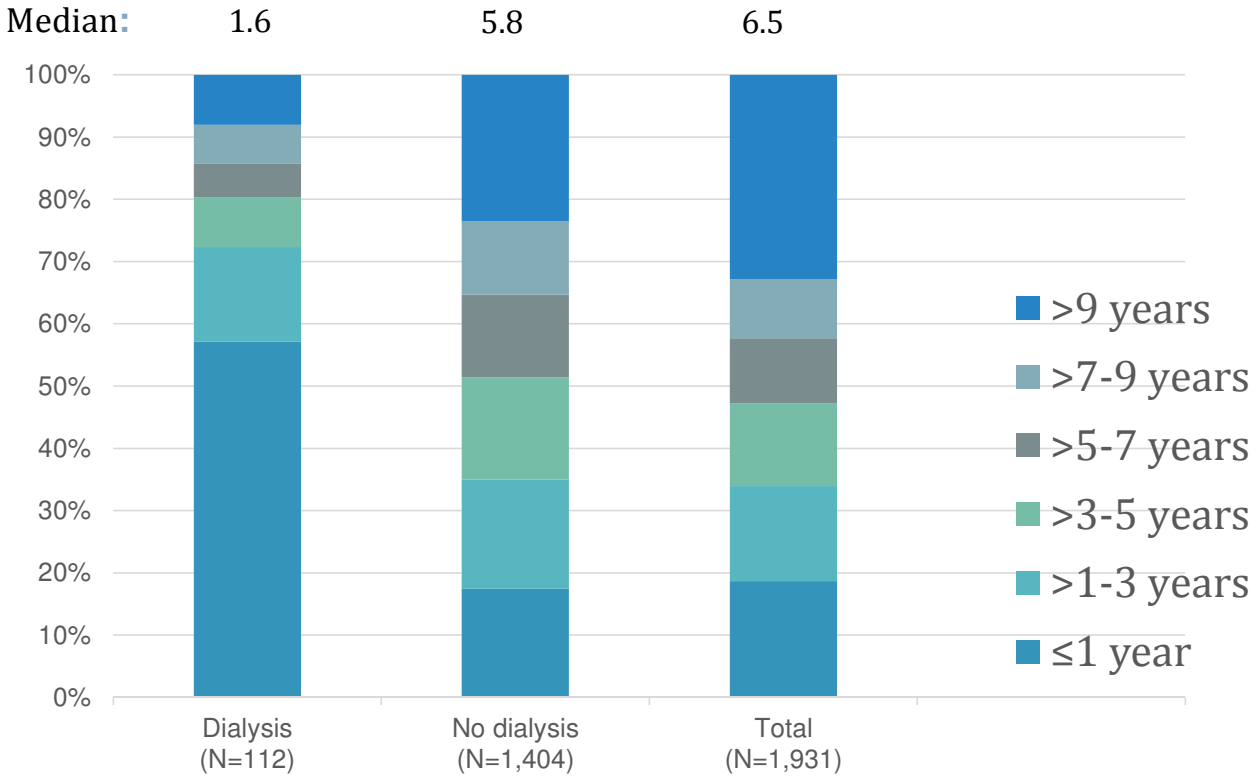
Time from liver txp to kidney listings by diagnosis at time of kidney listing (years)



Analyses are based on registrations added to the kidney alone waiting list for the first time during 2005-6/2013 after a liver alone transplant that was still functioning at the time of the subsequent kidney listing.

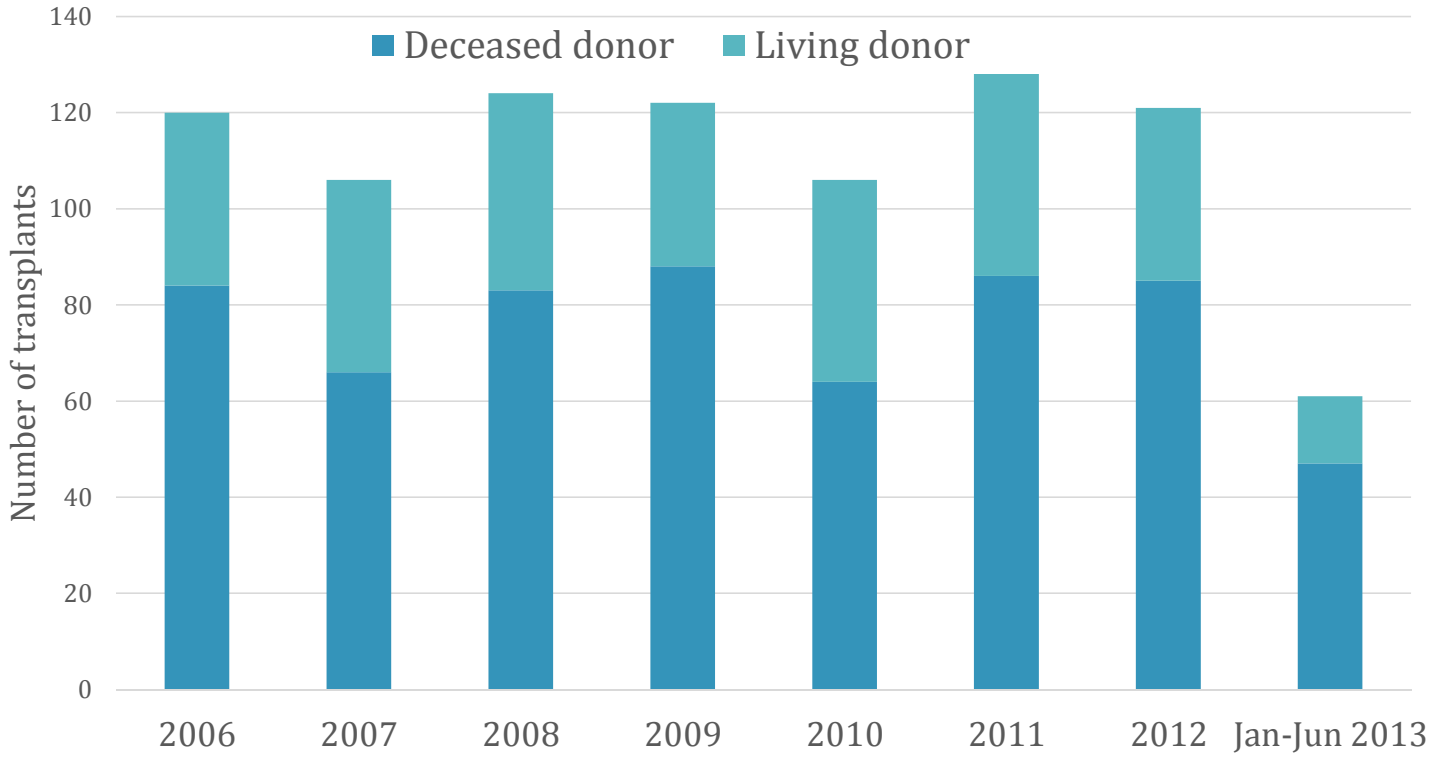
Kidney listings after liver transplants (2005-6/2013)

Time from liver txp to kidney listings by dialysis prior to liver transplant (years)



Analyses are based on registrations added to the kidney alone waiting list for the first time during 2005-6/2013 after a liver alone transplant that was still functioning at the time of the subsequent kidney listing.

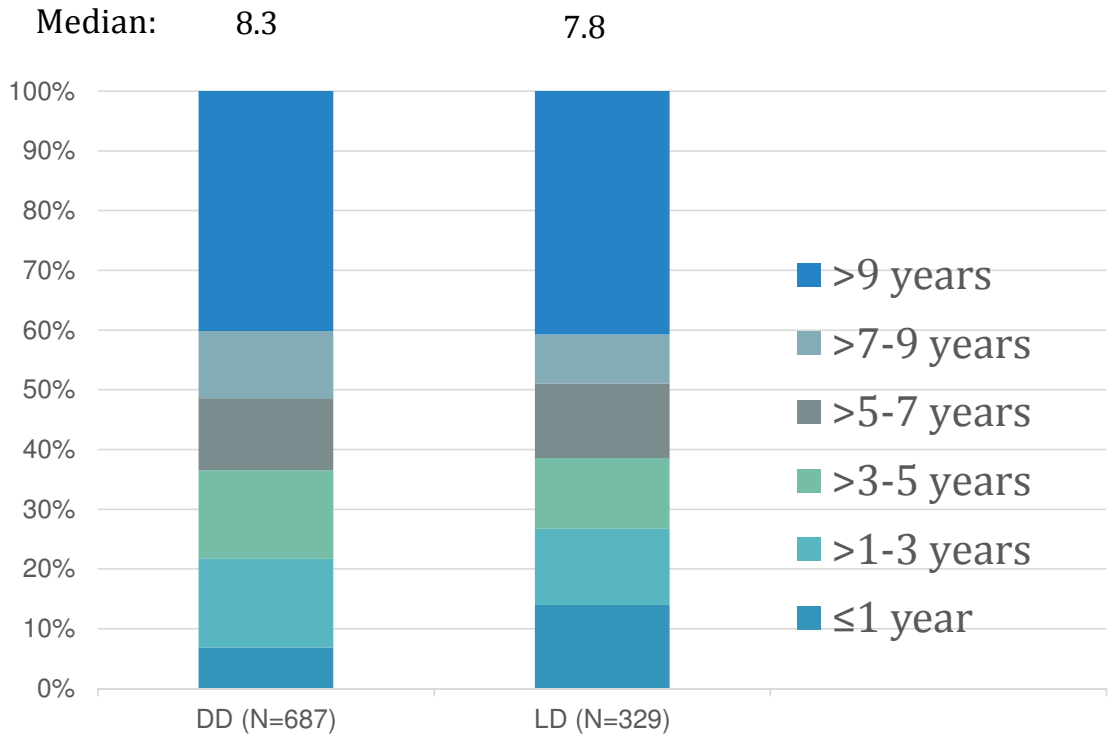
Kidney transplants after liver transplants (2005-6/2013) by kidney donor type



Analyses are based on first deceased and living donor kidney alone transplants that occurred during 2005-6/2013 and followed a liver alone transplant that was still functioning at the time of the subsequent kidney transplant.

Kidney transplants after liver transplants (2005-6/2013)

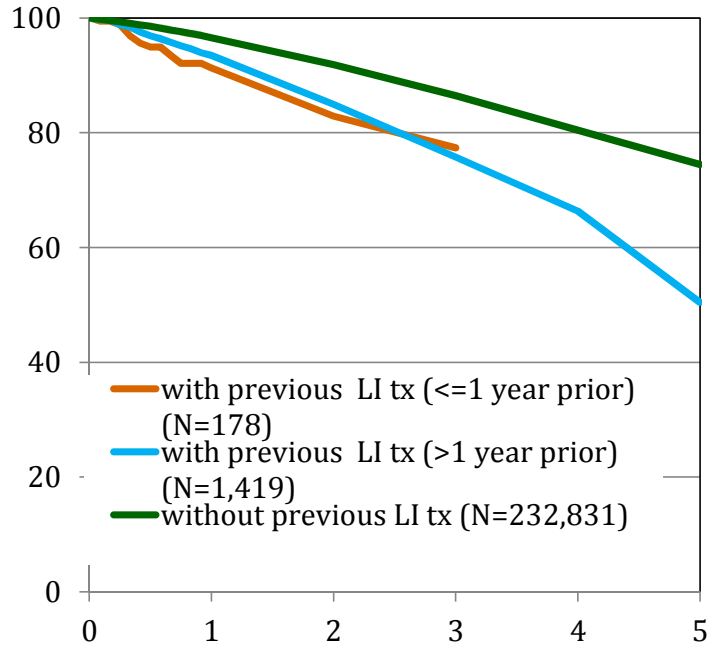
Time from liver transplants to subsequent kidney transplants by donor type (years)



Analyses are based on first deceased and living donor kidney alone transplants that occurred during 2005-6/2013 and followed a liver alone transplant that was still functioning at the time of the subsequent kidney transplant.

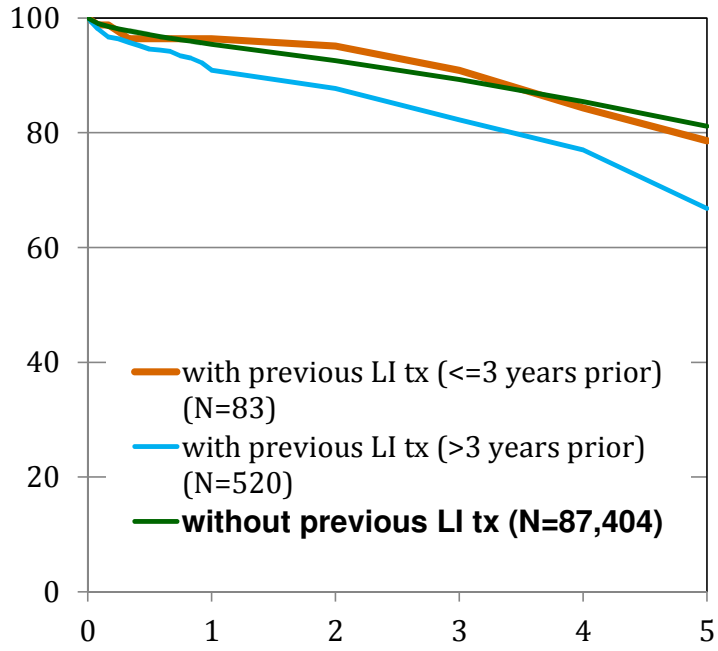
Kidney patient survival: with vs. without prior liver tx

Waiting list survival



	With LI (<=1)	With LI (>1)	W/t LI
White	75%	74%	45%
Age (median)	57	59	53

Recipient survival



	With LI (<=3)	With LI (>3)	W/t LI
White	70%	78%	45%
Age (median)	57	60	54

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.

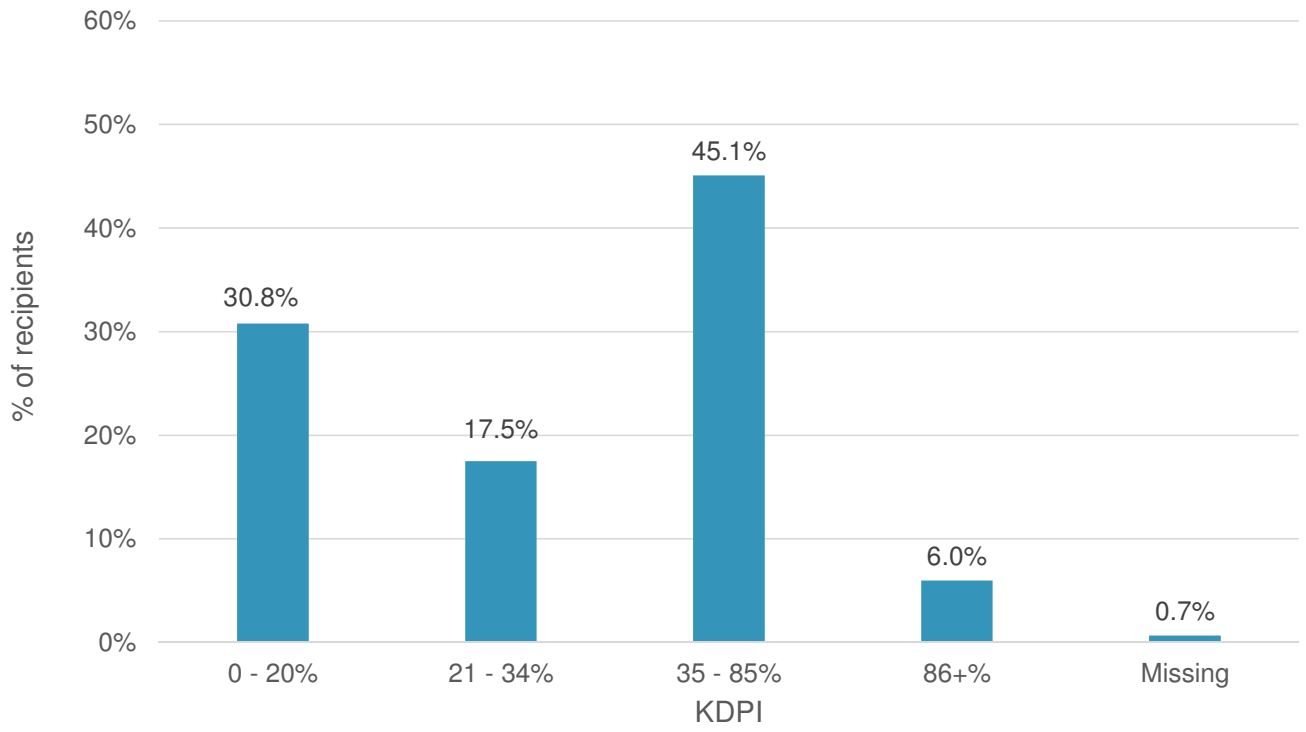
- To continue to be eligible, the transplant program must report at least once every 30 days that this medical criteria continues to be met. Once this has been confirmed for three consecutive periods, the candidate will be eligible indefinitely.

Sequence A KDPI <=20%	Sequence B KDPI >20% but <35%	Sequence C KDPI >=35% but <=85%	Sequence D KDPI>85%
Highly Sensitized	Highly Sensitized	Highly Sensitized	Highly Sensitized
0-ABDRmm	0-ABDRmm	0-ABDRmm	0-ABDRmm
Prior living donor	Prior living donor	Prior living donor	***Local safety net***
Local pediatrics	Local pediatrics	***Local safety net***	Local + Regional
Local top 20% EPTS	***Local safety net***	Local	National
0-ABDRmm (all)	Local adults	Regional	
Local (all)	Regional pediatrics	National	
Regional pediatrics	Regional adults		
Regional (top 20%)	National pediatrics		
Regional (all)	National adults		
National pediatrics			
National (top 20%)			
National (all)			

Extra slides

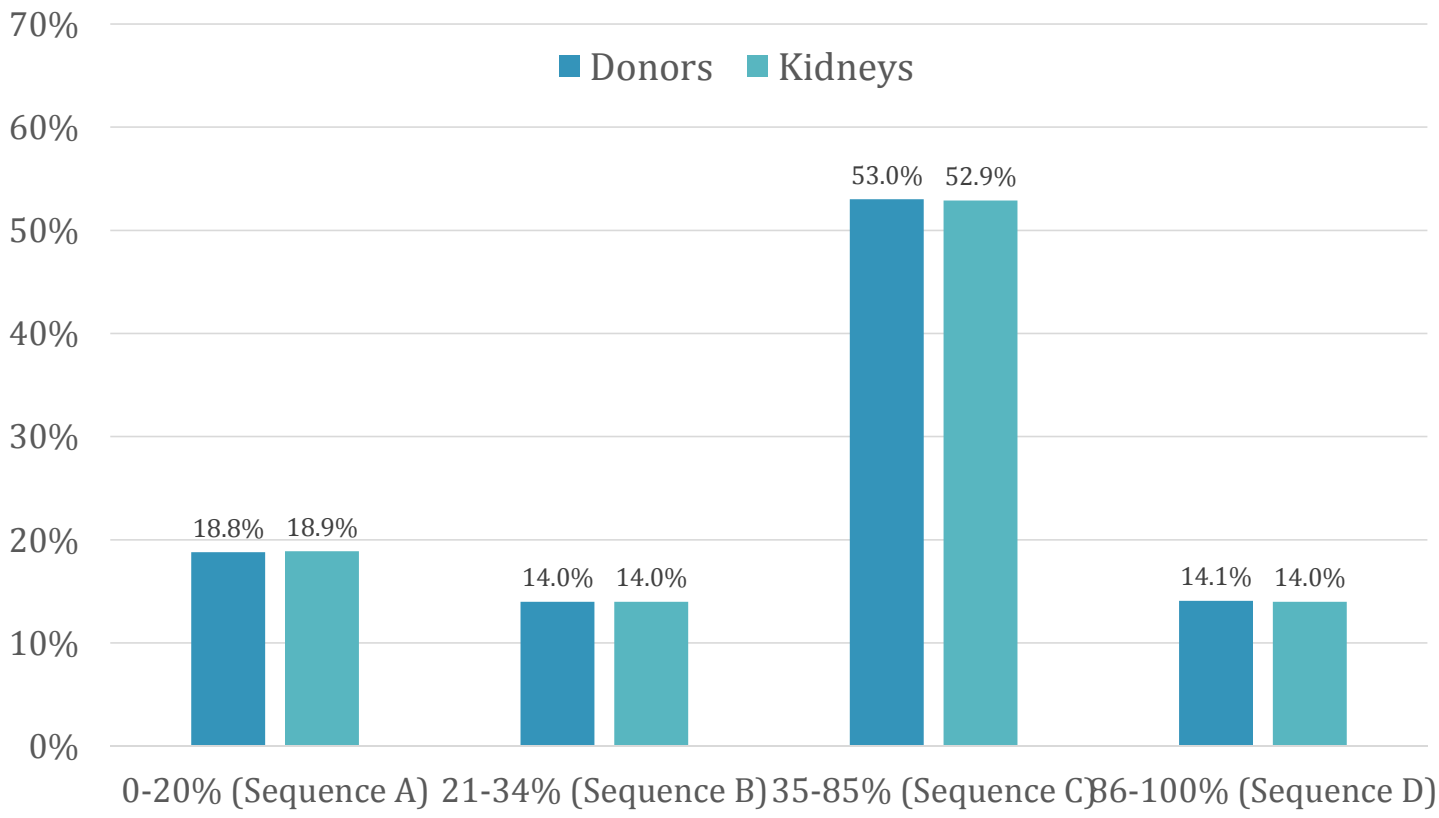
SLK recipients (2005-6/2013)

KDPI distribution

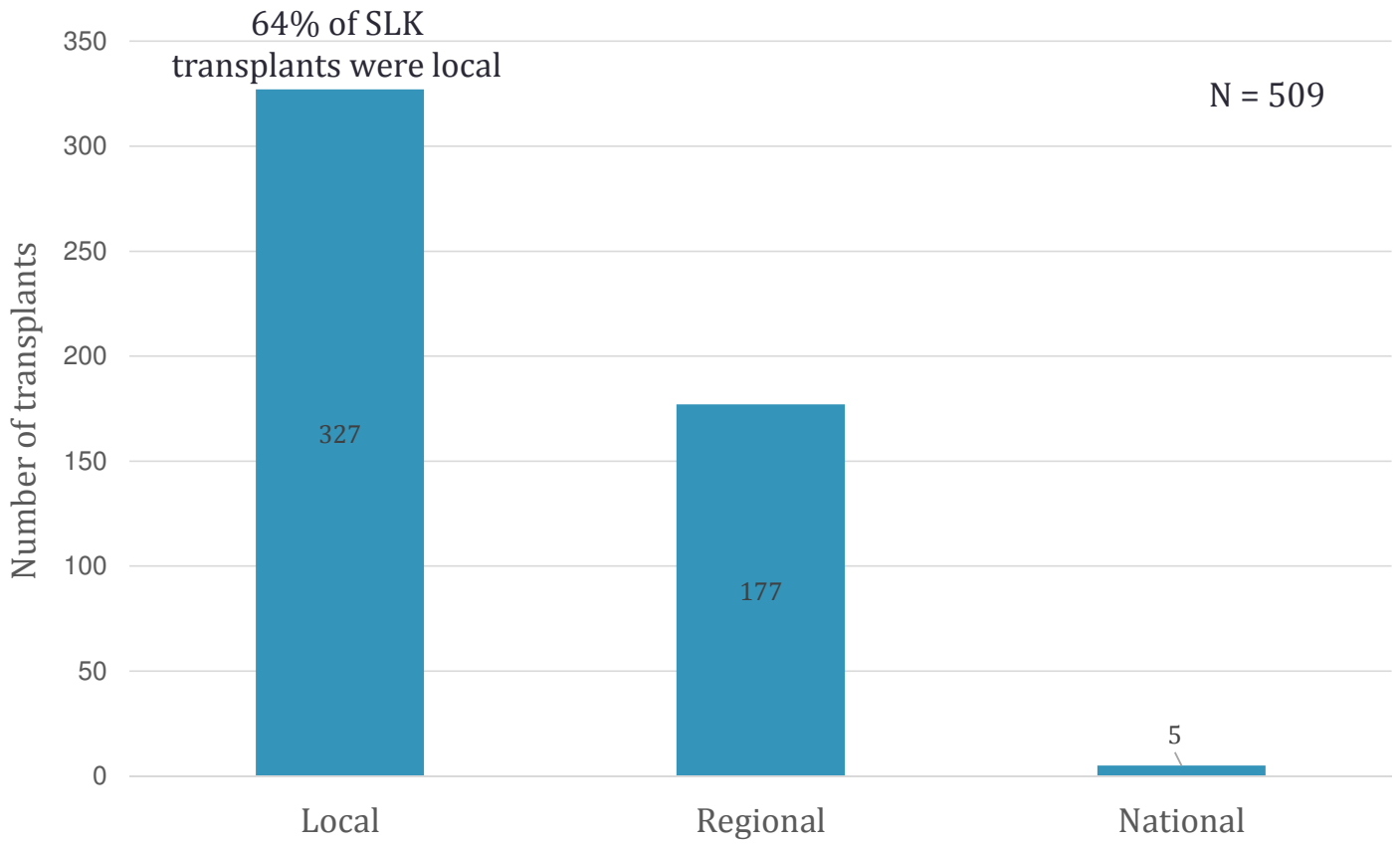


Analyses are based on deceased donor SLK transplants performed during 2005-6/2013. SLK transplants with other organs were excluded from the tabulation.

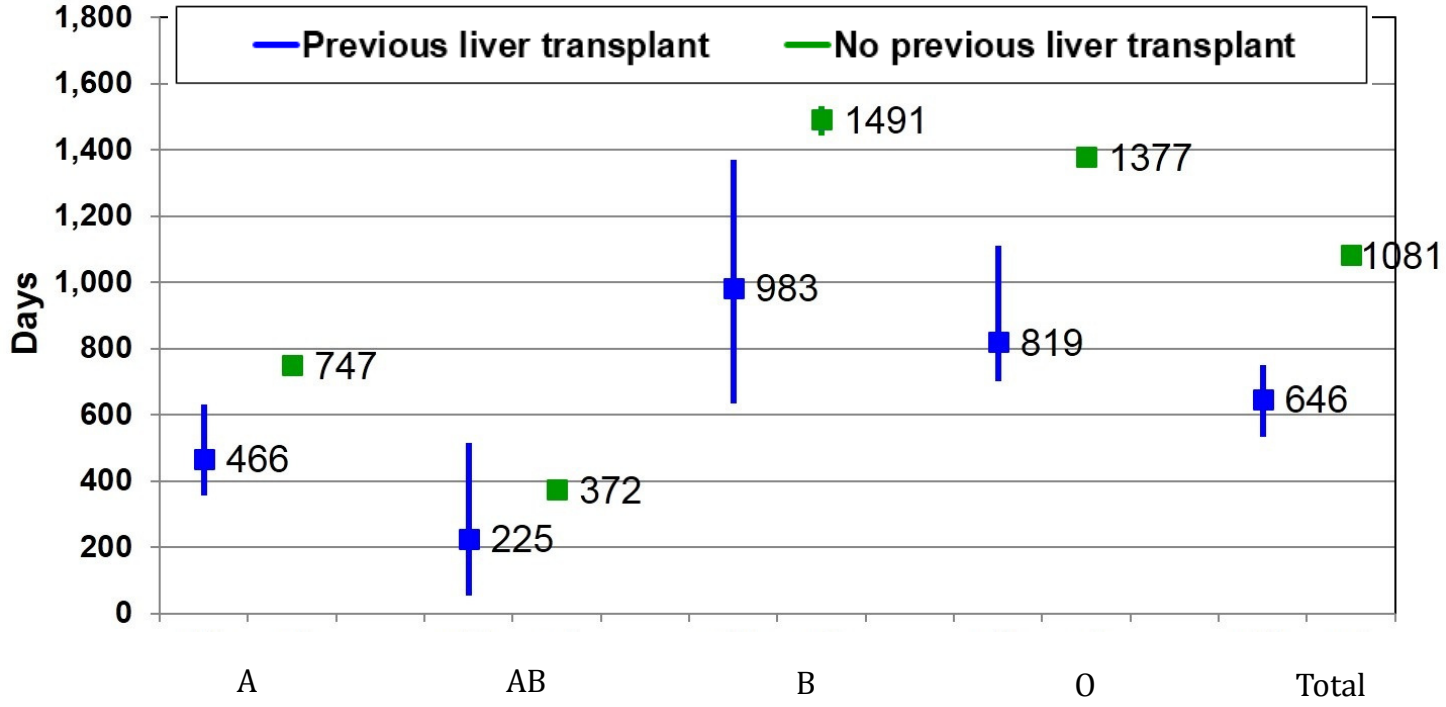
KPDI distribution for deceased donors recovered (12/04/14-05/31/15)



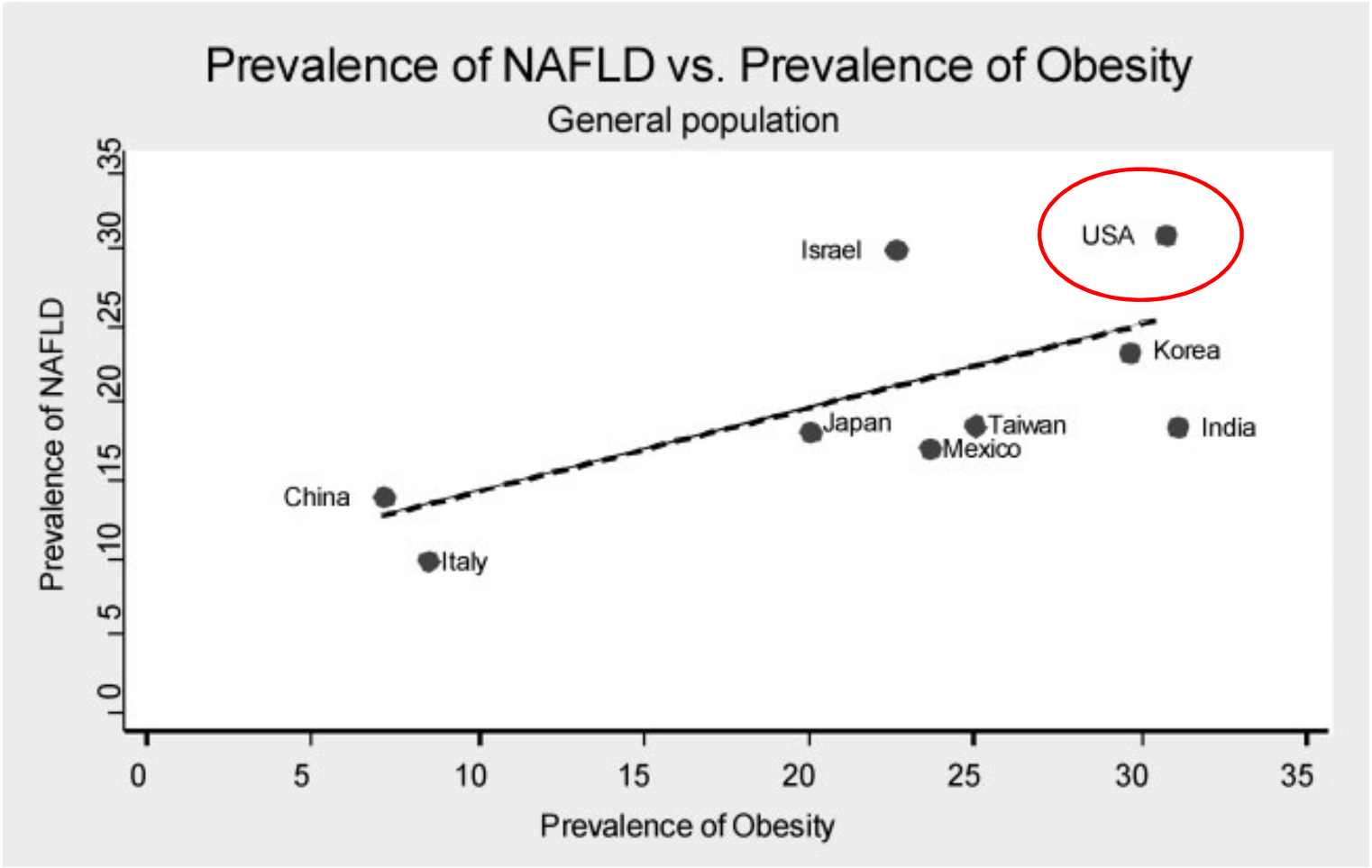
SLK transplants post KAS by sharing type (12/04/14-09/30/15)



25th percentiles of times to deceased donor kidney alone transplant for registrations added with and without a previous liver transplant (2003-2008)



Analyses are based on registrations added to the wait list during 2003-2008 with and without a previous liver transplant.



Lazo M & Clark JM, Semin Liver Dis 2008;(28)4

Risk factors

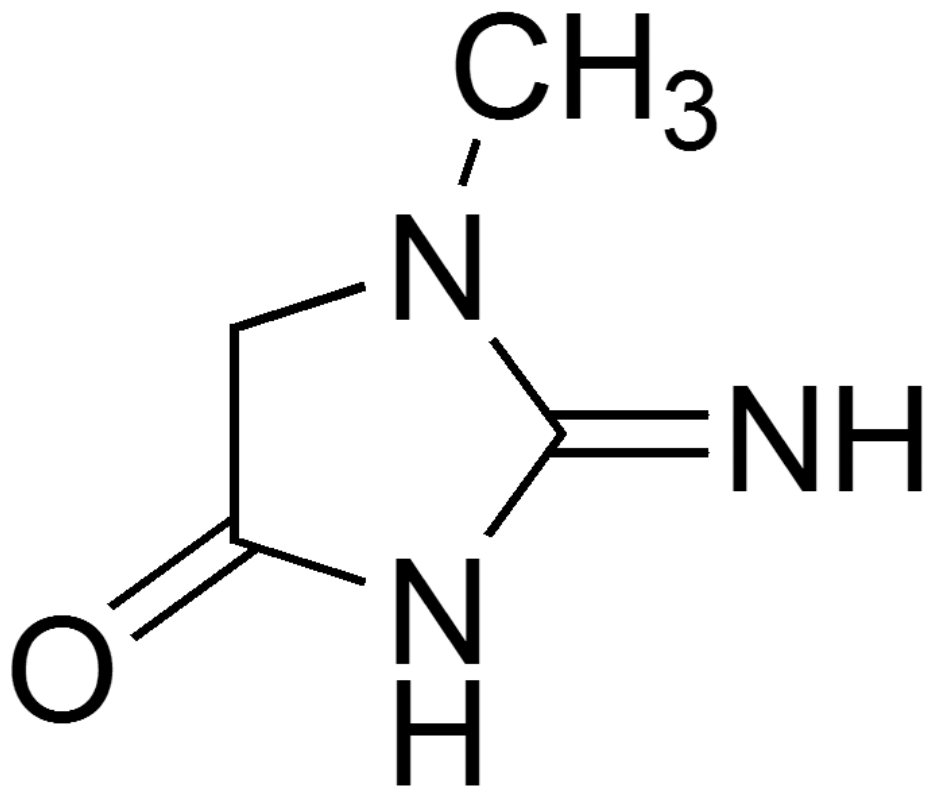
Table 4. Risk Factors Associated with NAFLD

Conditions with established association	Conditions with emerging association*
Obesity	Polycystic ovary syndrome
Type 2 diabetes mellitus	Hypothyroidism
Dyslipidemia	Obstructive Sleep apnea
Metabolic syndrome**	Hypopituitarism
	Hypogonadism
	Pancreato-duodenal resection

*Few studies suggested that individuals with type1 diabetes have increased prevalence of hepatic steatosis based on liver imaging, but there is limited histological evidence.

**The Adult Treatment Panel III clinical definition of the metabolic syndrome requires the presence of three or more of the following features: (1) waist circumference greater than 102 cm in men or greater than 88 cm in women; (2) triglyceride level 150 mg/dL or greater; (3) high-density lipoprotein (HDL) cholesterol level less than 40 mg/dL in men and less than 50 mg/dL in women; (4) systolic blood pressure 130 mm Hg or greater or diastolic pressure 85 mm Hg or greater; and (5) fasting plasma glucose level 110 mg/dL or greater.[199]

AASLD Guidelines 2014



Larger volume of distribution

Decrease production

Increased secretion

J Levitsky & J O'Leary AJT in submission.

Nephron *16:* 31–41 (1976)

Prediction of Creatinine Clearance from Serum Creatinine[1]

DONALD W. COCKCROFT and M. HENRY GAULT

Departments of Medicine, Queen Mary Veterans' Hospital, Montreal, Quebec,
and Memorial University, St. John's, Newfoundland

Table II. Age, renal function and creatinine excretion in 249 patients

Age range years	Mean age years	n	Mean S_{cr} mg/100 ml	Mean C_{cr} ml/min	Mean Cr excretion mg/kg/24 h and SD
18–29	24.6	22	0.99	114.9	23.6 ± 5.0
30–39	34.6	21	1.08	98.6	20.4 ± 5.1
40–49	46.2	28	1.17	95.4	19.2 ± 5.8
50–59	54.4	66	1.49	77.9	16.9 ± 4.6
60–69	64.6	53	1.39	57.6	15.2 ± 4.0
70–79	74.4	42	1.78	38.6	12.6 ± 3.5
80–92	85.1	17	1.39	37.4	12.1 ± 4.1

Cockcroft-Gault 1976

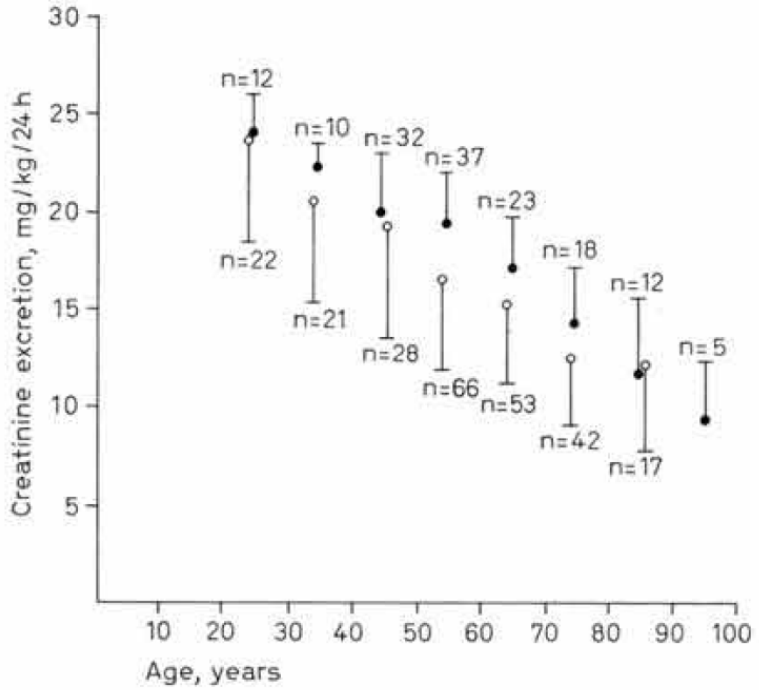


Fig. 1. Creatinine excretion. ● = SIERSBÆK-NIELSEN *et al.* [5], 149 males, age 20–99 years; ○ = present study, 249 males, age 18–92 years.

Cockcroft-Gault 1976

AGE CHANGES IN GLOMERULAR FILTRATION RATE, EFFECTIVE RENAL PLASMA FLOW, AND TUBULAR EXCRETORY CAPACITY IN ADULT MALES

By DEAN F. DAVIES [1] AND NATHAN W. SHOCK

(From the National Heart Institute, National Institutes of Health, Bethesda, Maryland; and the Gerontology Section, Baltimore City Hospitals, Baltimore)

(Submitted for publication October 25, 1949; accepted, December 28, 1949)

AGE CHANGES IN RENAL FUNCTION

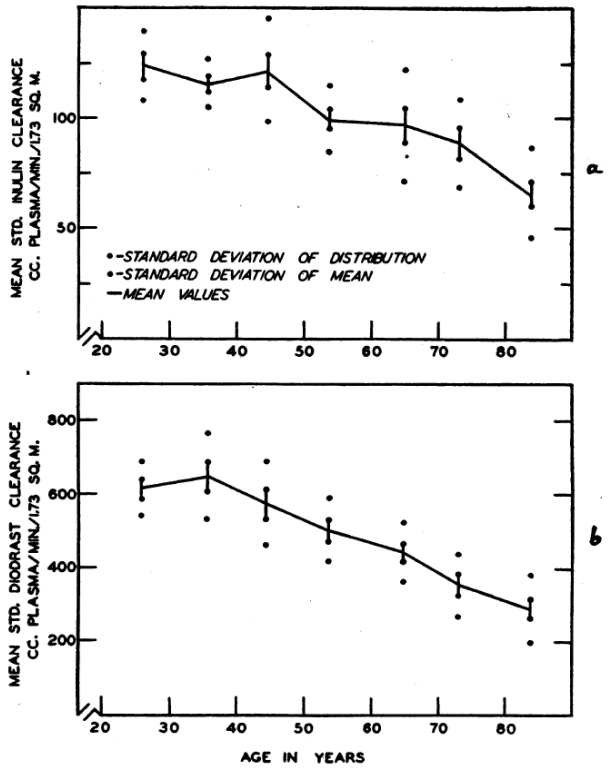


FIG. 1a. AVERAGE CHANGE IN STANDARD INULIN CLEARANCE OR GLOMERULAR FILTRATION RATE WITH AGE, CC. PLASMA/MIN./1.73 SQ.M. BODY SURFACE AREA

b. AVERAGE CHANGE IN STANDARD DIODRAST CLEARANCE OR EFFECTIVE RENAL PLASMA FLOW WITH AGE, CC. PLASMA/MIN./1.73 SQ.M. BODY SURFACE AREA

In all figures the vertical lines represent ± 1 standard deviation of the mean; the circles represent ± 1 standard deviation of the distribution.

Davies and Shock 1949

Journal of Gerontology
1976, Vol. 31, No. 2, 155-163

The Effect of Age on Creatinine Clearance in Men: A Cross-Sectional and Longitudinal Study[1]

John W. Rowe, MD, Reubin Andres, MD, Jordan D. Tobin, MD,
Arthur H. Norris, MS, and Nathan W. Shock, PhD[2]

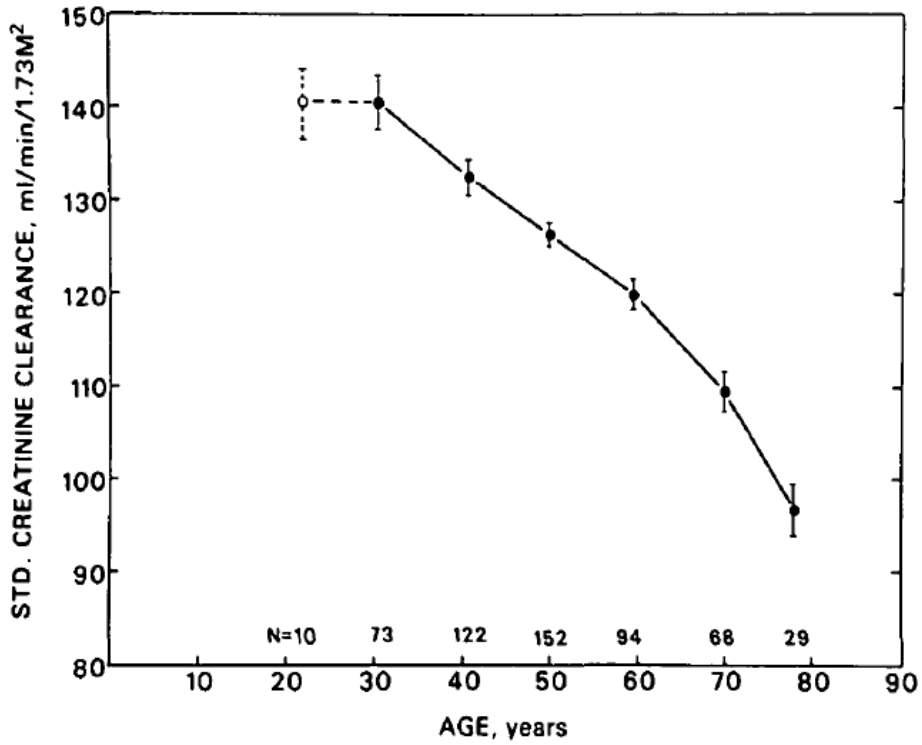


Fig. 2. Cross-sectional differences in standard creatinine clearance with age. The number of subjects in each age group is indicated above the abscissa. Values plotted indicate mean ± S.E.M.

Shock 1976

Unpredictability of Clinical Evaluation of Renal Function in Cirrhosis

Prospective Study

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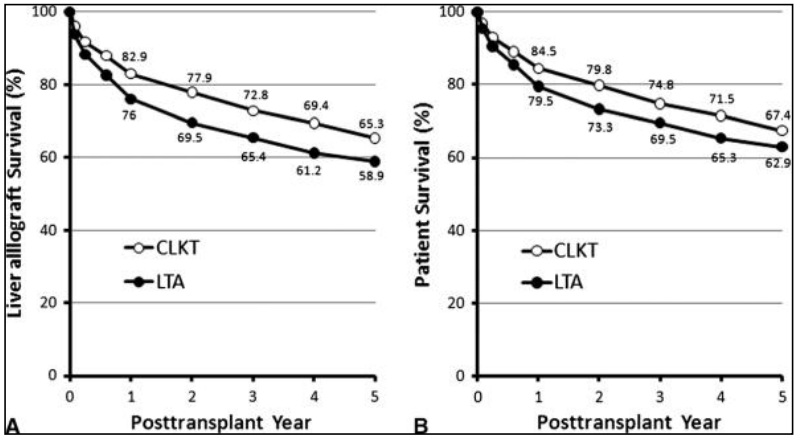
American Journal of Medicine 1987

TABLE III **Prospective Evaluation of Renal Function in Group III Cirrhotic Patients**

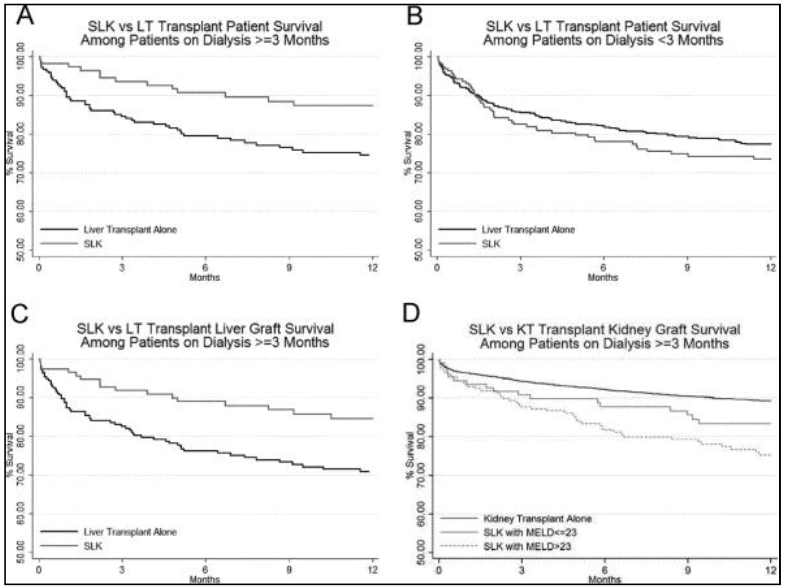
Patient Number	Glomerular Filtration Rate (ml/minute)	Method (type of clearance)	Serum Creatinine (mg/dl)	Interval (days)	Remarks
1	12	Inulin	1.1	1	Death from subarachnoid bleeding, coagulopathy
	0			320	
2	17	Inulin	1.0	1	
	14	Inulin	0.9	8	
3	30	Inulin	1.0	1	
	106	Inulin	1.0	23	
4	7	Inulin	1.0	1	
	51	Inulin	1.1	41	After LeVeen shunt
	51	Creatinine	2.0	562	
5	25	Inulin	1.4	1	
	34	Inulin	1.2	12	
	31	Inulin	1.2	22	
6	23	Inulin	1.3	1	Death from hemorrhage, encephalopathy
	10	Creatinine	2.3	4	
	15	Creatinine	2.2	5	
	18	Creatinine	2.1	8	
	0				
7	36	Inulin	1.4	1	Death from encephalopathy
	37	Creatinine	1.5	8	
	23	Creatinine	1.5	27	
	62	Creatinine	1.1	90	
	30	Creatinine	1.7	147	
	19	Creatinine	2.6	223	
	0			224	
8	32	Creatinine	1.5	1	Death from hepatorenal syndrome
	25	Creatinine	1.9	4	
	22	Creatinine	2.2	9	
	19	Creatinine	2.5	27	
	19	Inulin	2.0	104	
	8	Creatinine	4.9	162	
	5	Creatinine	4.7	189	
	0			197	
9	50	Creatinine	1.5	1	Death from encephalopathy
	41	Creatinine	1.9	320	
	14	Inulin	2.2	343	
	15	Inulin	2.2	353	
	14	Creatinine	2.7	410	
	6	Inulin	2.8	589	
	0			628	
10	38	Creatinine	1.1	1	
	28	Creatinine	2.0	9	
	81	Creatinine	0.6	20	After LeVeen shunt
11	59	Inulin	1.4	1	Death from hemorrhage, encephalopathy
	39	Creatinine	2.9	5	
	40	Creatinine	2.1	7	
	4	Creatinine	4.3	9	
	0			11	

Medical Eligibility Criteria



Combined Liver-Kidney Transplantation Is Preferable to Liver Transplant Alone for Cirrhotic Patients With Renal Failure.
Fong, Tse-Ling; Khemichian, Saro; Shah, Tariq; Hutchinson, Ian; Cho, Yong

Transplantation. 94(4):411-416, August 27, 2012.



Declining Outcomes in Simultaneous Liver-Kidney Transplantation in the MELD Era: Ineffective Usage of Renal Allografts.
Locke, Jayme; Warren, Daniel; Singer, Andrew; Segev, Dorry; Simpkins, Christopher; Maley, Warren; Montgomery, Robert; Danovitch, Gabriel; Cameron, Andrew

Transplantation. 85(7):935-942, April 15, 2008.