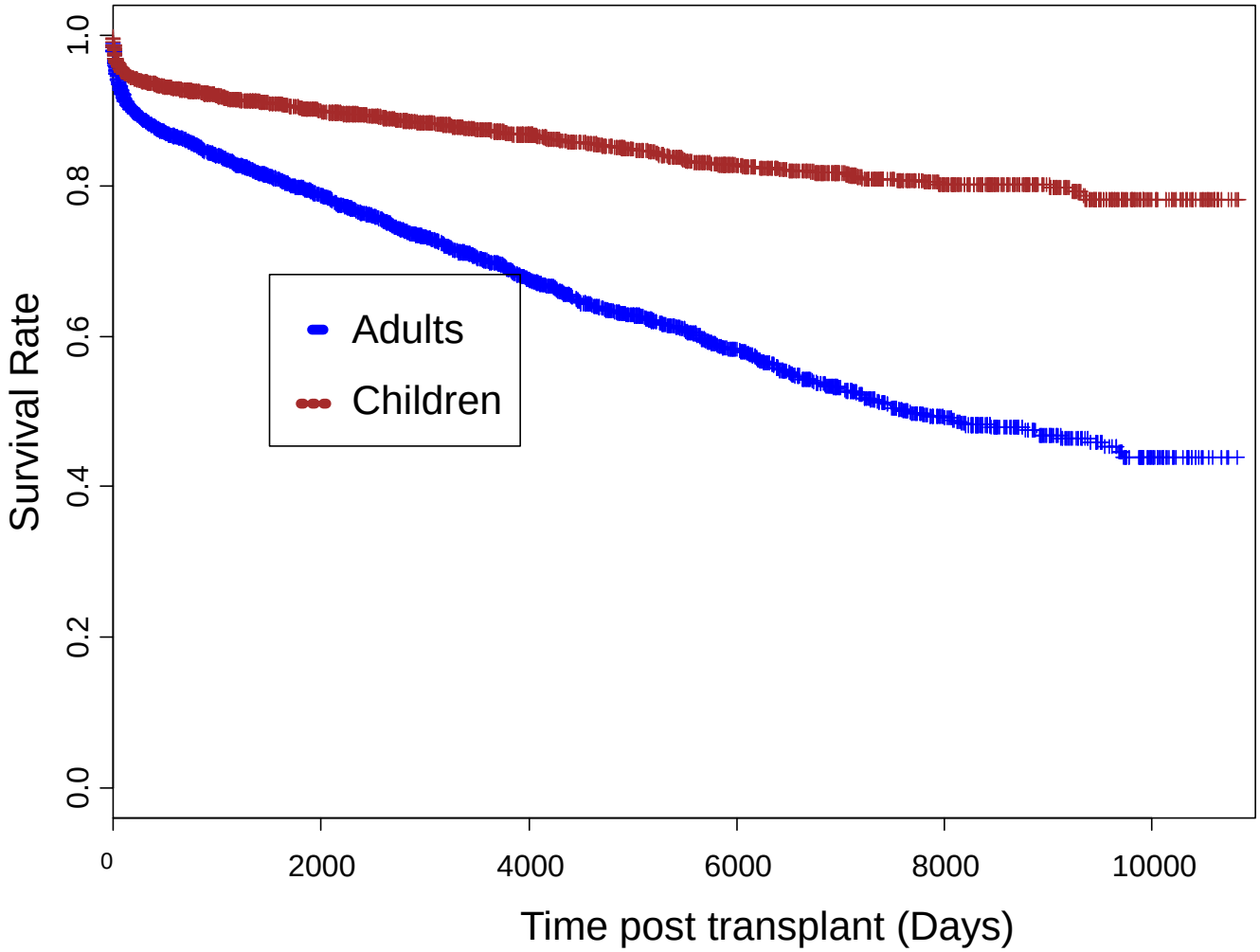
Update in Pediatric Liver

- Pat McKiernan
- Children’s Hospital of Pittsburgh and University of Pittsburgh

- Conflicts to report

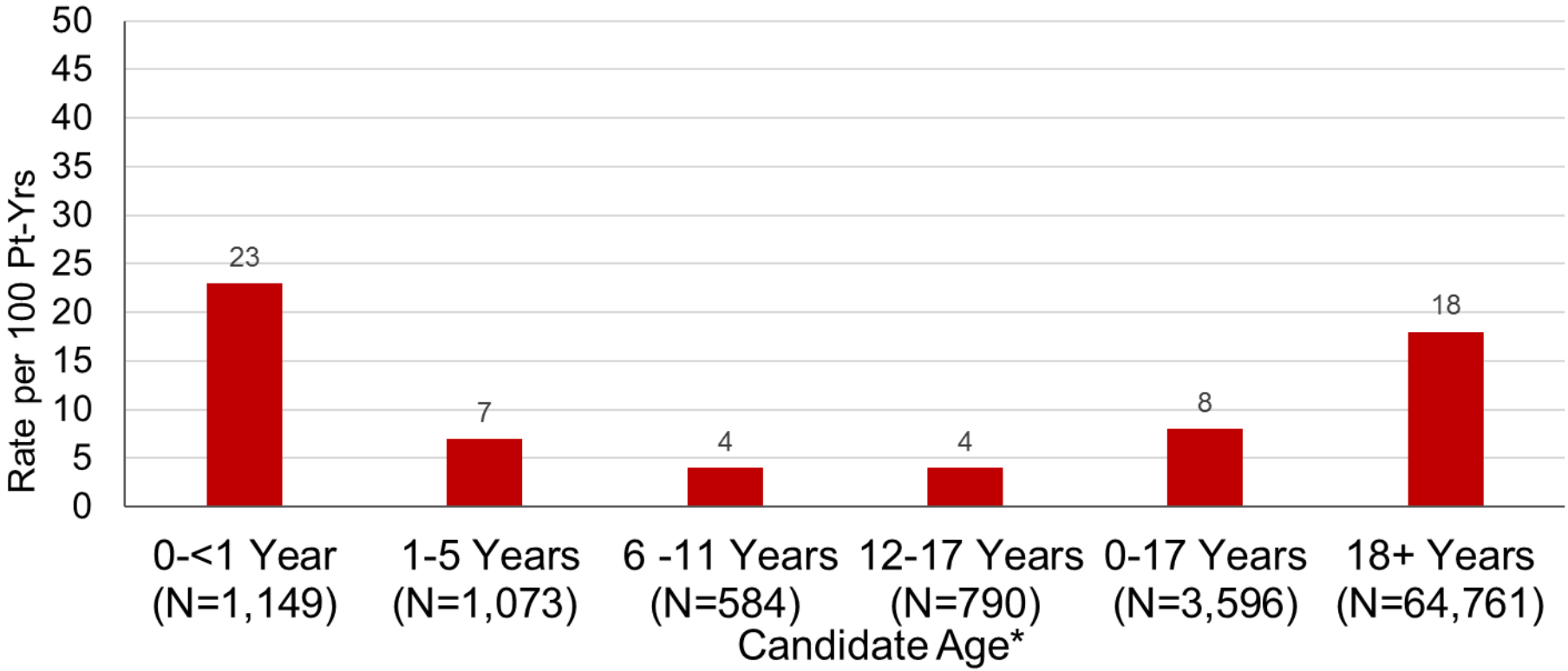
- Consultant for Albireo

Liver transplant for metabolic disease in US 1987-2017 patient survival: children versus adults



UPMC | CHILDREN'S HOSPITAL OF PITTSBURGH

Summary of problem: 1. Death Rate per 100 Patient Years for Candidates Ever Waiting for Liver Alone Transplants during 2011-2015 by Age



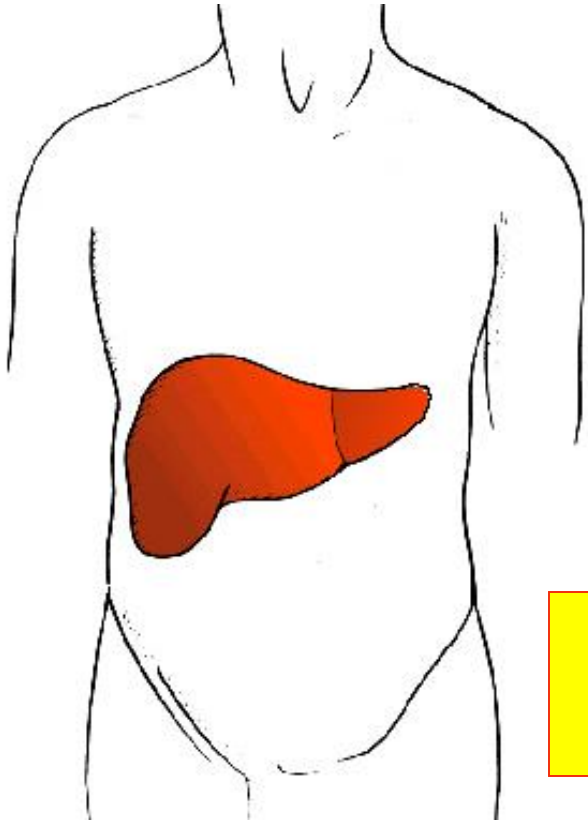
*Age is maximum of age at listing or age at beginning of the study cohort.

UPMC | CHILDREN'S HOSPITAL OF PITTSBURGH

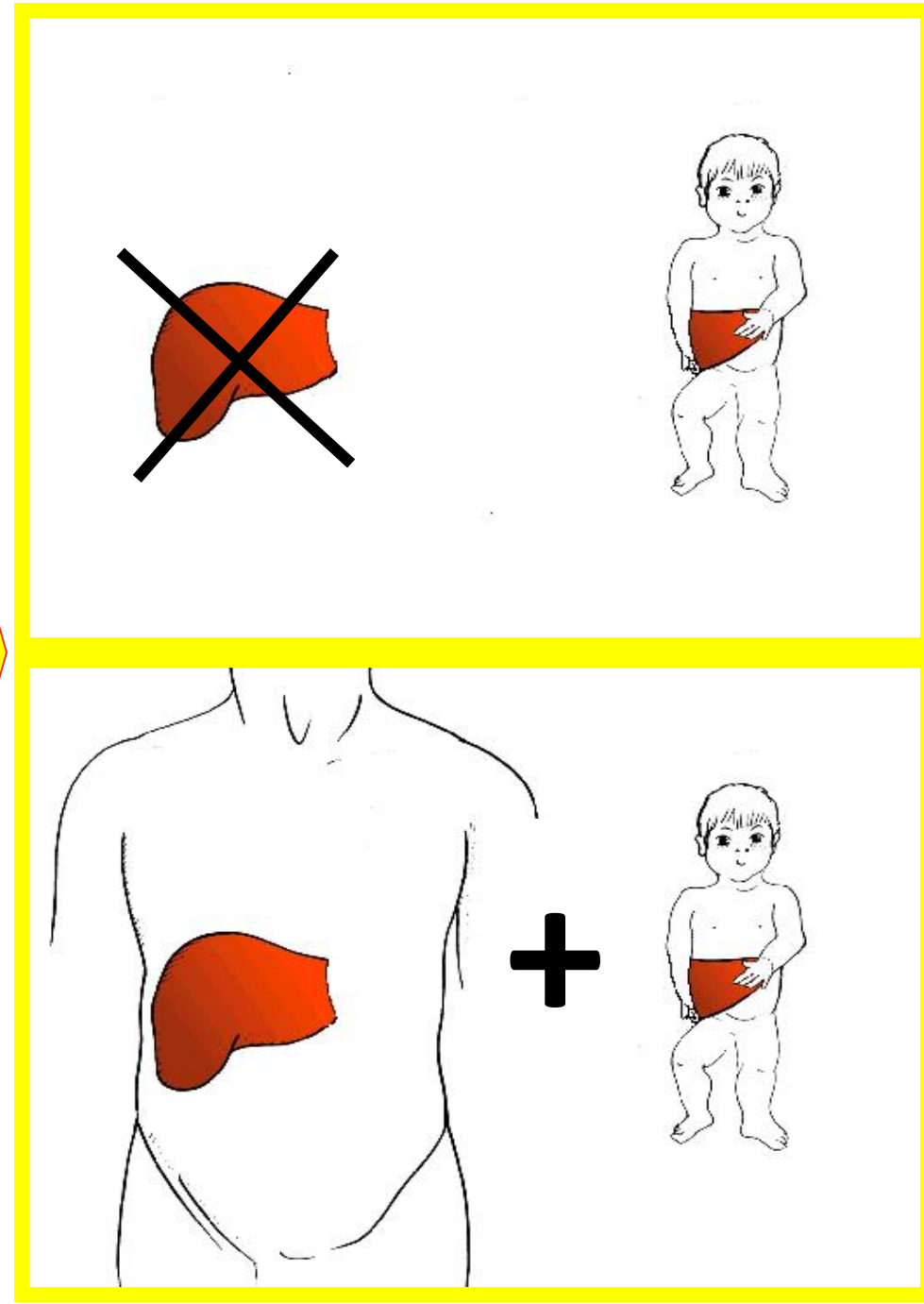
Placement of pediatric deceased donors whose livers were ultimately transplanted
UNOS 2010 -2105

	All Recipients (n = 3,318)	Pediatric <12yr (n = 1,692)	Pediatric 12-17yr (n = 221)	Adult Recipients (n = 1,569)
Median Age in Years (IQR)	12 (3-16)	3 (1-9)	15 (11-16)	15 (13-17)

J Ge et al Hepatology 2018,



From
Cutting down
To splitting



Potential splittable livers UNOS 2010 to 2015

Deceased donor liver transplants in the U.S. 1/1/2010-12/31/2015 = 37,333

EXCLUDED, not favorable for split: 33,134

1,872	Deceased after cardiac death
21,711	Age >40 years or <18 years
3,161	BMI ≥ 30
2,188	Sodium ≥ 155 meq/L
858	Required >1 vasopressor
1,184	Hospitalized ≥ 7d before procurement
2,087	Terminal AST or ALT ≥ 100 IU/L, or terminal total bili ≥ 3 mg/dL
73	Cardiac arrest since neuro event leading to brain death, with known arrest time ≥ 30 min or time missing

Transplanted livers with donors 18-40 years of age, with potential for split transplant = 4,199

EXCLUDED, high-risk donor characteristics: 1,760

272	Hep C, Hep B core Ab + or Hep B Sag +
115	Donor biopsy with >10% steatosis
752	High-risk donor by CDC criteria
433	Utilized for multi-organ transplant
188	Bloodstream infection

Transplanted livers with donors who met all criteria for split eligibility =

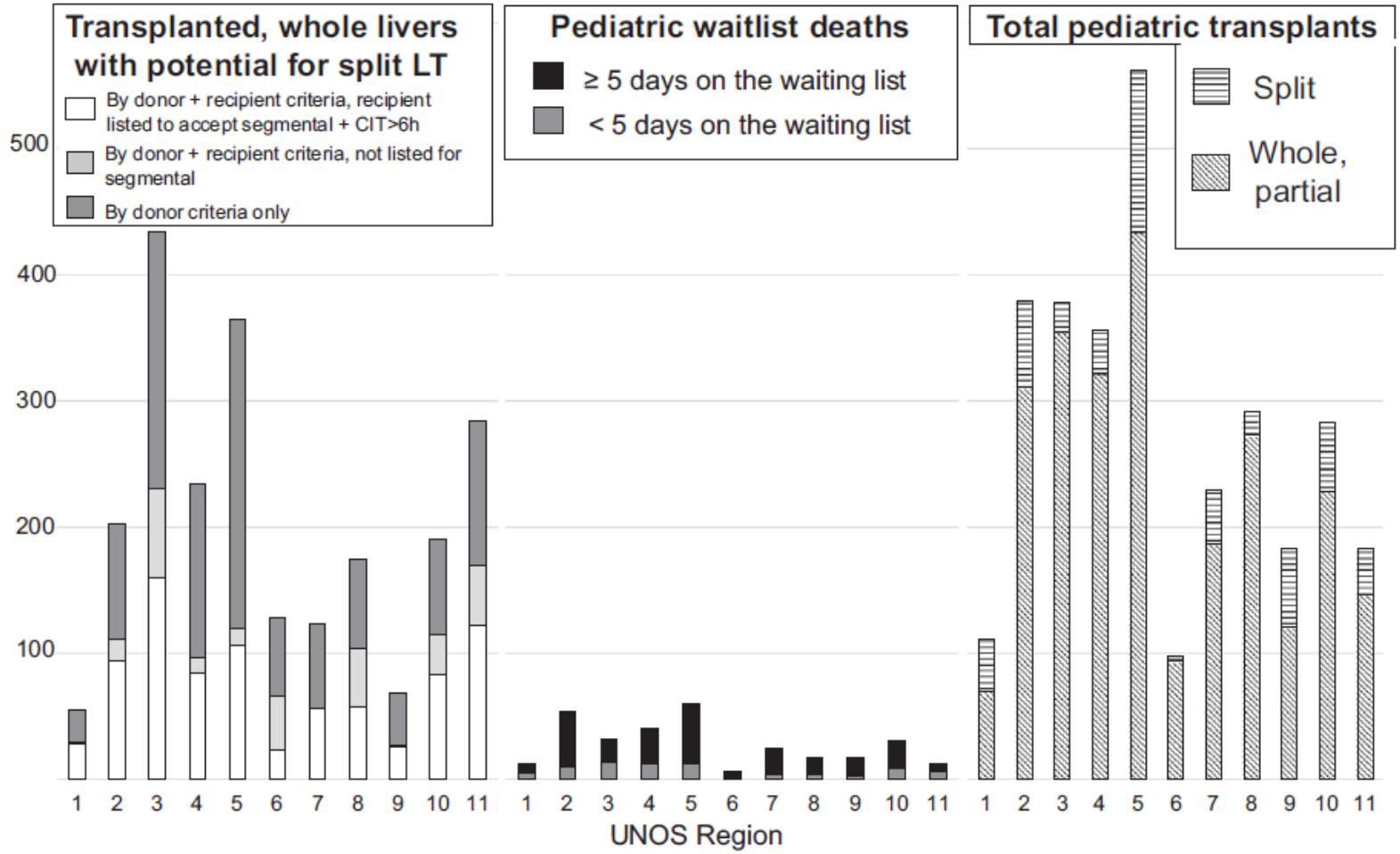
	Donors	Recipients
Total	2,369	2,439
Whole/Partial	2,278	2,278
Split	91	161

EXCLUDED, recipient (primary allocation) not favorable for split: 1,137

150	Status 1A
163	Re-transplant
241	>300 miles from donor hospital
317	BMI > 34
266	MELD ≥ 40 or in the ICU at transplant

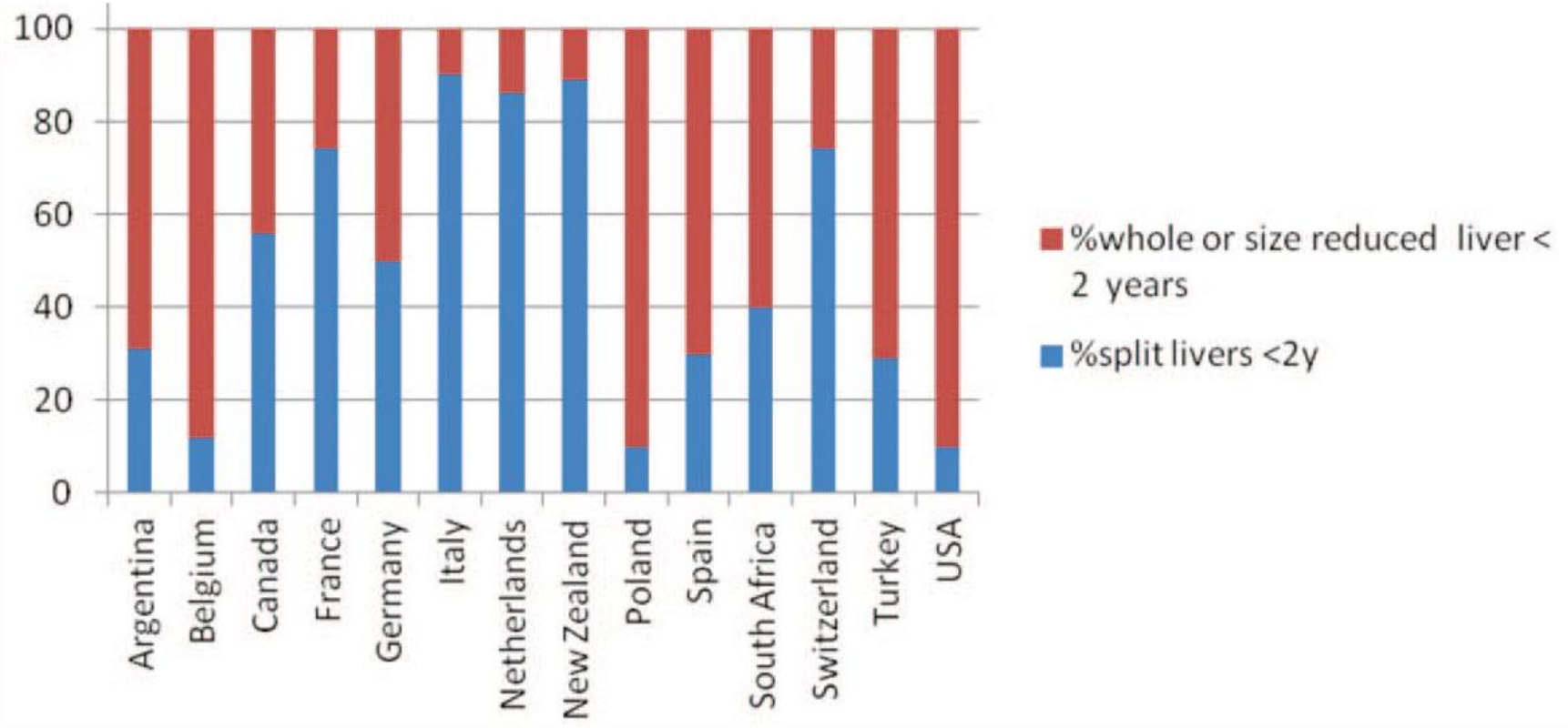
Perito et al Transplantation March 2019

Potential splittable livers and pediatric mortality and



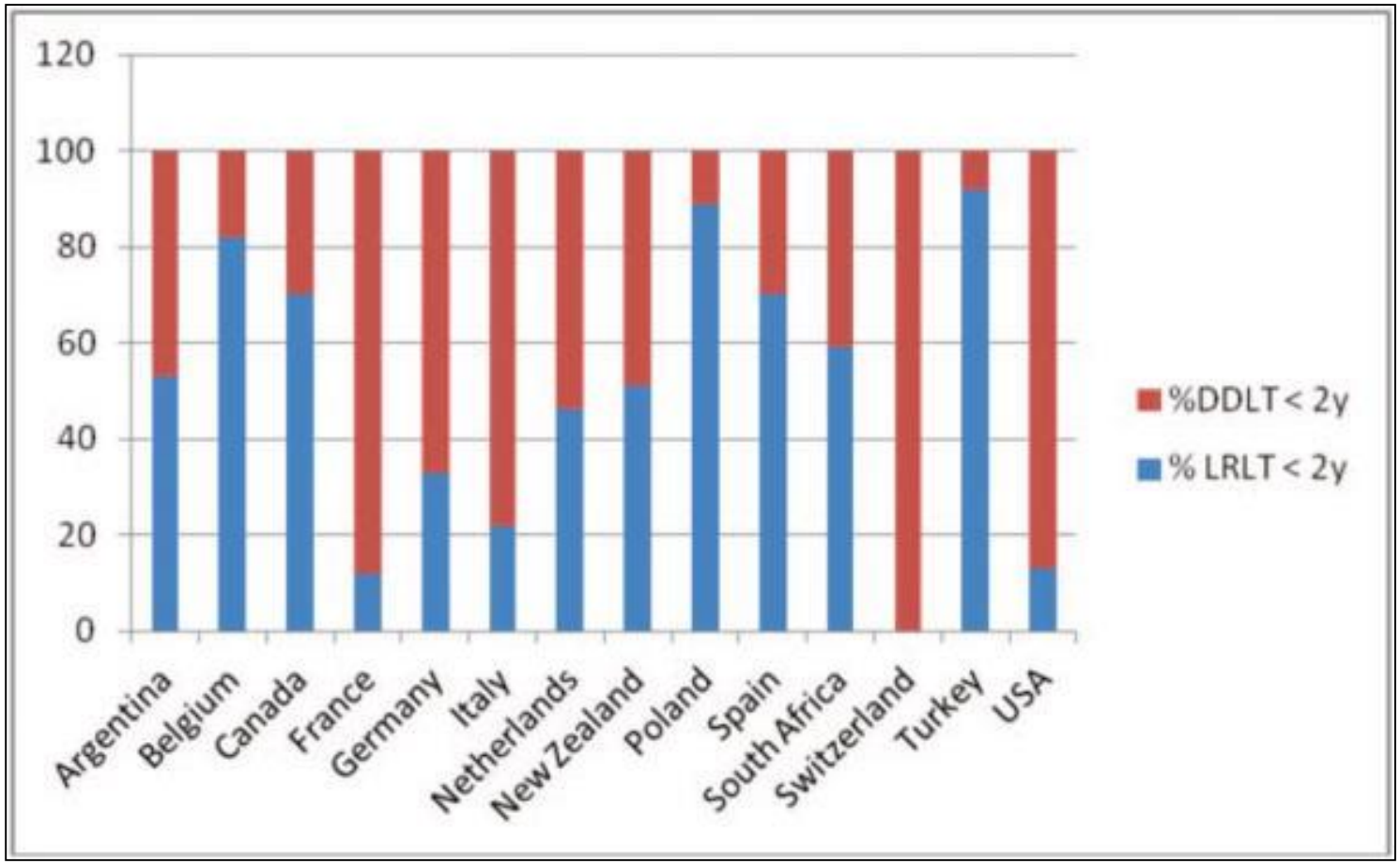
Perito et al Transplantation March 2019

Type of organ in DDLT recipient < 2 years



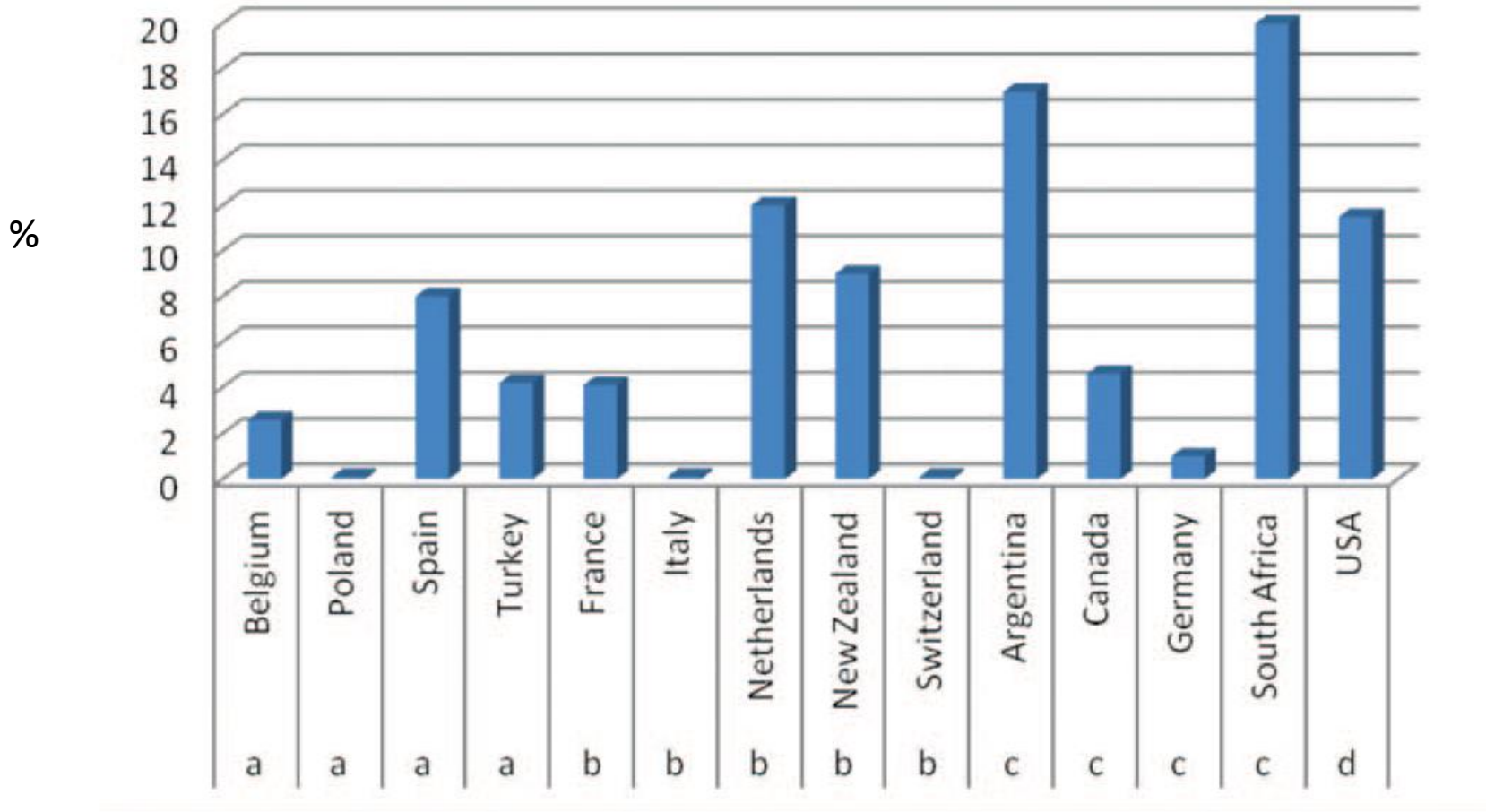
Fischler et al. JPGN May 2019

Percentage of DDLT and living donor liver transplantation in recipients < 2 years.



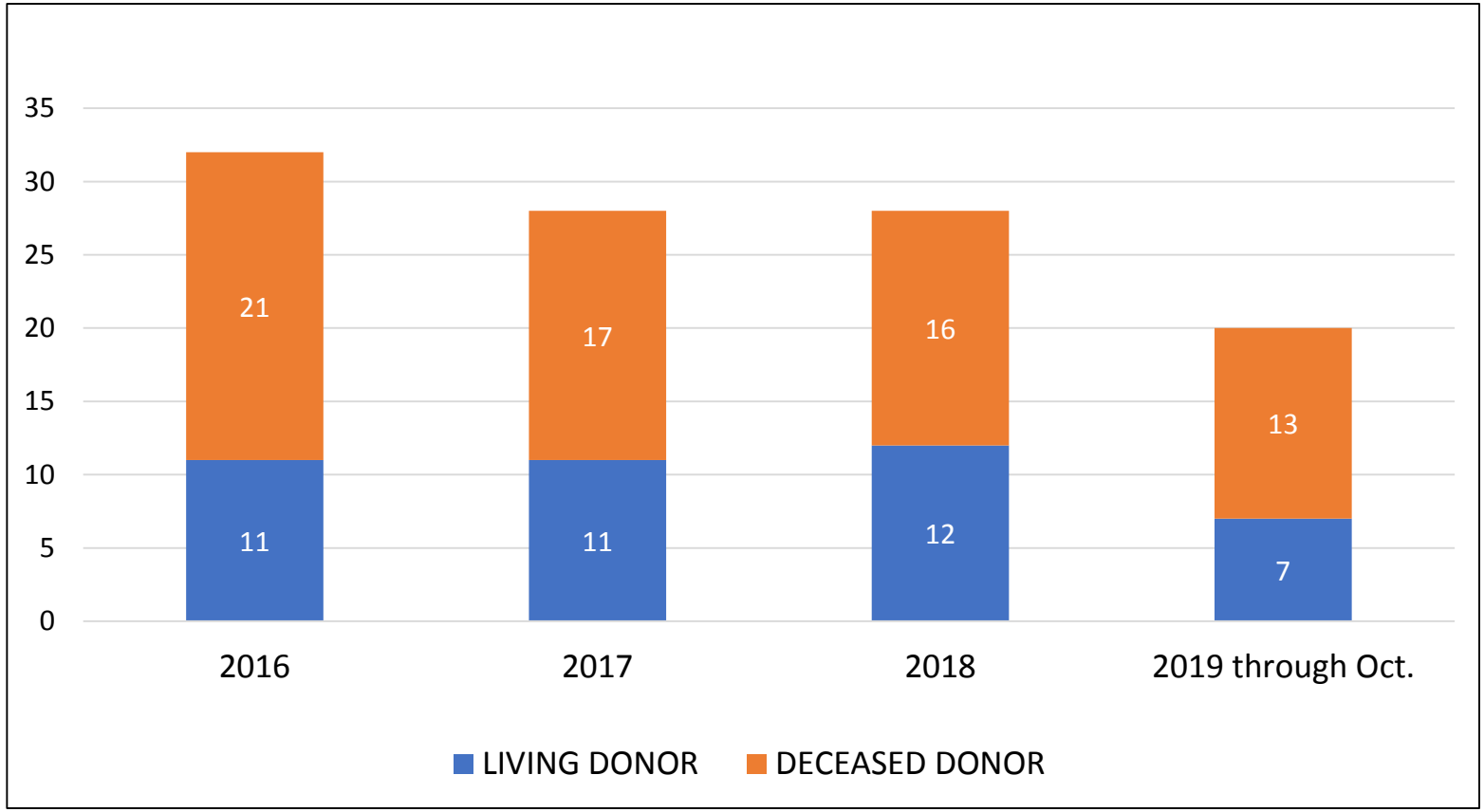
Fischler et al. JPGN May 2019

Waiting list mortality for children <2 years of age

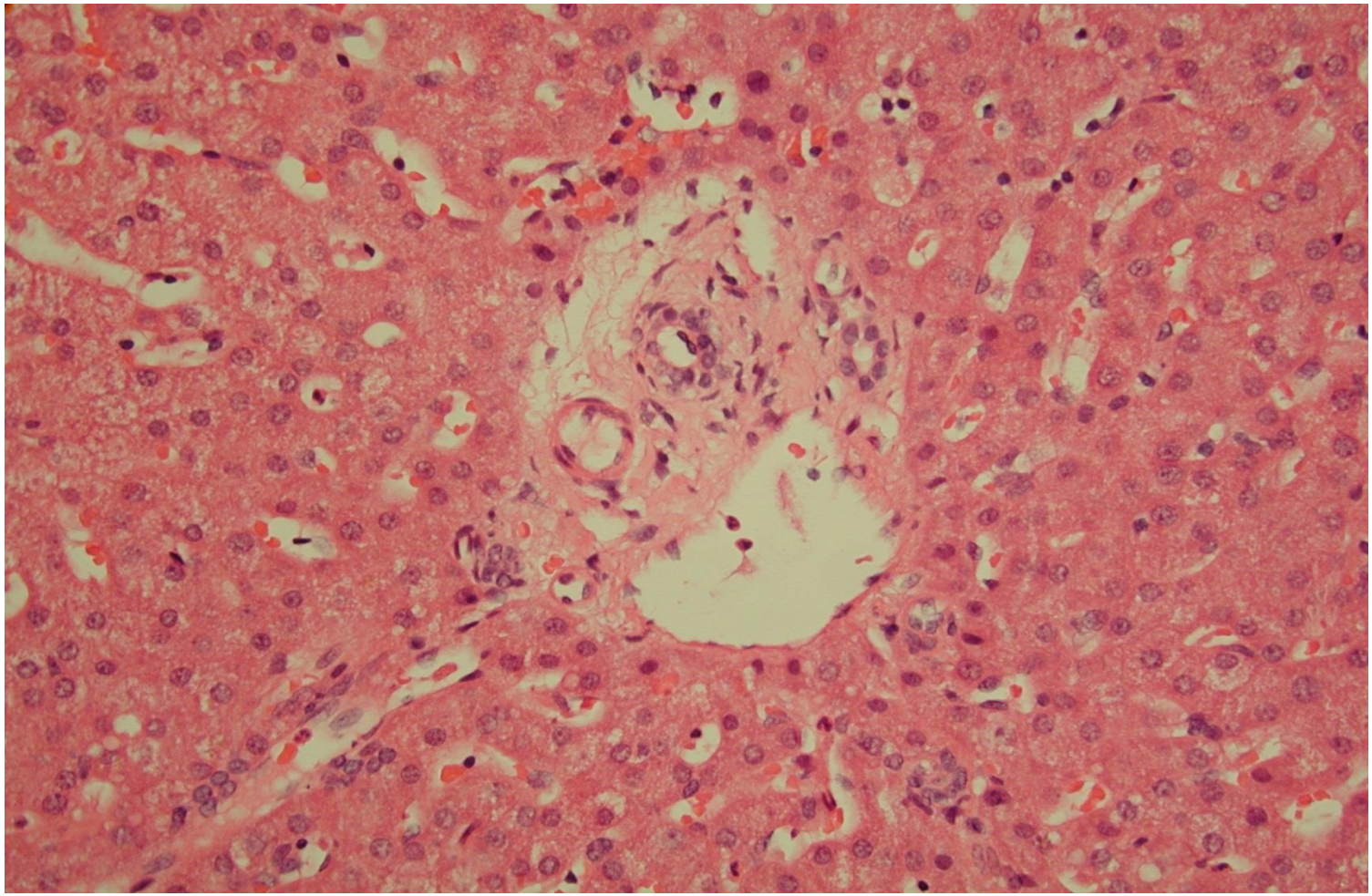


Fischler et al. JPGN May 2019

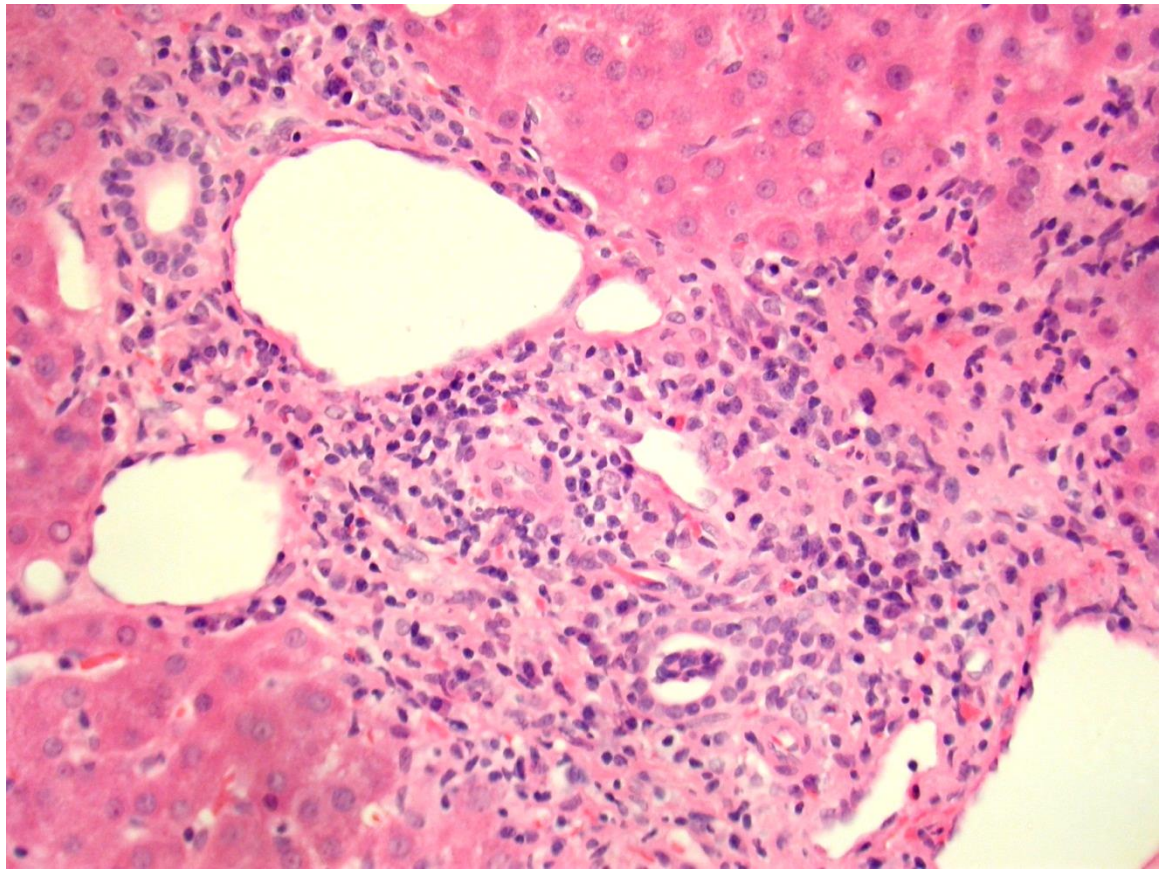
Donor type at CHP



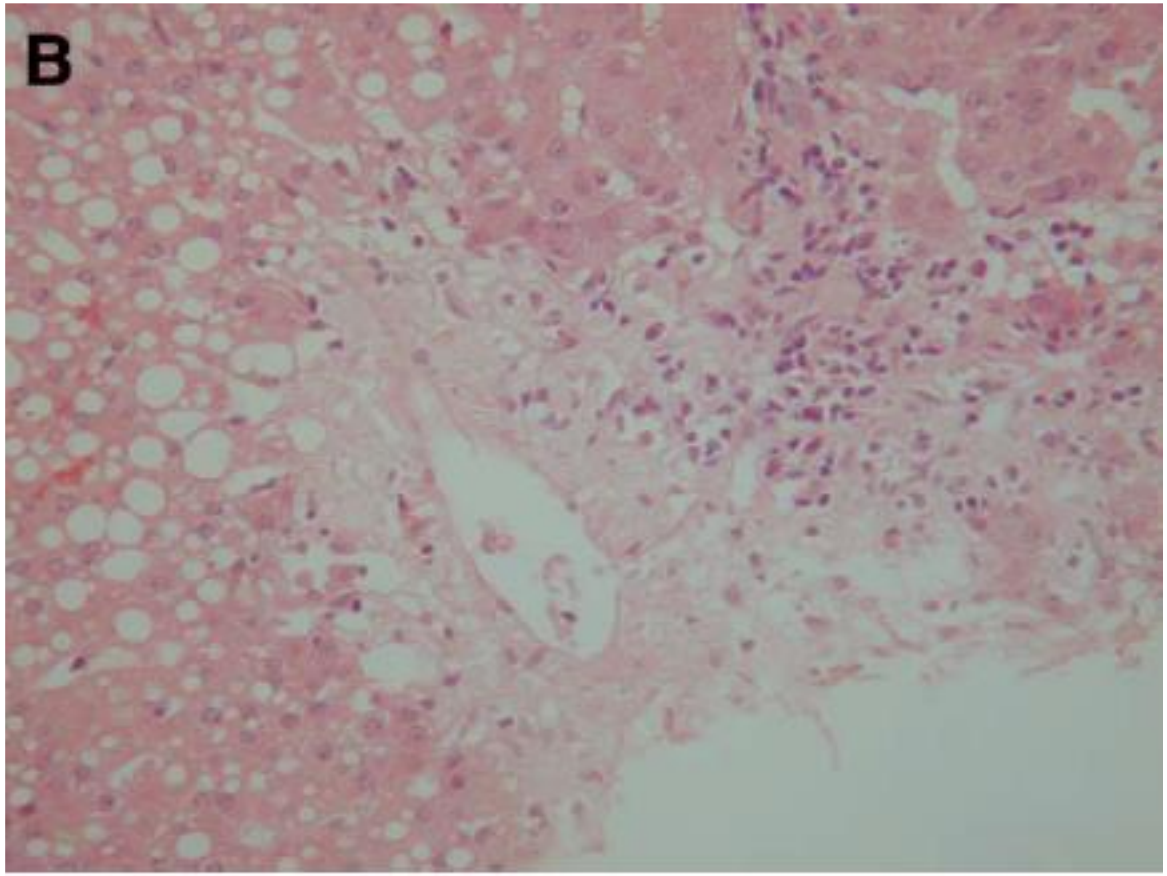
Normal post transplant liver biopsy



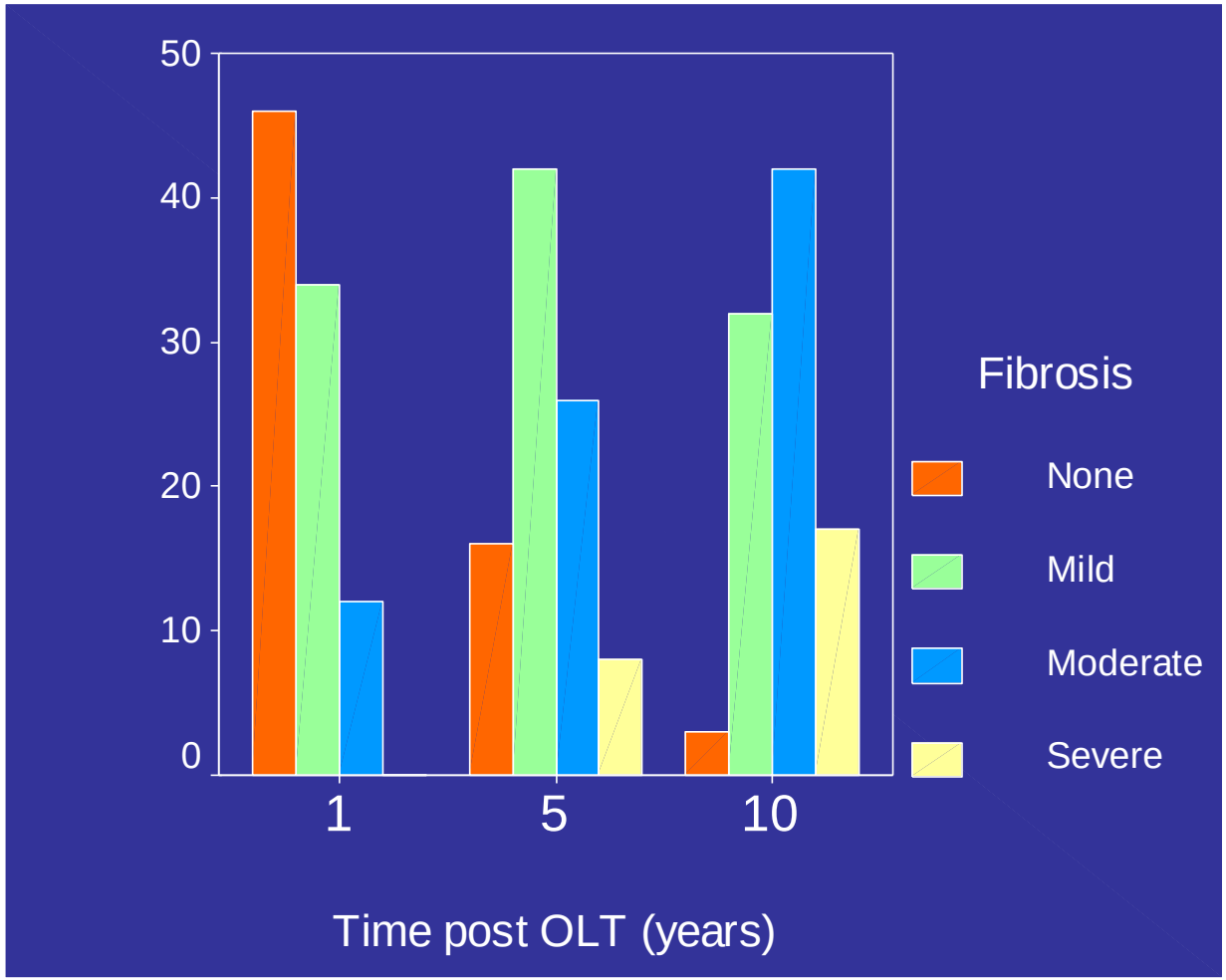
Post transplant chronic hepatitis



Posttransplant perivenular inflammation



Fibrosis grade in children with chronic hepatitis at 1, 5 and 10 years post OLT



Evans H et al; Hepatology 2006

Subclinical Damage in Long-term Pediatric Liver Transplant Allografts

- Screening for iWITH study
- 2909 recipients at 12 centres
- 584 met medical criterion
- 355 met medical criterion and logistics
- 276 approached
- 161 agreed
- 157 enrolled

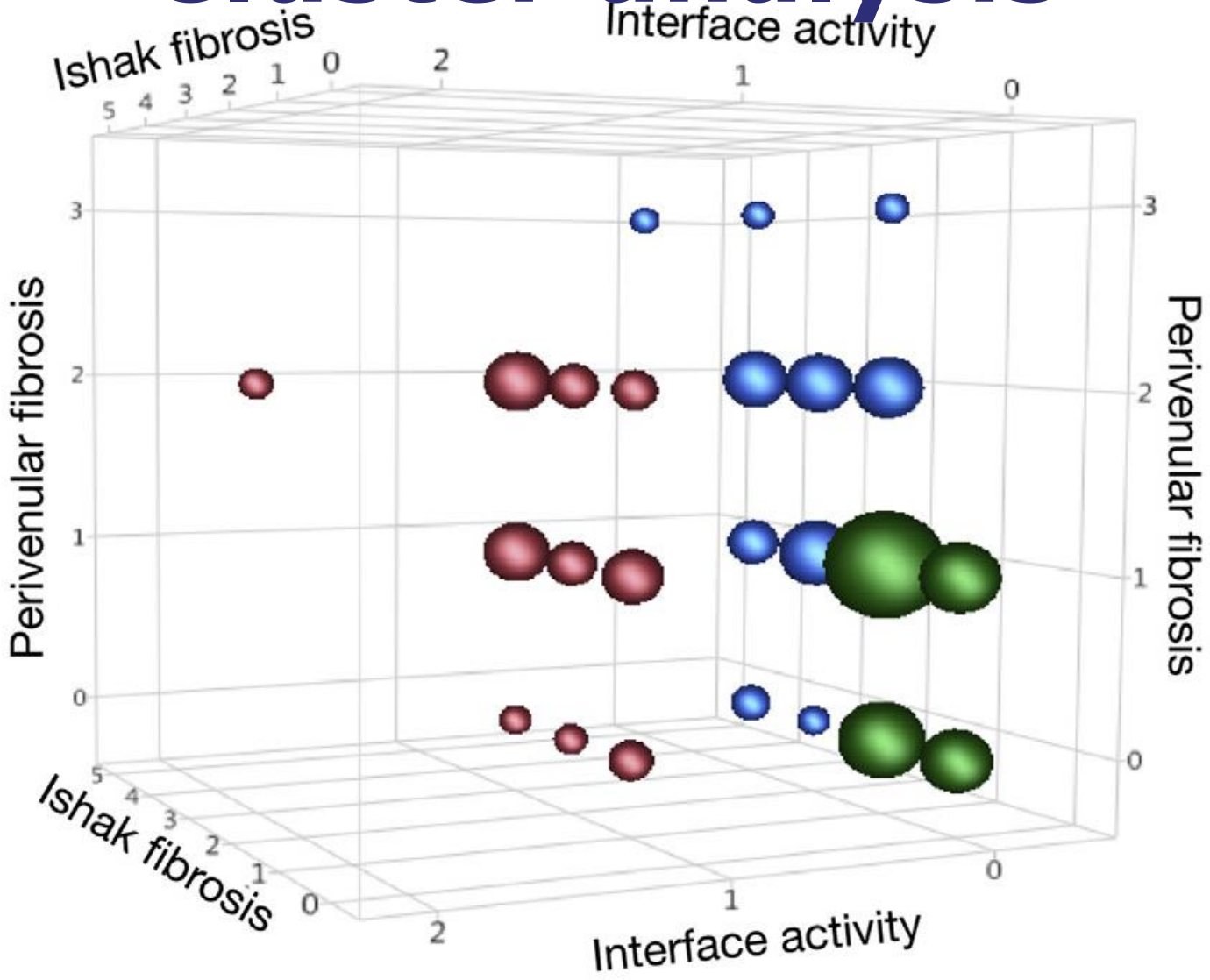
Feng et al. Gastroenterology 2018;155:1838–1851

Frequency of histological abnormalities

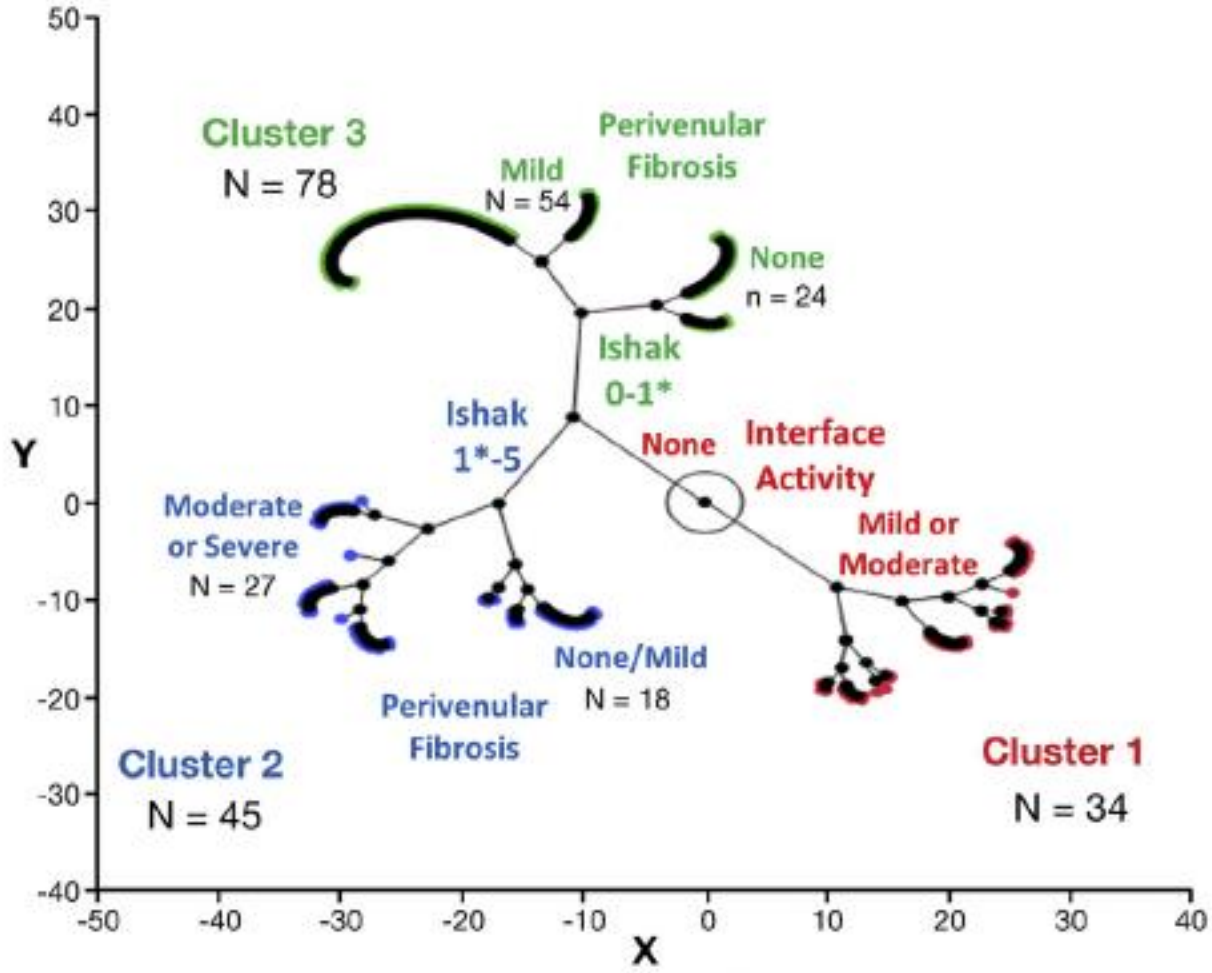
	Inflammation				Bile Duct Damage	Peri-venular Fibrosis	Ishak Fibrosis Stage	
N = 157	Portal	Interface	Lobular	Peri-venular				
None	57 36%	123 78%	120 76%	130 83%	148 94%	31 20%	0-1	96 61%
Mild	92 59%	33 21%	36 23%	27 17%	9 6%	85 54%	2	27 17%
Moderate	8 5%	1 1%	1 1%	0	0	38 24%	3	33 21%
Severe	0	0	0	0	0	3 2%	4-5	1 (1%)

Feng et al. Gastroenterology 2018;155:1838–1851

Cluster analysis

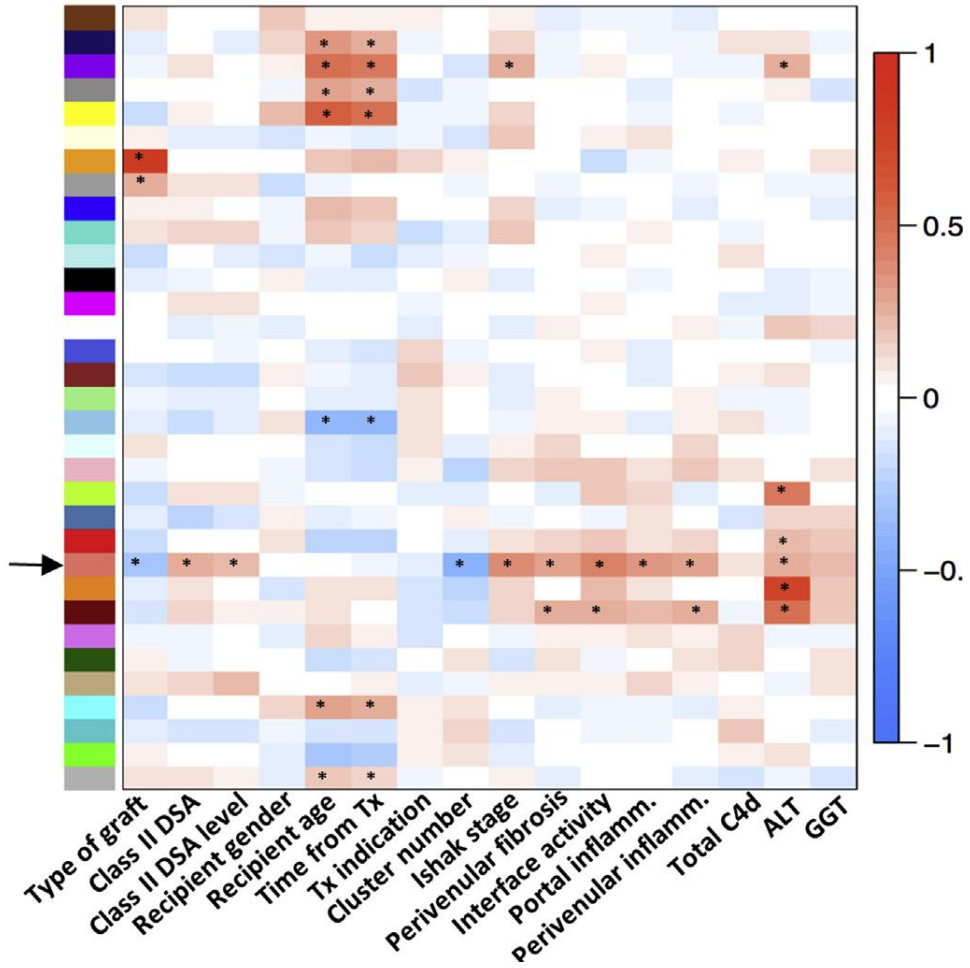


3 distinct histological clusters



Feng et al. Gastroenterology 2018;155:1838–1851

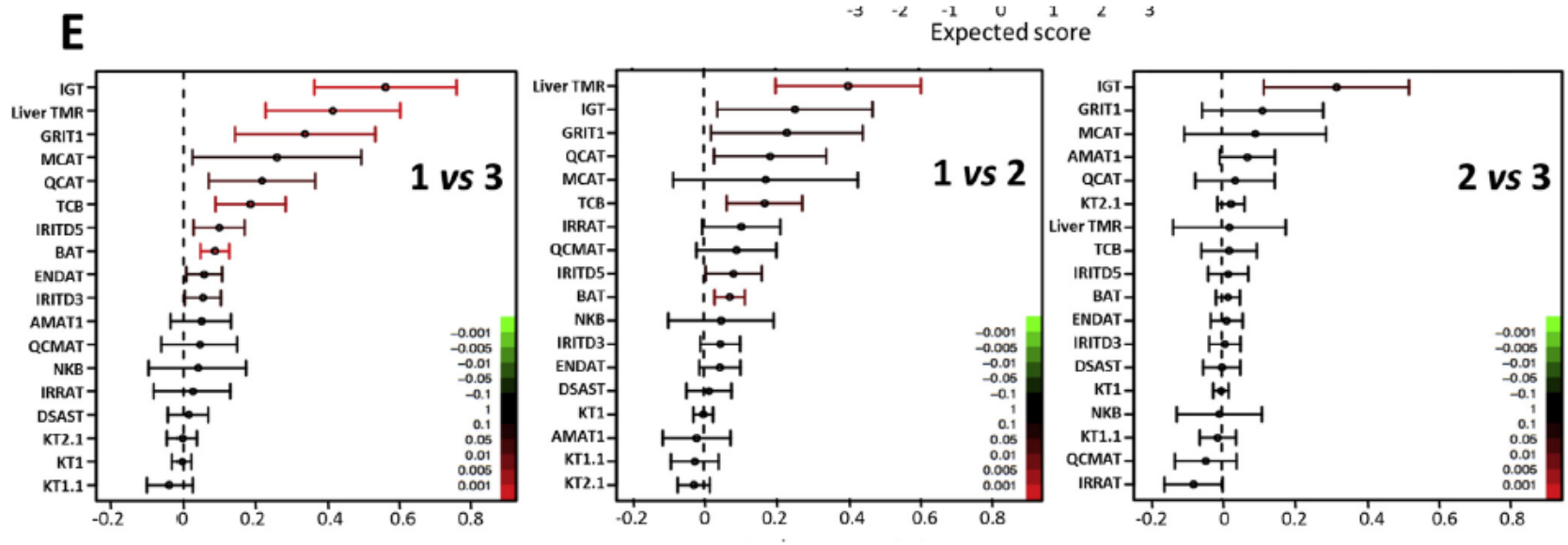
Gene coexpression modules network analysis of the liver



Feng et al. Gastroenterology 2018;155:1838–1851

Differential gene expression between clusters.

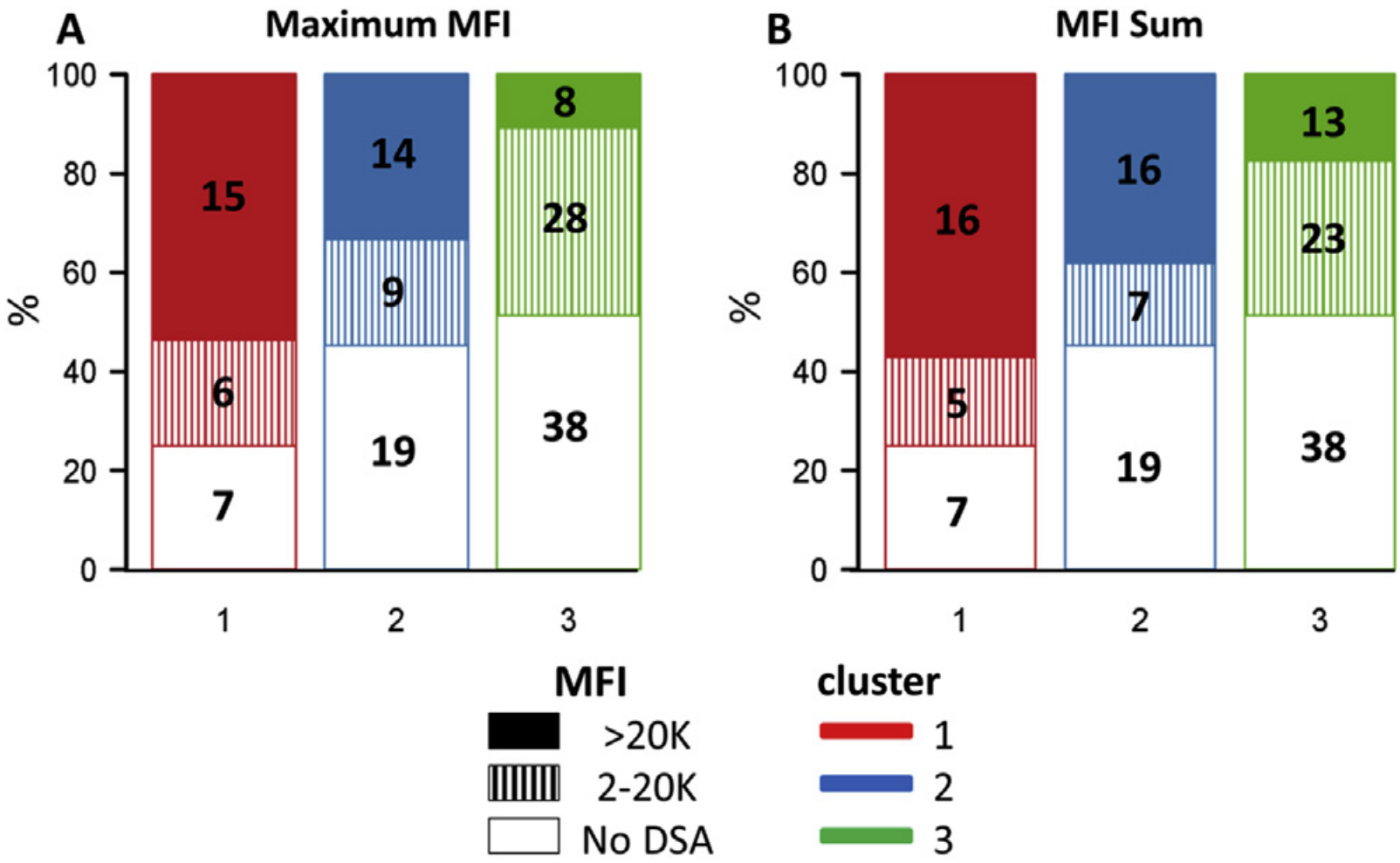
Genes associated with T-cell rejection increased in cluster 1



No increase in intragraft endothelial- or natural killer cell–related gene signatures

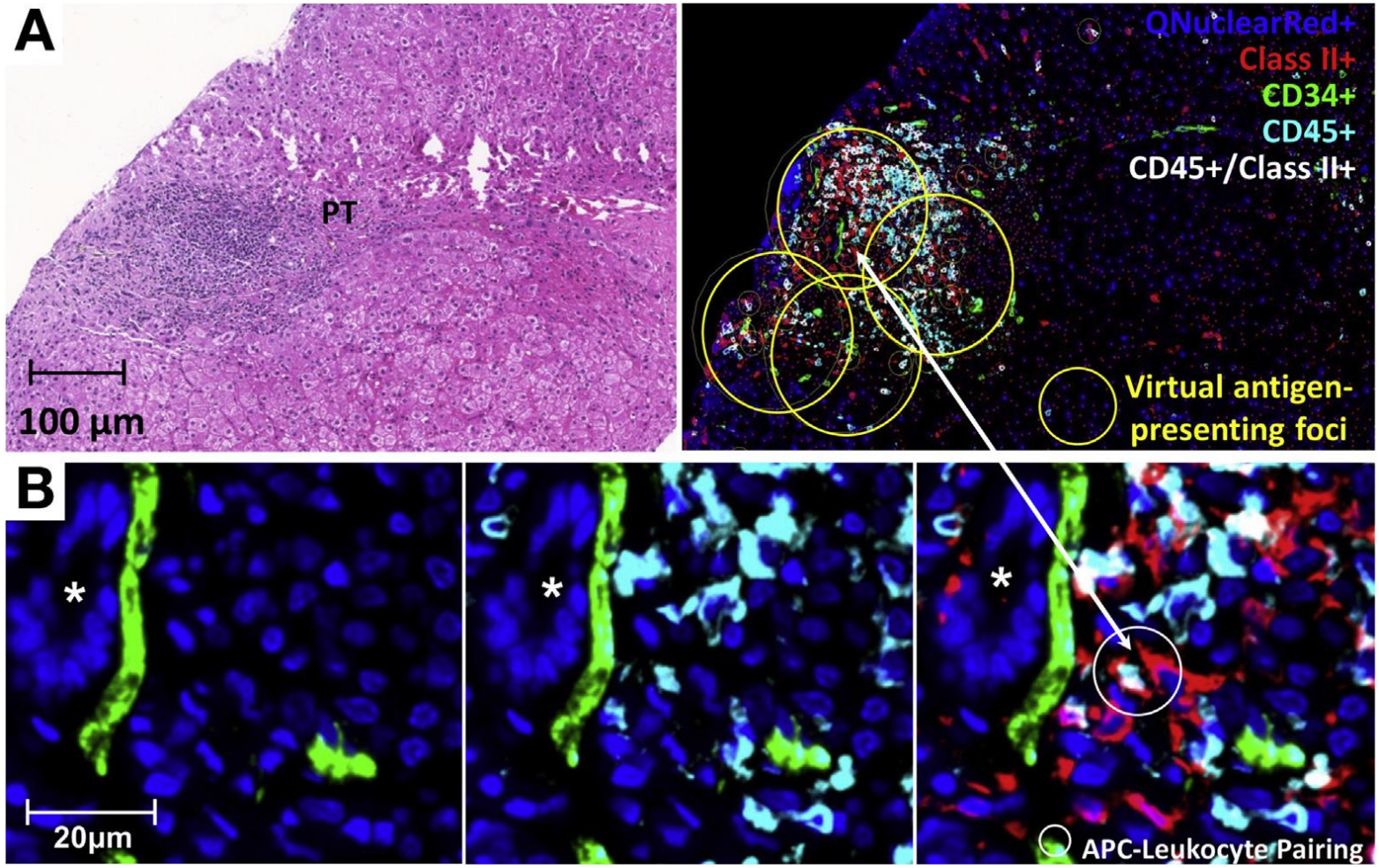
Feng et al. Gastroenterology 2018;155:1838–1851

Class II DSA MFI by cluster.



Feng et al. Gastroenterology 2018;155:1838–1851

Antigen-presenting foci localized primarily to portal tracts in cluster 1



Treatment cohorts at BCH

Cohort	Mono (CNI) (n=130)	Combo (CNI+Pred) (n=128)
Era	1983-1996	2000 to 2009
Transplantation	isolated and first liver graft only	
Induction IS	Ciclosporine + Prednisolone (3months) +Azathioprine (12 months)	Tacrolimus/Ciclosporine +Prednisolone +Basiliximab (at Tx)
Maintenance IS	Ciclosporine	Tacrolimus/Ciclosporine +Prednisolone
Demographics	Age at Transplant, CMV status, blood group	
Tx related factors	Donor age, graft type, CMV status, cold ischaemic time, rejection episodes	
Protocol visit	at 5 and 10yrs liver biopsy and blood tests (ALT, GGT, IGG, autoantibodies)	
Exclusion criteria		
all patients retransplanted before baseline or until first protocol visit		
all patients transplanted for IFALD		

* IS=immunosuppression

** Tx=transplant

Haller et al IPTA 2019

Demographics

	Mono (CNI) (n=130)	Combo (CNI+Pred) (n=128)	p-value
Age at transplant [median/range, yrs]	3 (1 - 8)	2 (1 - 5)	**0.02**
Recipient [n male, %]	64 (49%)	56 (44%)	ns
Graft type [n, %]			
whole	60 (46%)	18 (14%)	**<0.001**
split	2 (2%)	69 (54%)	**<0.001**
reduced	68 (52%)	41 (32%)	ns
Donor age [median/range, yrs]	10 (6 - 17)	22 (13 - 34)	**<0.001**
CMV pos [n, %]			
Recipient	44 (34%)	33 (26%)	ns
Donor	46 (36%)	47 (37%)	ns
Blood group ABO mismatch [n, %]	17 (13%)	16 (13%)	ns
Cold ischemic time [median/range, min]	709 (487 - 814)	594 (510 - 681)	**<0.001**
Rejection [n, %]			
acute	63 (50%)	69 (54%)	ns
chronic	11 (9%)	6 (5%)	ns

Haller et al IPTA 2019

Protocol blood tests

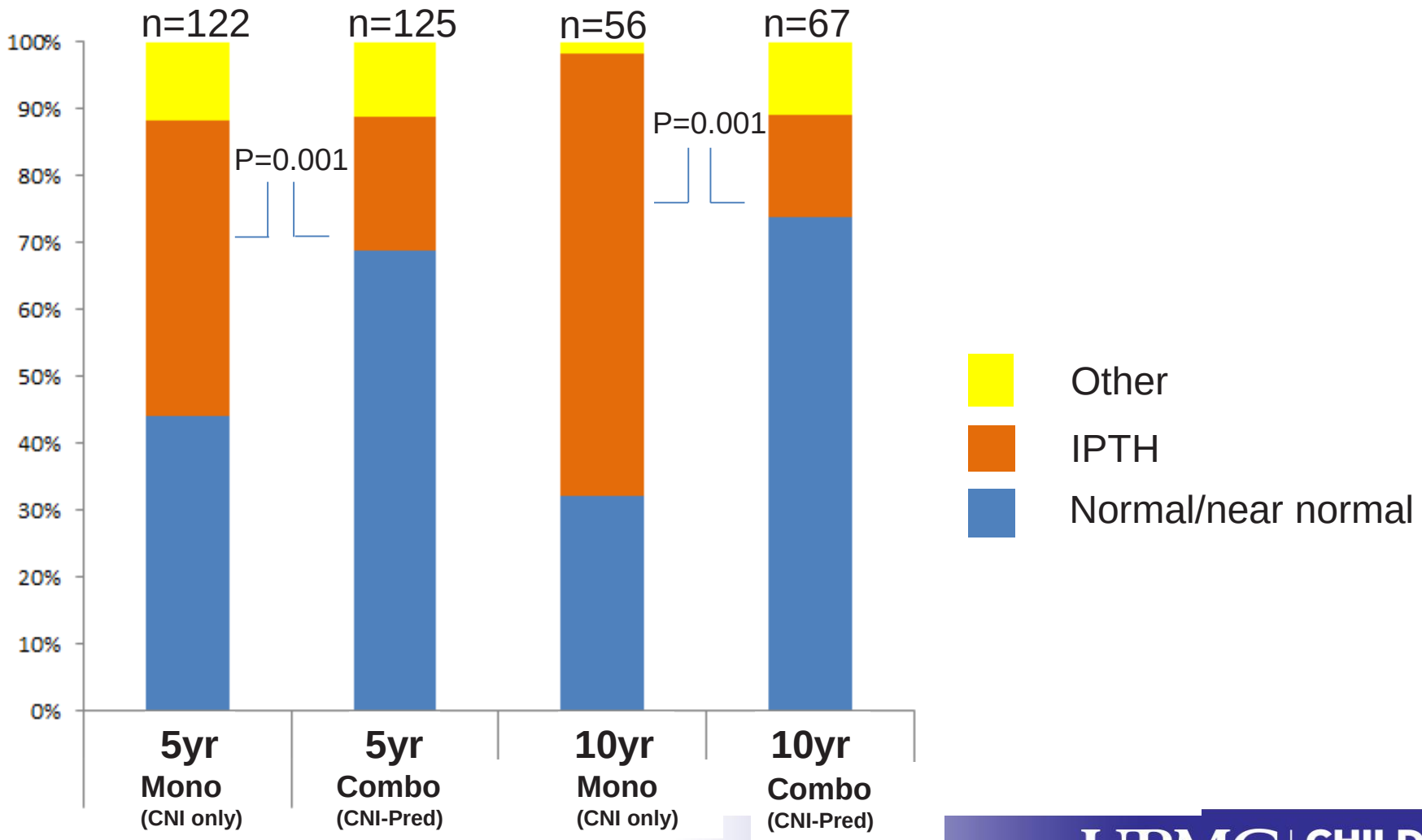
Blood tests	Mono (CNI)	Combo (CNI+Pred)	p-value
5 years	n= 122	n=125	
ALT	30 (22 - 62)	20 (15 - 29)	**<0.001**
GGT	23 (18 - 58)	15 (12 - 26)	**<0.001**
IgG	13 (11 - 16)	10 (8 - 13)	**<0.001**
Autoantibodies** pos	55/120 (46%)	22/125 (18%)	**<0.001**
10 years	n= 56	n=67	
ALT	27 (18 - 44)	20 (16 - 27)	**0.001**
GGT	24 (19 - 57)	17 (13 - 34)	**0.002**
IgG	14 (11 - 15)	11 (9 - 12)	**<0.001**
Autoantibodies** pos	37/54 (69%)	3/67 (5%)	**<0.001**

*All units in IU/l, g/l with IQR (interquartile range)

**Autoantibodies incl ANA, SMA or LKM

Haller et al IPTA 2019

Histological diagnosis



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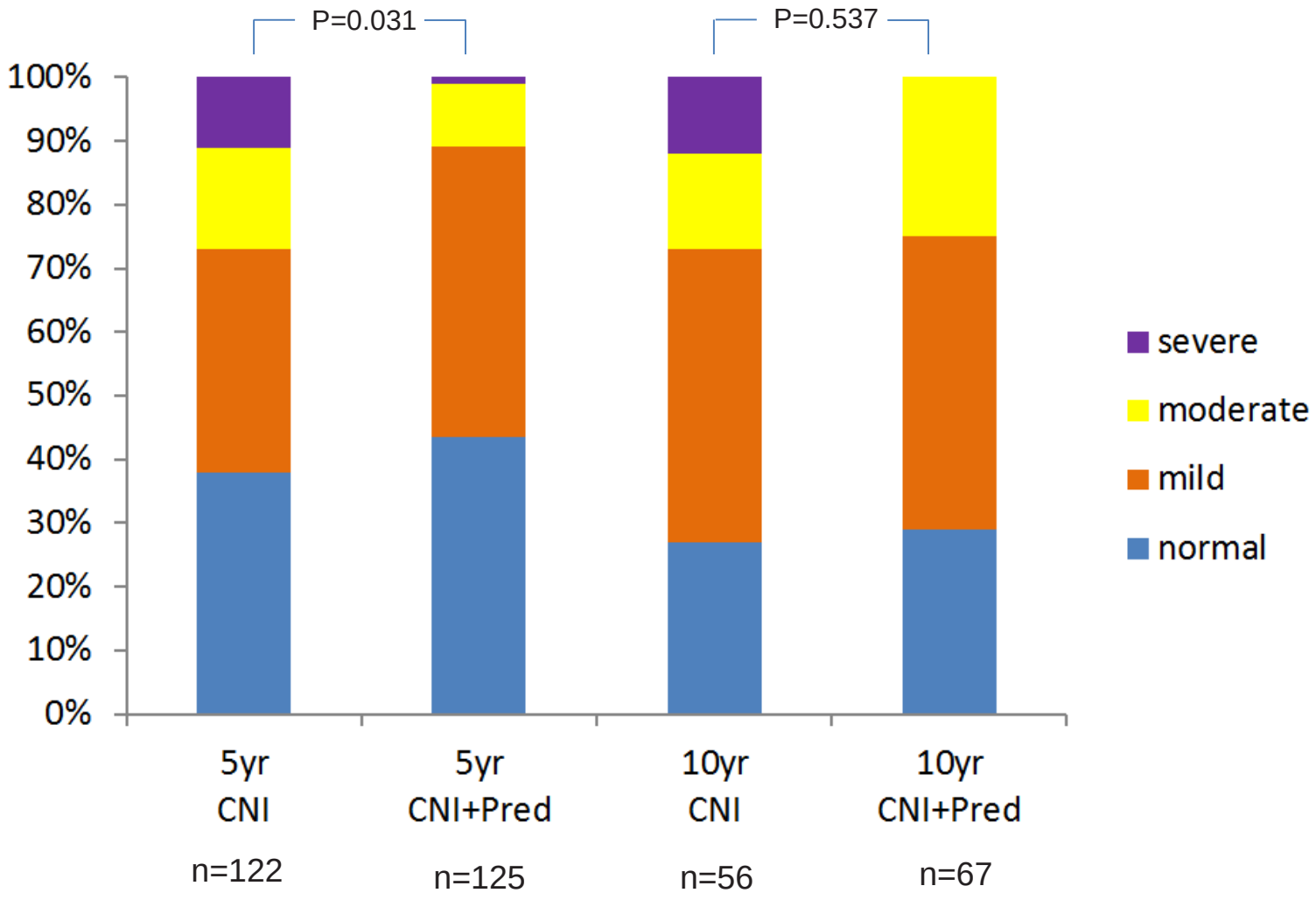
Allograft fibrosis



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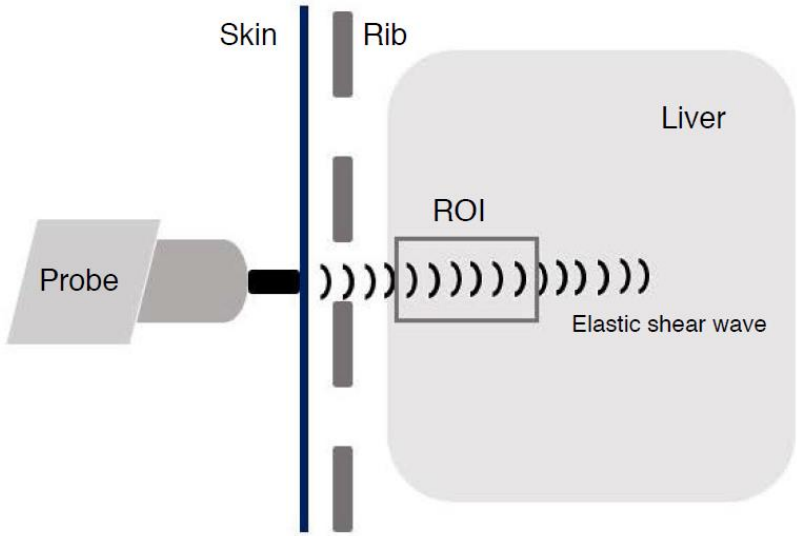
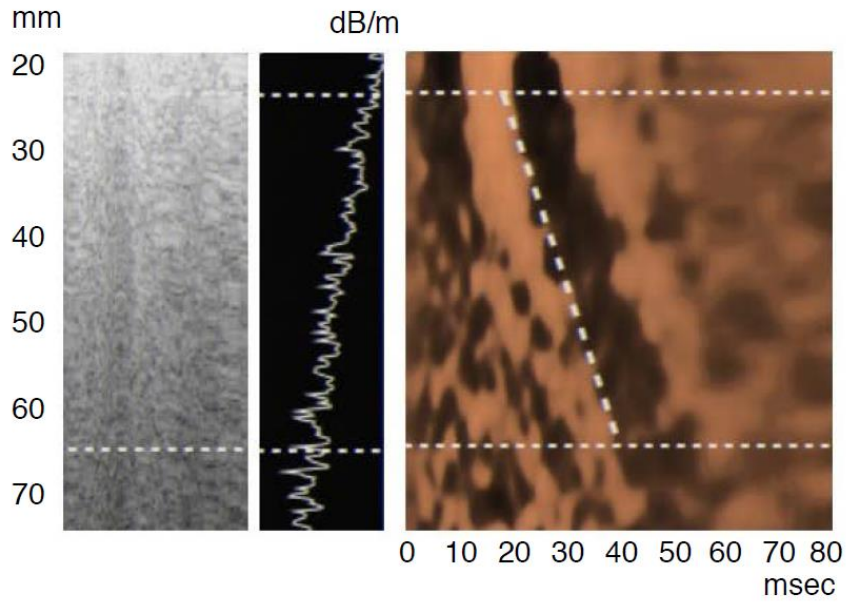




From Yu JH, Ultrasonography 2017;36:86-94

Background

Increasing use of transient elastography to assess liver stiffness

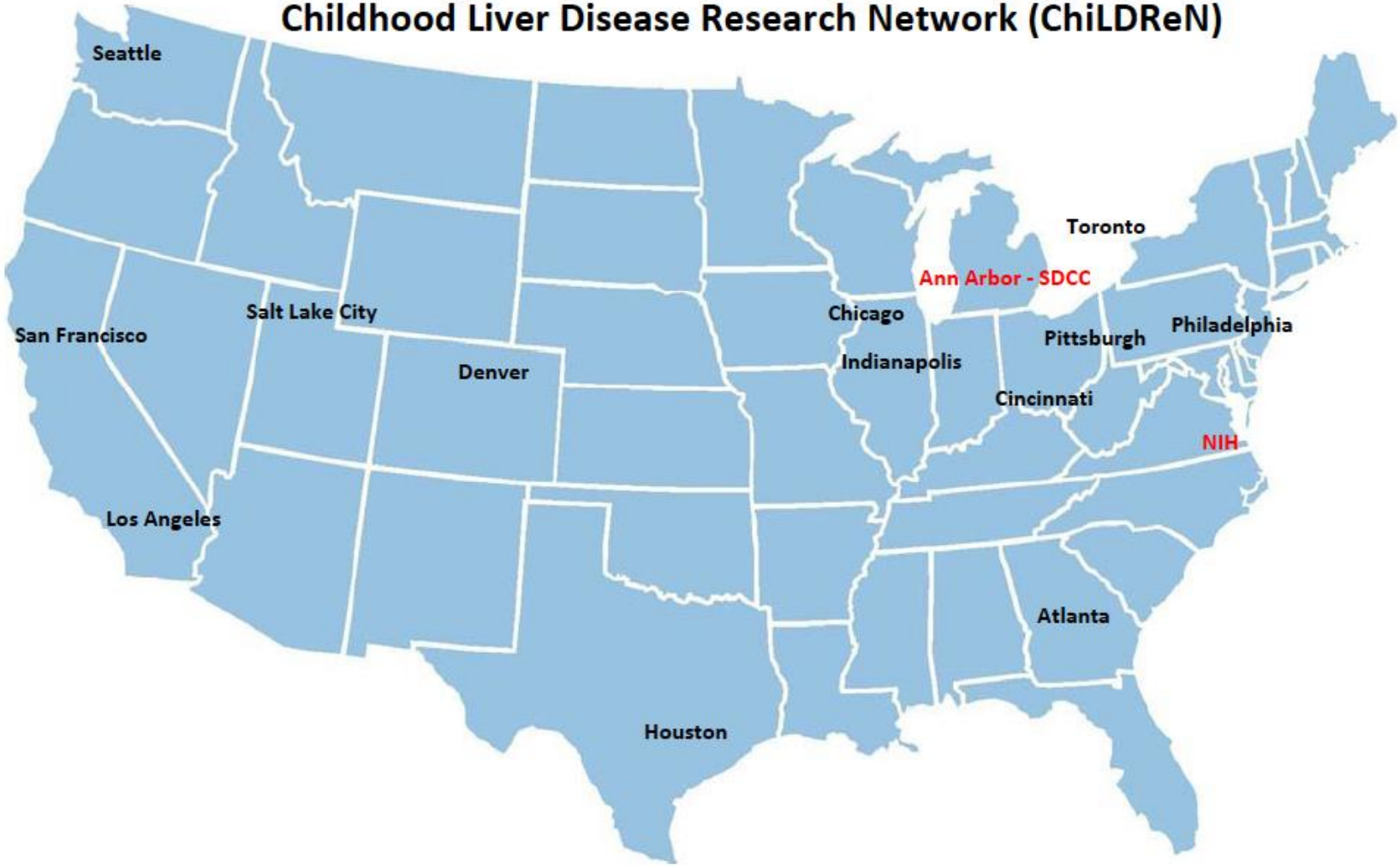
Limited but increased experience in pediatrics

Preponderance in biliary atresia and cystic fibrosis

Mostly single center experiences

FORCE Study Sites

Childhood Liver Disease Research Network (ChiLDReN)



Study Aims

- To prospectively assess whether LSM are associated with clinical and laboratory features of portal hypertension and liver disease in children with biliary atresia (BA), Alagille syndrome (ALGS) and alpha-1 antitrypsin deficiency (A1AT)
- To confirm the feasibility of obtaining LSM in children with cholestatic liver diseases

NCT02922751

Clinically Evident Portal Hypertension

- Definite CEPH
  - Spleen > 2cm BCM and Platelet < 150,000 or
  - History of clinically evident ascites or
  - Endoscopic esophageal or gastric varices
- Possible CEPH
  - Spleen > 2cm BCM **or** platelet <150,000
- Absent CEPH not definite or possible

Bass L. *J. Pediatr. Gastroenterol. Nutr.* 2019;68:763-7

Results - Enrollment

- Between Nov 2016 and August 2019

Number of participants enrolled in FORCE

BA	A1AT	ALGS	Total
301	130	119	550

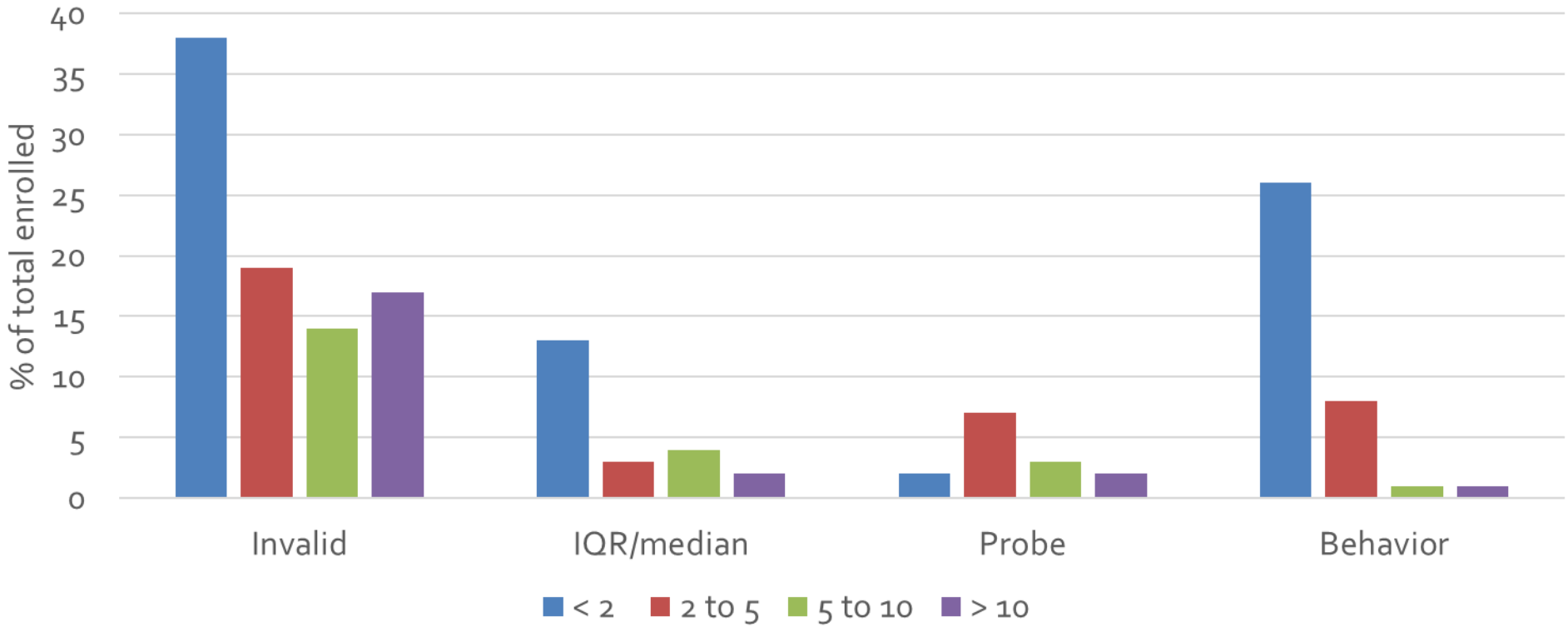
Exclusion	BA	A1AT	ALGS	Total
No valid measurements	20	21	14	55
<10 valid measurements	9	4	2	15
IQR/Median >30%	18	1	3	22
Total	47	26	19	92

Number of participants with valid baseline FibroScans

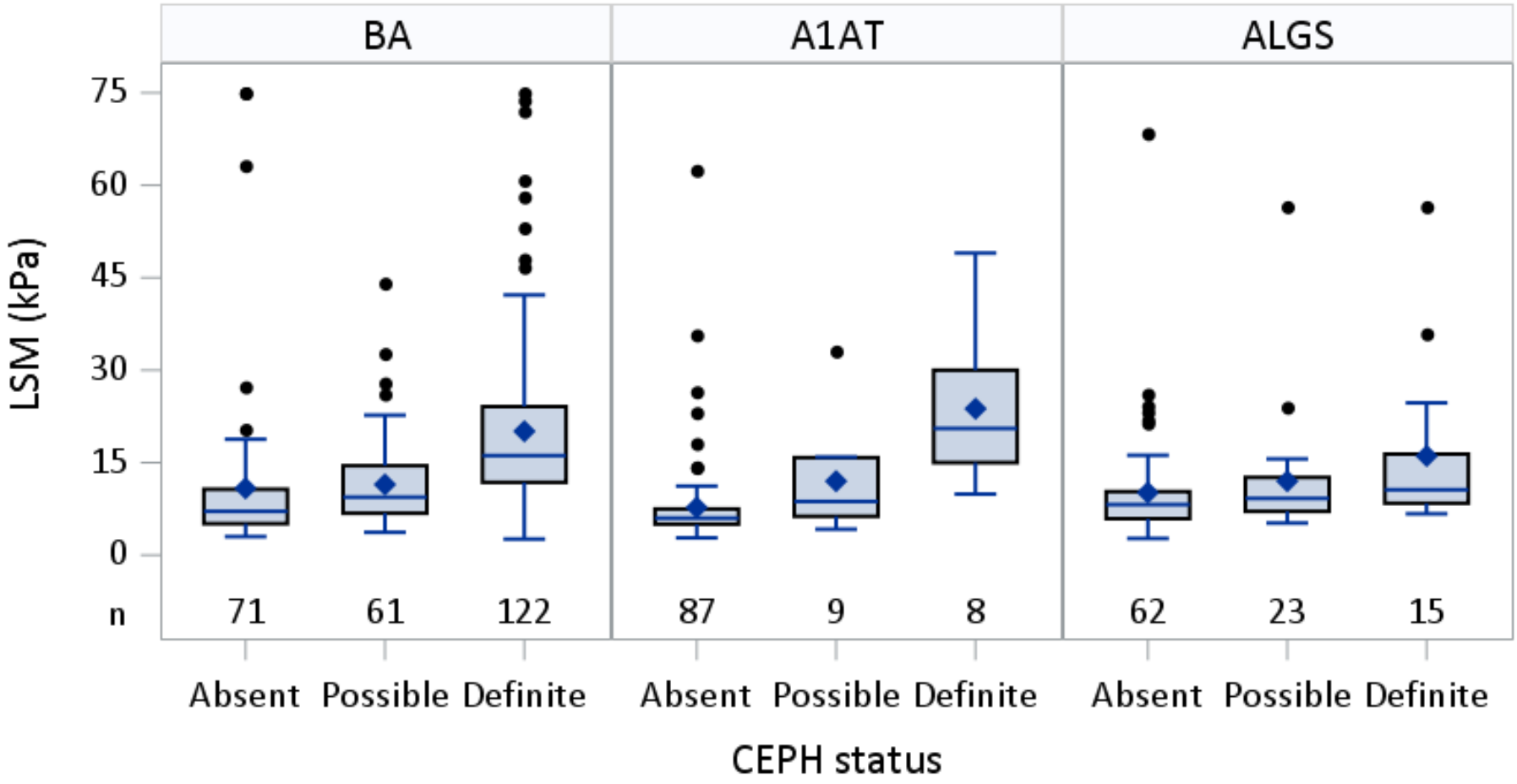
BA	A1AT	ALGS	Total
254	104	100	458

Results - Feasibility

Feasibility 82.9%
95% CI: 79.8-86.1%



Results – LSM v CEPH



Summary

- Longterm outlook post pediatric liver transplantation is excellent
- Current waiting list management does not give children sufficient priority
- The ideal very longterm immunosuppressant regimen not yet clear
- Elastography is valid in children with some modification

- Mention use of fibroscan elastography and use the shnedirer slides