
2018
NCSCG
4TH ANNUAL
POST-AASLD
SYMPOSIUM
Rehoboth McKinley Christian Health Care Services
Jointly provided by the New Mexico Medical Society (NMMS) through the joint providership of Rehoboth McKinley Christian Health Care Services (RMCHCS) and the Northern California Society for Clinical Gastroenterology
Northern California Society for Clinical Gastroenterology

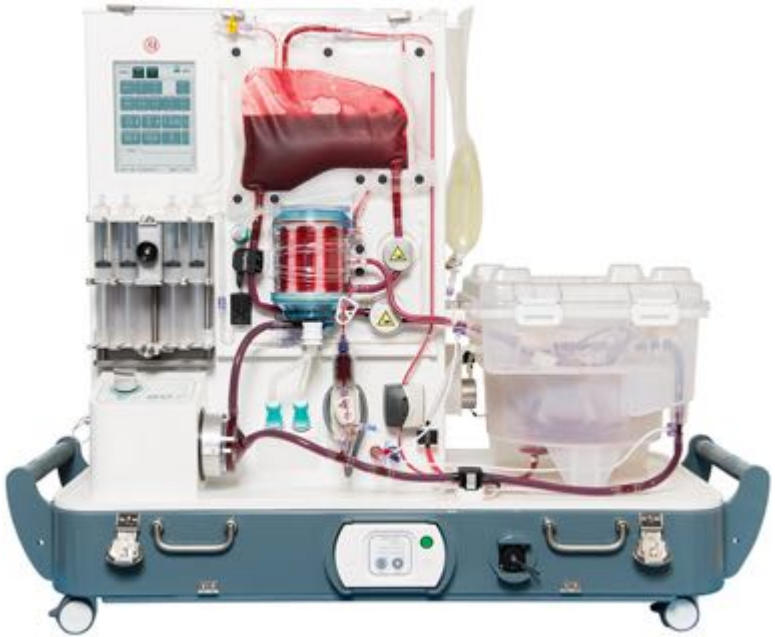
Liver Transplantation

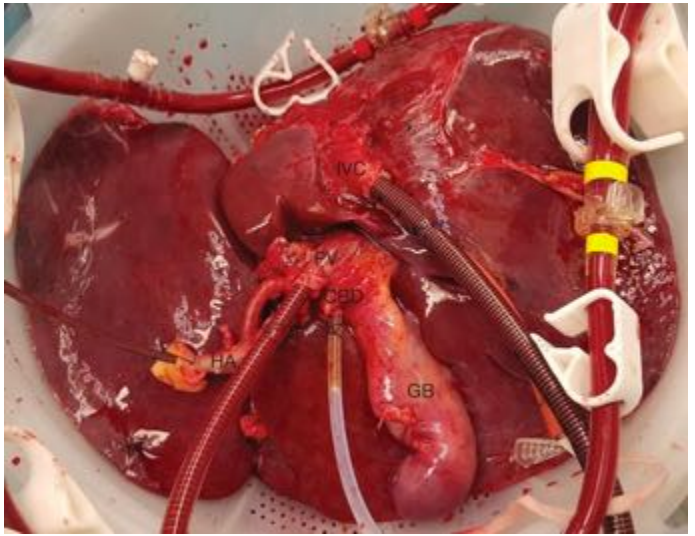
Glen Lutchman MD, MHSc.

Background

- Shortage of donor organs
- Sub-optimal livers do not tolerate conventional cold storage and there is a high discard rate
- Cooling partially slows metabolism but ROS are still generated
- Cooling prevents functional assessment
- This is an even greater problem in higher-risk donors e.g. DCD, fatty liver
- A method of keeping the donor liver in a physiologic state, avoiding cooling and which allows for recovery and functional testing is needed.

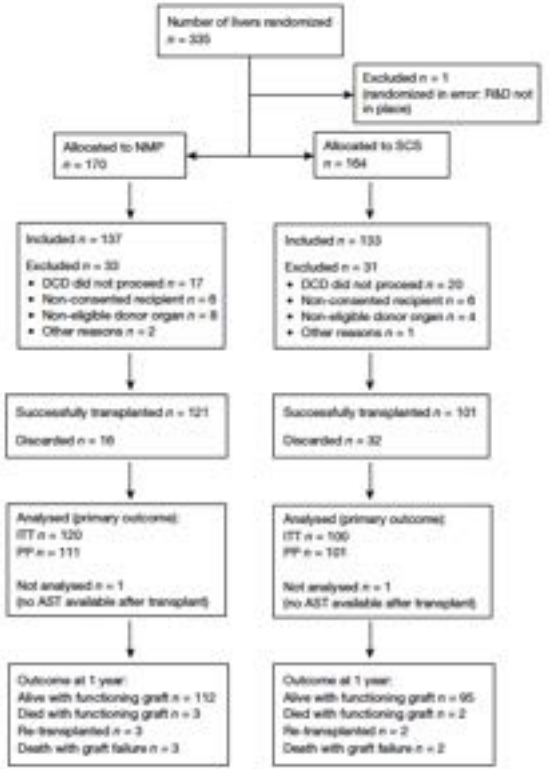
Background: Normothermic Machine Prefusion

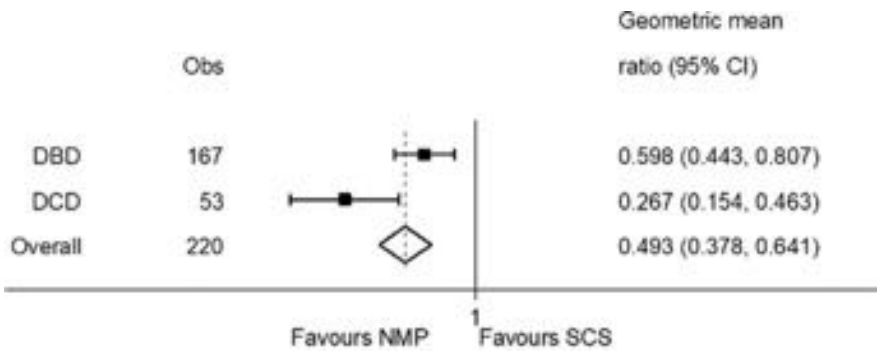




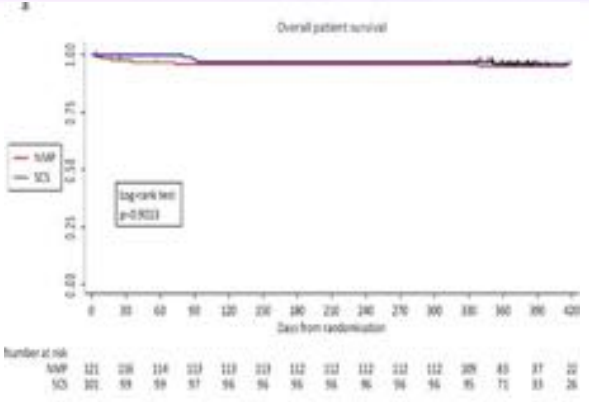
A randomized trial of normothermic preservation in liver transplantation. *Nature* volume 557, pages50–56 (2018)

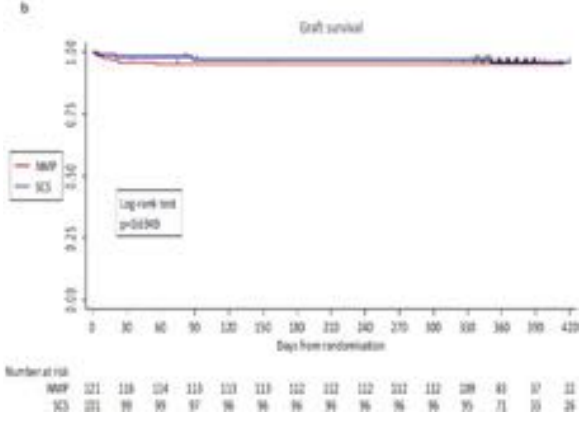
- 220 liver transplantations, compared to conventional static cold storage
- Normothermic preservation is associated with a 50% lower level of graft injury, despite a 50% lower rate of organ discard and a 54% longer mean preservation time.
- There was no significant difference in bile duct complications, graft or patient survival.





Forest plot of peak AST by donor type



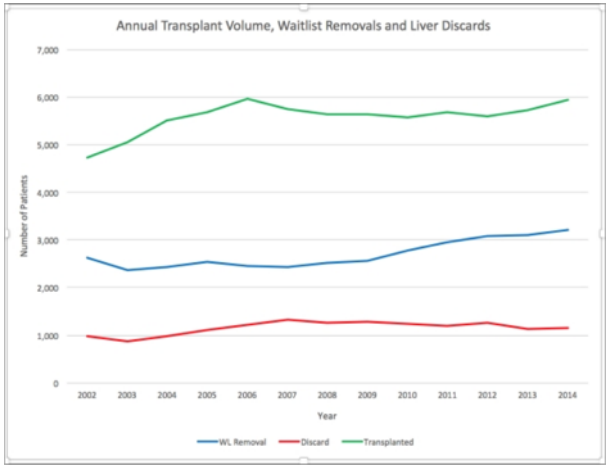


#1. Transplantation of discarded livers after viability testing with normothermic perfusion: The VITTAL trial

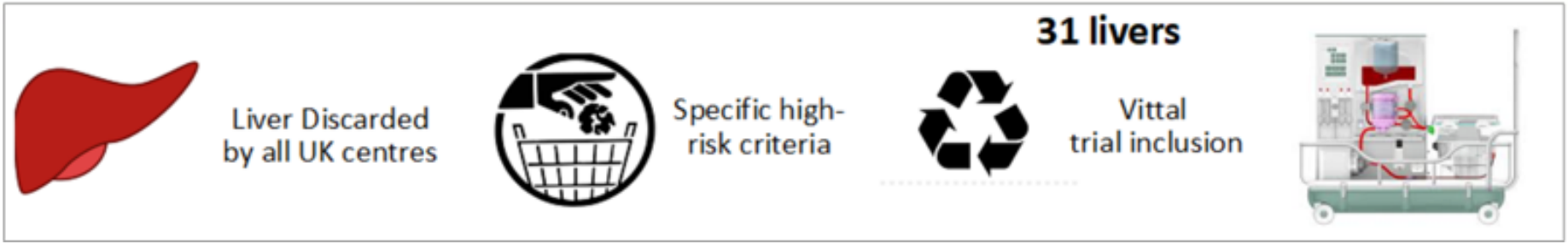
Mergental et al

- Livers from high-risk donors are frequently rejected
- This compromises the only increasing and underutilized donor resource

Aim: Determine whether NMP can A) provide an objective assessment of discarded marginal livers to achieve successful transplantation and B) enable the salvage of >50% of the livers tested.

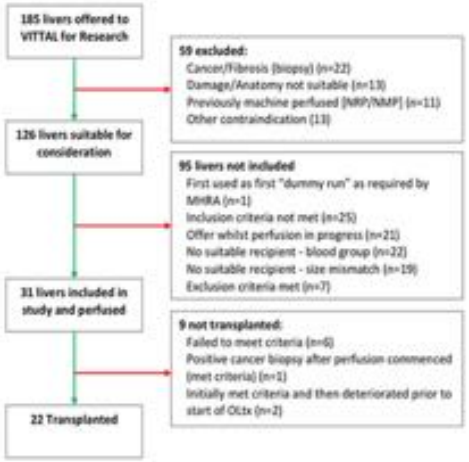


Methods

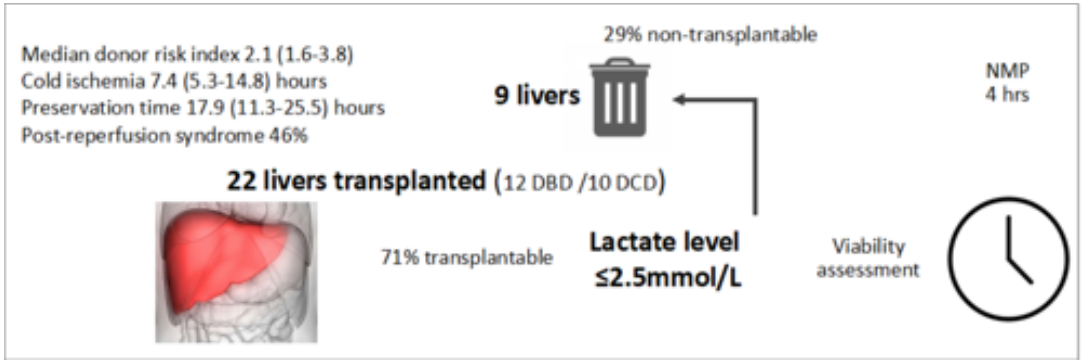


Methods: Prospective, single-arm adaptive phase II trial on donor livers discarded by all U.K. transplant centres that met specific high-risk criteria, consisting of any of the following parameters: donor risk index >2.0, biopsy proven macrosteatosis >30%, transaminases >1000 IU/mL, warm ischaemic time >30 mins in DCD livers or extensive cold ischaemia (>12 hrs DBD or >8hrs DCD). Livers meeting the viability criteria were transplanted into patients without portal vein thrombosis or significant cardiovascular comorbidities receiving their first liver.

Results



Inclusion criteria	Transplanted livers (n=22)	%	Non-transplanted livers (n=9)	%
DRI	16	73%	7	78%
BAR score	2	9%	-	-
Steatosis ≥30%	2	9%	1	11%
Extensive CIT	6	27%	4	44%
dWIT ≥30mins	3	14%	-	-
Poor flush	4	18%	2	22%
AST/ALT ≥1000 IU/L	2	9%	3	33%



Results

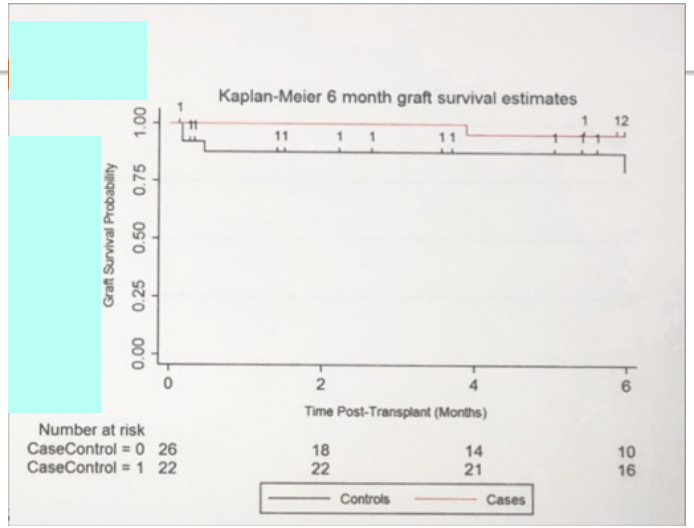
100% 90-day patient survival, 71% resuscitation success rate (co-primary endpoints)

90-day outcomes

100% graft survival
32% early allograft dysfunction
27% Clavien-Dindo complication ≥3
18% need for RRT
Median intensive care unit stay 3.5 (2-38) days
Median in hospital stay 10 (6-46) days

180-day outcomes

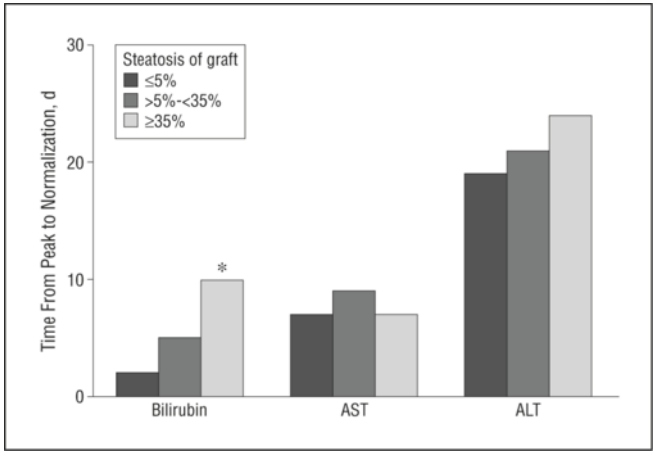
100% patients survival
90% graft survival
Graft-loss for non-anastomotic biliary strictures in DCDs
Results similar to matched controls



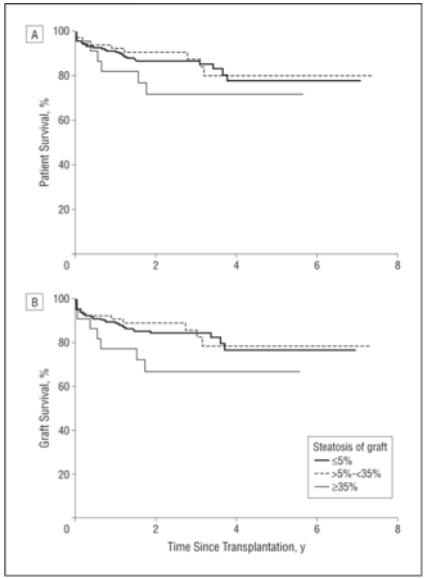
Conclusions

Conclusions: NMP provides objective assessment of high-risk organs and enabled 71% of tested, currently unutilised livers, to be transplanted without compromising recipient safety.

Hepatic Steatosis in the Donor Liver



Time to recovery of bilirubin and transaminases



Kaplan-Meier curves of patient (A) and graft (B) survival.
There was no difference in patient or graph survival among the groups, suggesting no adverse long-term effects of using steatotic grafts, even grafts with 35% or more steatosis.

Table 5. Multivariate Analysis Performed on All Factors That Demonstrated Significance on Univariate Analysis

Output Variable Tested	*P* Value
Intensive care unit stay	.01
Hospital stay	.002
Packed red blood cell transfusion	<.001
Fresh frozen plasma transfusion	.01
Aspartate aminotransferase peak	<.001
Alanine aminotransferase peak	<.001
Time for bilirubin to return to normal	<.001

Short- and Long-term Outcomes After Steatotic Liver Transplantation. Arch Surg. 2010;145(7):653-660.

#2

Pharmacological defatting of steatotic human donor livers during *ex situ* normothermic machine perfusion

Boteon,Y et al

Aim: Assess the feasibility of defatting of human donor livers during *ex situ* normothermic machine perfusion and its effects on the metabolic functional recovery of the organs.

Methods: Delivery of a combination of defatting drugs to discarded human donor livers during normothermic machine perfusion

Methods

- 10 human donor livers discarded for transplantation due to visual assessment of steatosis by the retrieval/transplant surgeon
- Randomly allocated to the experimental groups using covariate adaptive randomization method that accounted for donor time and cold ischaemia time

Defatting cocktail of drugs
(GW7647, GW501516, Hypericin, Scorparone, Forskolin, and visfatin)
Negretti O, et al. Metabolic Engineering 2009

Defatting group

<0.1% DMSO

Control group

12 hours

- Perfusion parameters analysed (Vascular flow and resistance)
- Functional parameters (lactate clearance, bile production, bile pH, glucose metabolism, perfusate pH)
- Macrovesicular steatosis assessment, H&E, paraffin sections
- Tissue triglyceride (ICT) (ab65336)
- Ketone bodies (MAK134 Sigma) -3-hydroxybutyric acid and acetoacetic acid

Standard organ procurement and static cold storage (UW)

0

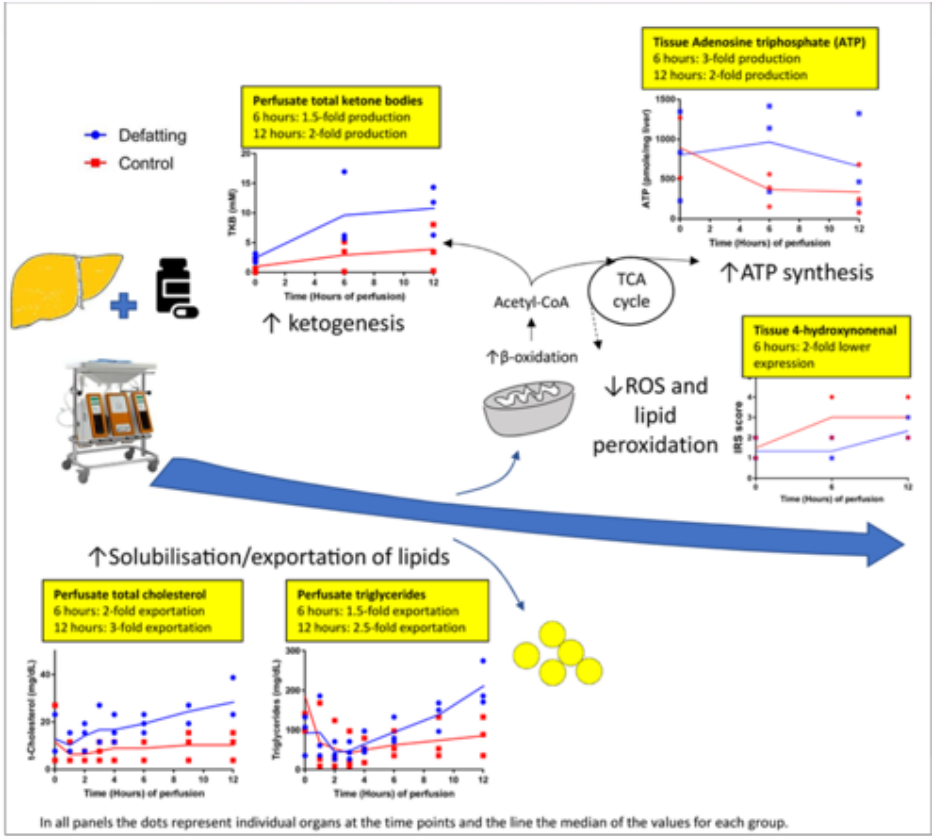
Rewarming period

0.5

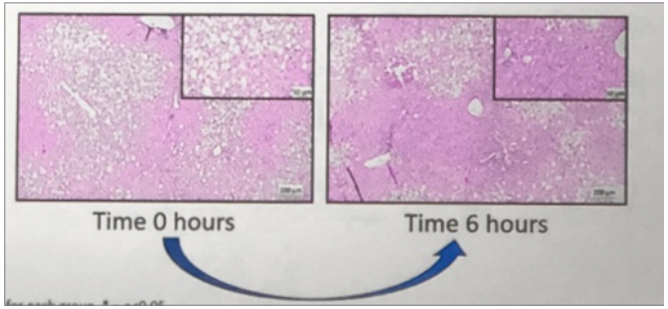
Ex situ Normothermic Machine Perfusion

hours

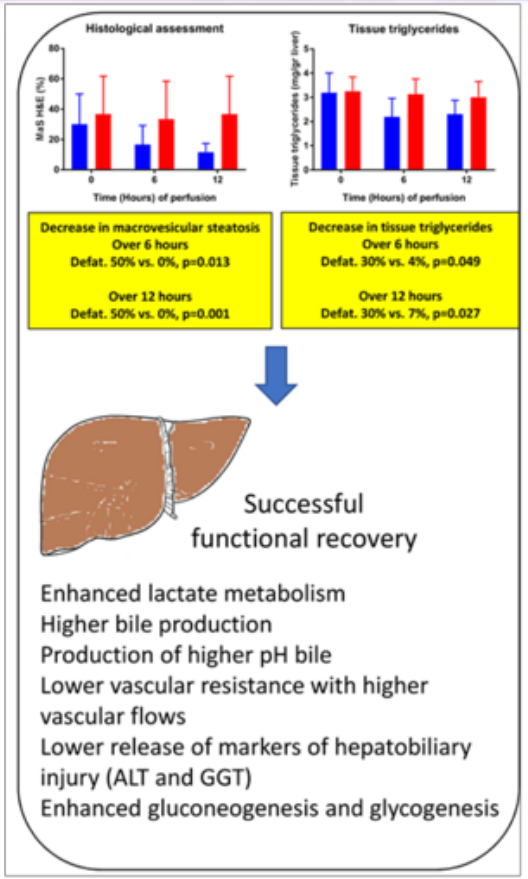
Methods


Defatting
Control
Perfusate total ketone bodies
6 hours: 1.5-fold production
12 hours: 2-fold production
TKB (mM)
Time (Hours of perfusion)
↑ ketogenesis
Tissue Adenosine triphosphate (ATP)
6 hours: 3-fold production
12 hours: 2-fold production
ATP (pmole/mg liver)
Time (Hours) of perfusion
↑ATP synthesis
Acetyl-CoA
TCA cycle
↑β-oxidation
↓ROS and lipid peroxidation
Tissue 4-hydroxynonenal
6 hours: 2-fold lower expression
IRS score
Time (Hours) of perfusion
↑Solubilisation/exportation of lipids
Perfusate total cholesterol
6 hours: 2-fold exportation
12 hours: 3-fold exportation
t-Cholesterol (mg/dL)
Time (Hours) of perfusion
Perfusate triglycerides
6 hours: 1.5-fold exportation
12 hours: 2.5-fold exportation
Triglycerides (mg/dL)
Time (Hours) of perfusion
In all panels the dots represent individual organs at the time points and the line the median of the values for each group.

Results



Conclusions: Pharmacological defatting of human donor livers is achievable within 6 hours and it was associated with an enhanced mitochondrial oxidative function, attenuated reperfusion injury, and successful recovery of metabolic functions of the organs.



#3 Normothermic machine perfusion and defatting adjuncts can reduce liver fat and enhance function

Aims:
To explore the effects of defatting interventions on liver fat content.

Methods:
- Livers perfused for 48 h in 3 treatment groups:
  - NMP alone (group 1)
  - NMP + lipoprotein apheresis filtration (LAF) (group 2)
  - NMP + LAF + forskolin, l-carnitine, ↓ insulin, ↓ glucose (group 3)
- Regular perfusate and biopsy samples obtained to explore effects of interventions.

Conclusions:
Liver fat content can be significantly reduced by *ex situ* interventions during NMP

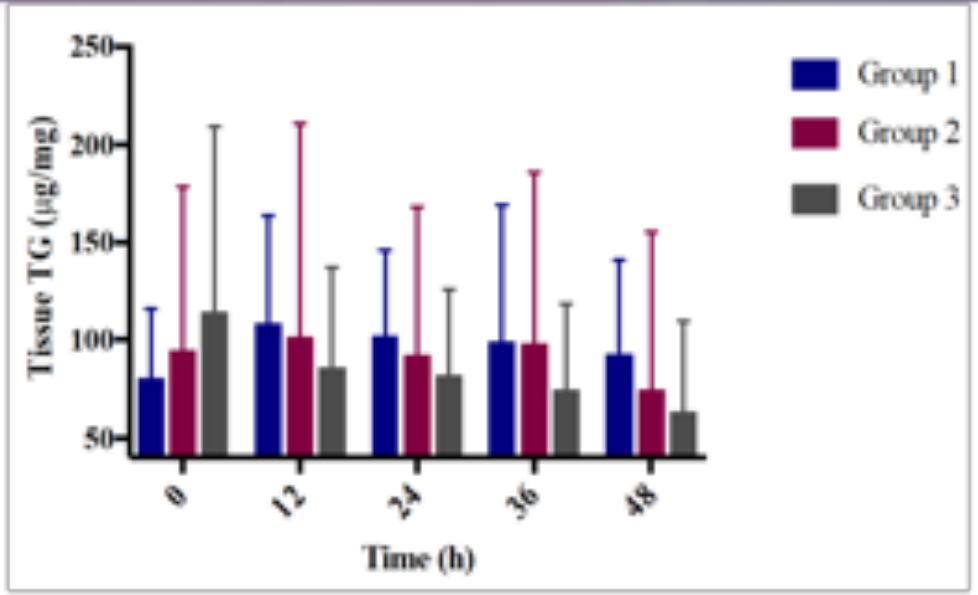
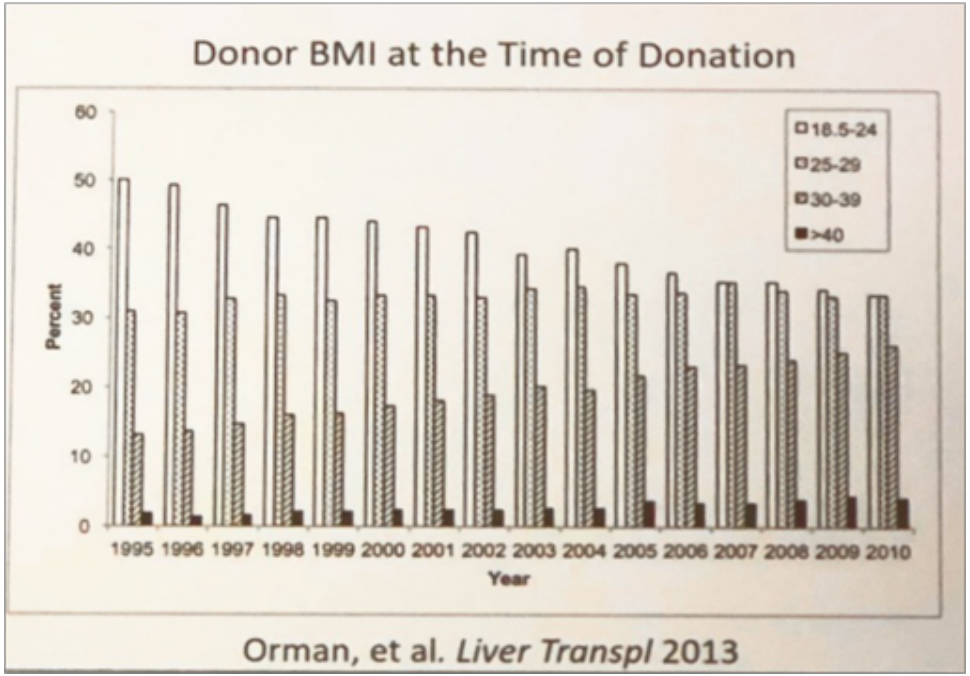


Figure 1. Change in tissue TG (µg TG/mg tissue) over time for each group. Data presented as mean ± SD.

Ceresa C, et al., Abstract 3

#4. Widespread obesity and the future of liver transplantation: Macrosteatotic liver allografts leads to significantly worse outcomes in obese recipients. Northup P, et al

- The obesity epidemic has changed both liver and donor recipient characteristics
- Established data on the safety of high macro steatosis grafts (HSGs) are based on historical data when HCV was the predominant liver disease and obesity was less prevalent

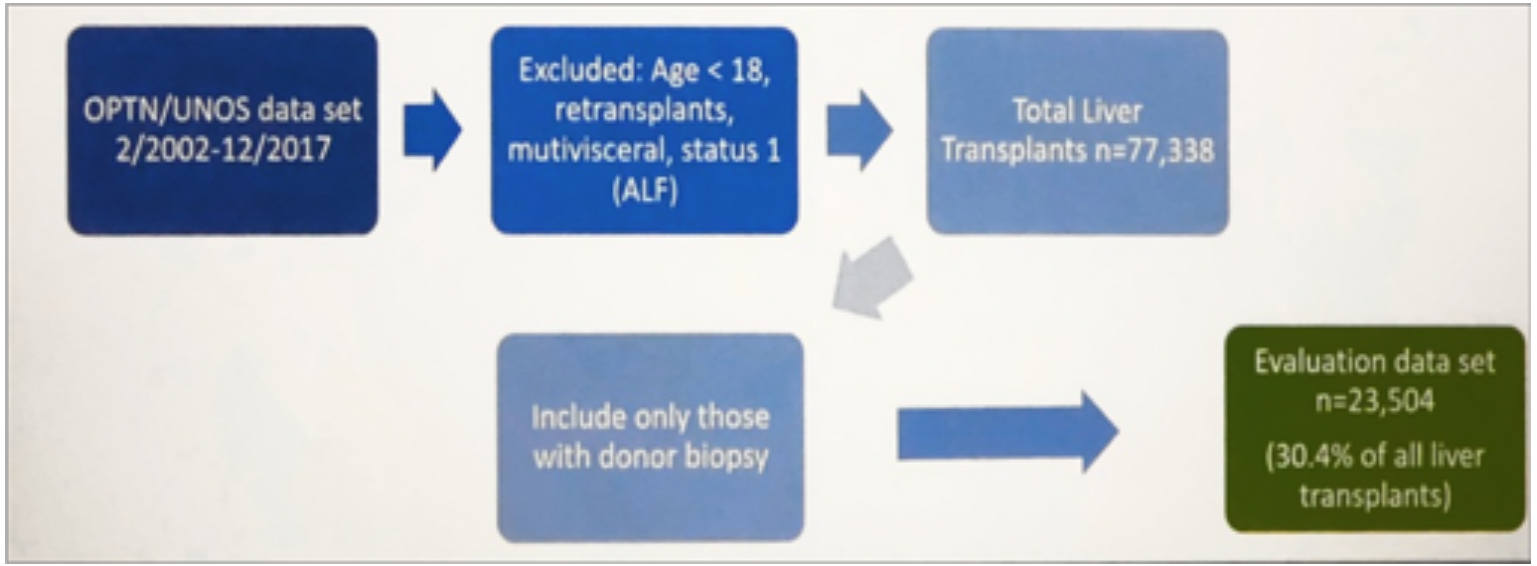


Definitions

- Donor graft macro steatosis: Greater than or equal to 30% macro steatosis (HSG)

- Recipient Obesity: High BMI (HBMI) defined as BMI greater than 35 kg/m2 after adjustment for ascites at transplant

Methods: Study Population



Methods: Analysis Populations

	High Steatosis Graft (HSG)	Non-High Steatosis Graft (NHSG)
Recipient High BMI (HBMI)	HSG/HBMI	NHSG/HBMI
Recipient Non-High BMI (NHBMI)	HSG/NHBMI	NHSG/NHBMI

Results: Demographics

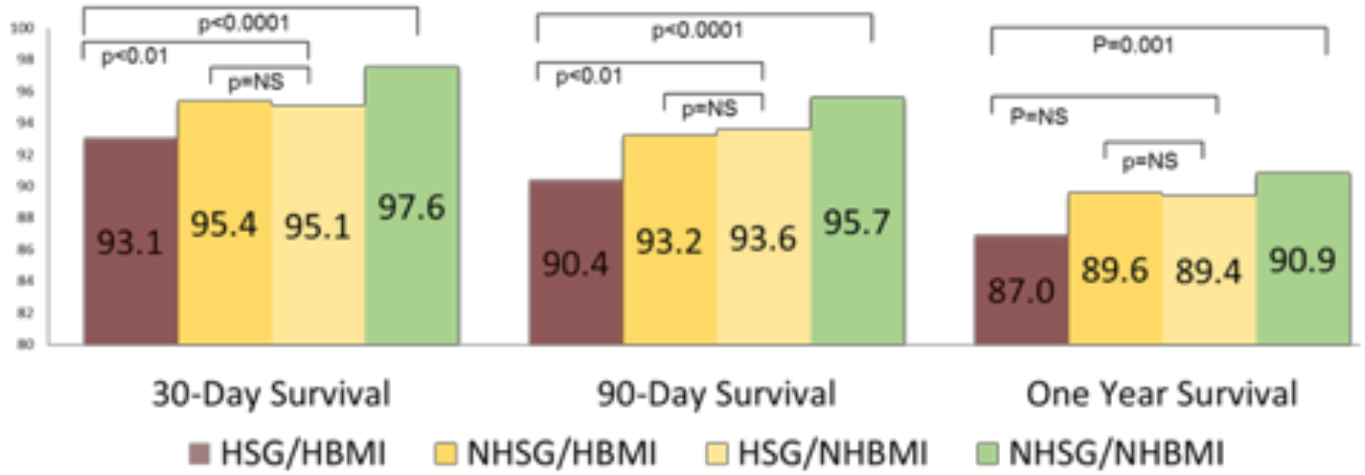
	HSG and HBMI (n=261)	NHSG but HBMI (n= 2,414)	HSG but NHBMI (n=1,741)	NHSG and NHBM (n=19,088)
Age at transplant, years	55.0	54.9	55.7	55.7
Recipient gender male	71.26%	64.13%	74.84%	70.68%
NASH/Cryptogenic	25.29%	24.52%	12.58%	11.74%
MELD at transplant	21.10	21.76	19.60	20.51
Donor risk index, mean*	1.827	1.897	1.881	1.913
Recipient BMI, kg/m^2	38.33	38.49	26.37	26.43
Graft macrosteatosis, mean	39.3	5.83	39.9	5.74

Results

	30 - Days* Hazard Ratio	30 - Days 95% CI	One Year* Hazard Ratio	One Year 95% CI
Age	1.02	1.01-1.03	1.02	1.02-1.03
Recipient BMI > 35	1.78	1.47-2.16	1.18 ¶	1.04-1.34
Graft macrosteatosis >= 30%	2.05	1.66-2.53	1.27 ¶	1.10-1.46
Donor risk index	1.44	1.17-1.71	1.50	1.37-1.65
MELD at transplant	1.03	1.03-1.04	1.03	1.02-1.03

*p<0.0001 except as shown. ¶ p<0.01

Results

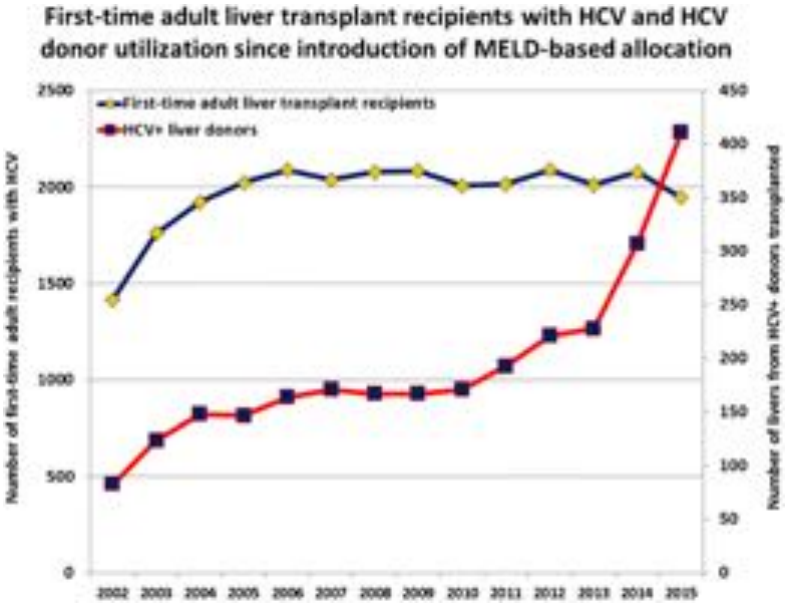

p<0.0001
p<0.01
p=NS
93.1
95.4
95.1
97.6
p<0.0001
p<0.01
p=NS
90.4
93.2
93.6
95.7
P=0.001
P=NS
p=NS
87.0
89.6
89.4
90.9
30-Day Survival
90-Day Survival
One Year Survival
HSG/HBMI
NHSG/HBMI
HSG/NHBMI
NHSG/NHBMI

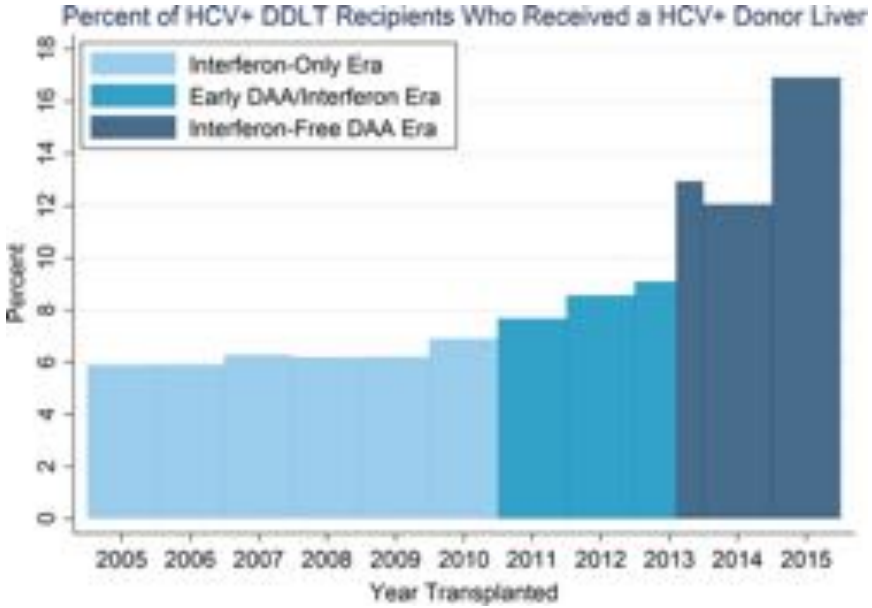
Conclusions

Conclusions: In the modern era of epidemic obesity and MELD allocation:

- Graft steatosis greater than or equal to 30% and recipient BMI greater than 35 are both independent predictors of increased mortality after liver transplant.
- HSGs transplanted into obese recipients have the highest relative mortality.
- The increase in mortality associated with an HSG into a non-obese recipient is similar in magnitude to a graft with lower macrosteatosis placed into an obese recipient.

Background:
Use of HCV positive livers in solid organ transplants





#5 # Preemptive pan-genotypic direct-acting antiviral therapy in HCV D+R- cardiac transplantation

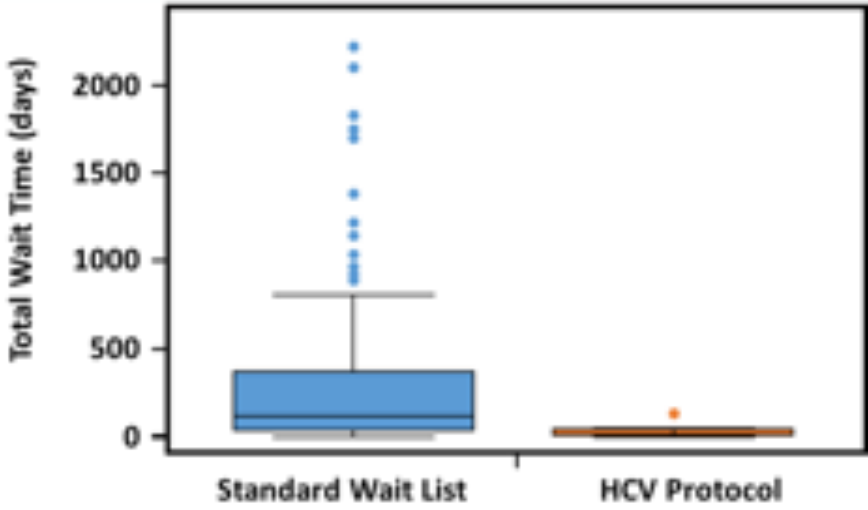
Background: With the rising number of HCV-positive donors, there is a time-sensitive and critical need to document both efficacy and detailed implementation strategies surrounding successful use of HCV-positive organs.

Aim: Determine if preemptive administration of pan-genotypic direct-acting antiviral (DAA) therapy prevents the development of chronic HCV infection in HCV donor-positive to recipient-negative cardiac transplantation

Methods:

- Open-label, single-center, single-arm, proof-of-concept trial
- Population: HCV-negative patients awaiting liver transplant

Main findings:
This novel strategy has the potential to increase the static donor pool, decrease heart transplant wait times, and improve health outcomes.



Conclusions:
Preemptive DAA therapy can prevent the development of chronic HCV infection in HCV D+R- cardiac transplant.

Bethea ED, et al., Abstract 7

#7. Multi-Center Study of Age, Frailty, and Waitlist Mortality in Liver Transplant Candidates

- Frailty, a construct developed in geriatrics, is a state of decreased physiologic reserve.
- Frailty has been shown to be prevalent and predictive of waitlist mortality in adults with cirrhosis of all ages awaiting liver transplantation (LT).
- The relationship between frailty, age, and waitlist mortality has not been explored.

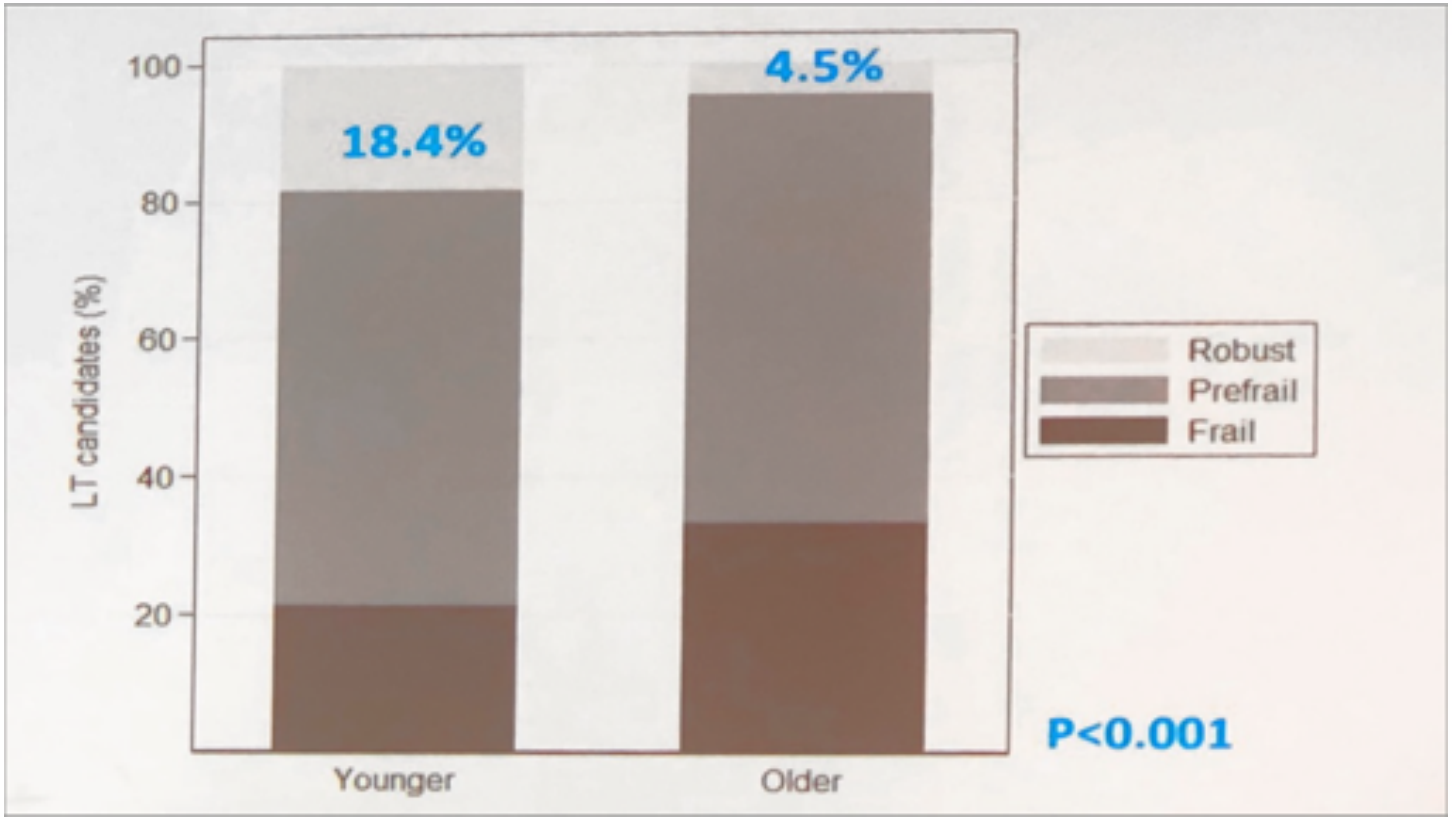
Methods

- 886 adult LT candidates without HCC at JHH and UCSF from 2012-2018
- Liver Frailty Index (LFI) collected at outpatient evaluation clinic
  - Frail = LFI ≥ 4.5
  - Prefrail= LFI 3.2 to < 4.5
  - Robust= LFI < 3.2

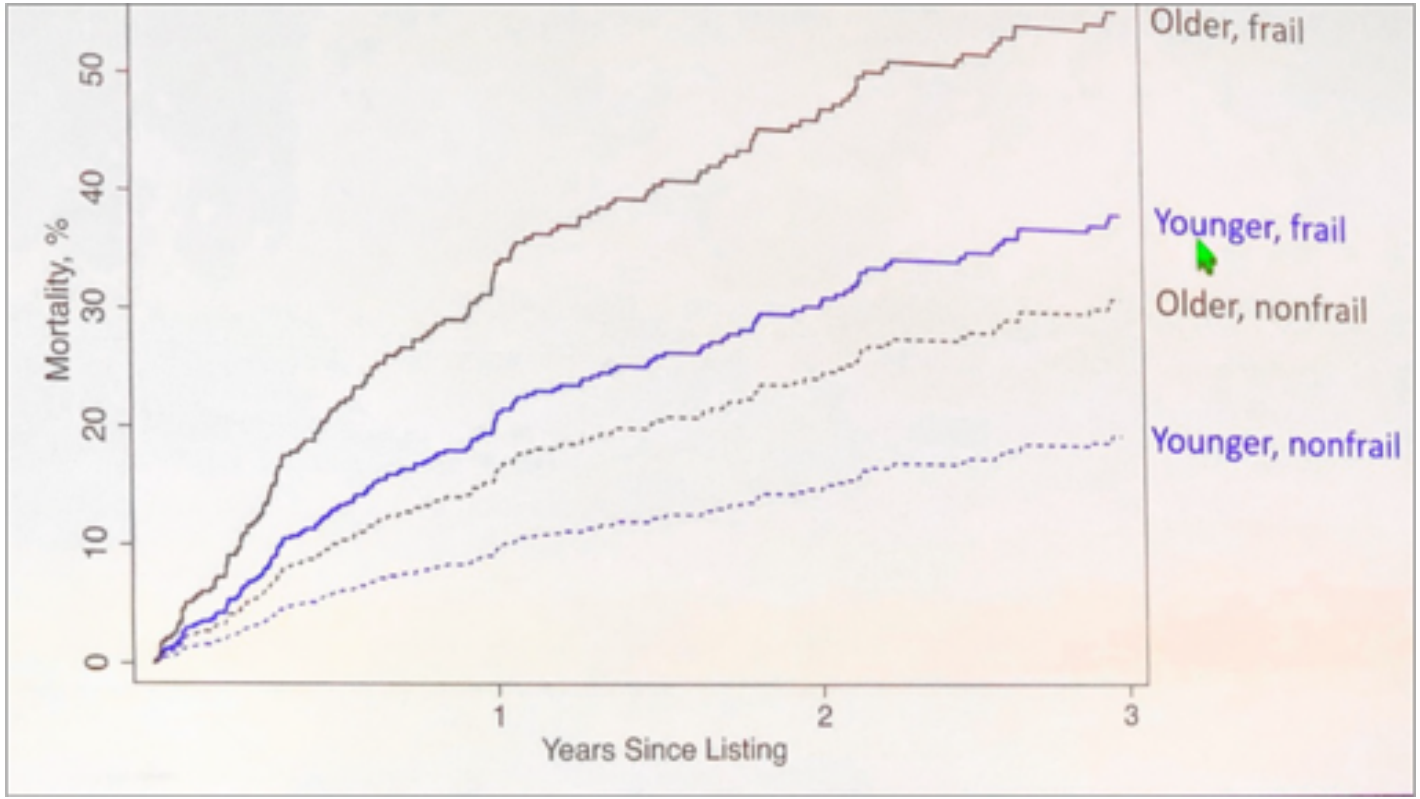
Methods

- Older candidates : age ≥ 65
- Outcomes:
  - Components of LFI score by candidate age (older vs. younger with Wilcoxon rank sum test
  - Waitlist mortality, frailty and candidate age association with competing risks regression and interaction term

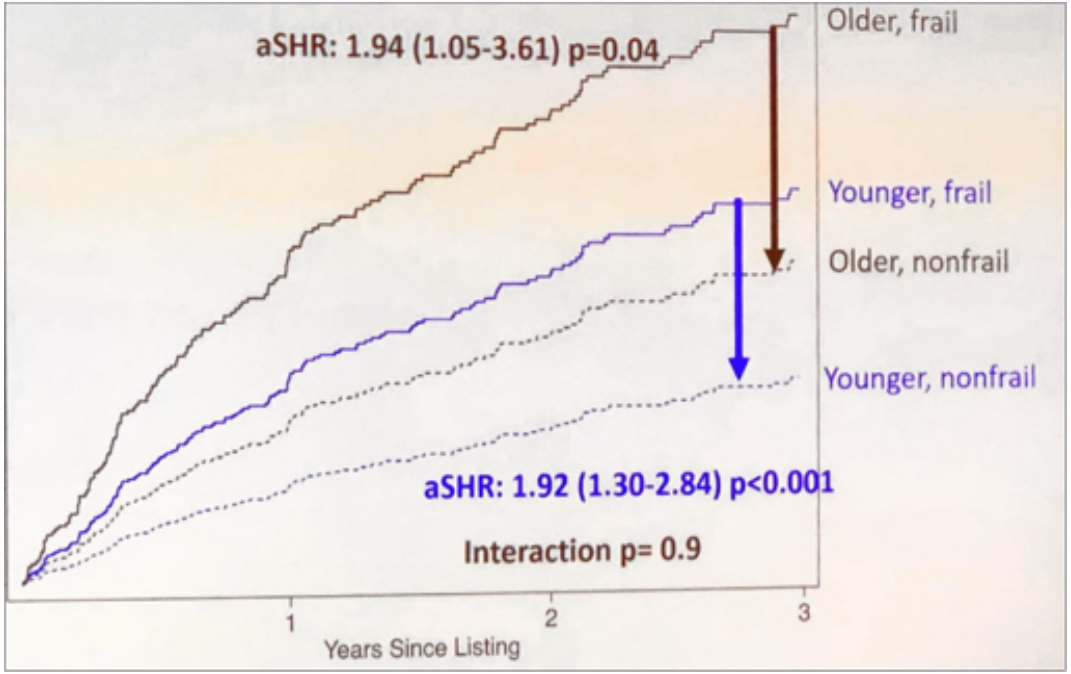
Results


100
80
60
40
20
LT candidates (%)
18.4%
4.5%
Robust
Prefrail
Frail
P<0.001
Younger
Older

Results


Mortality, %
0
10
20
30
40
50
1
2
3
Years Since Listing
Older, frail
Younger, frail
Older, nonfrail
Younger, nonfrail

Results



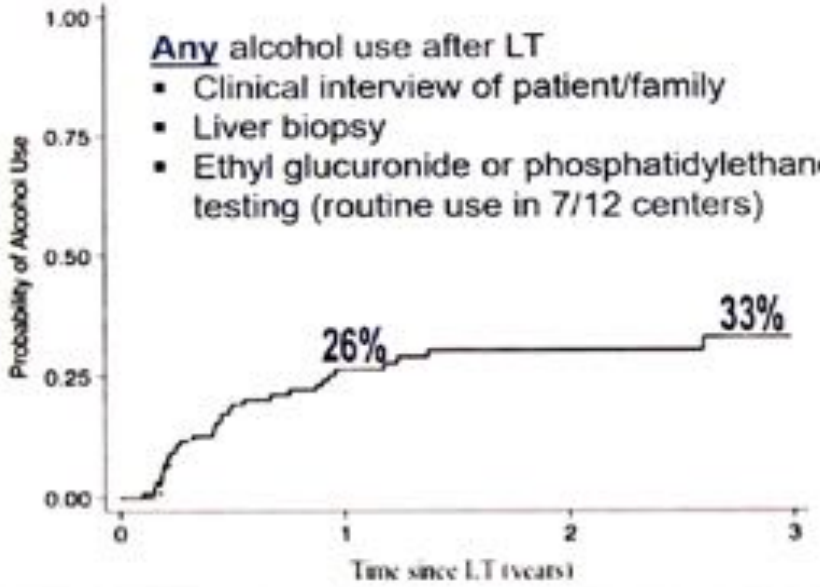
- **In adjusted analysis, both older age and frailty were associated with significantly higher risk of waitlist mortality.**
- **However, the association between waitlist mortality and frailty did not vary by candidate age**
- **Frail older candidates had a higher risk waitlist mortality compared to non-frail older candidates as well as frail younger candidates compared to non-frail younger candidates**

Conclusions

- Older LT candidates experienced higher rates of frailty than younger candidates and worse scores in each component of the LFI.
- However, regardless of age frailty is associated with nearly 2-fold increased risk of waitlist mortality.
- Our data support the applicability of the frailty concept to the whole LT population and can guide the development of prehabilitation programs targeting frailty in LT patients, regardless of age.

Background

Alcohol Use after Liver Transplant



- **Non-Sustained** = alcohol use, but stopped drinking at last follow-up
  - Not associated with significantly higher risk of death (HR=1.61, p=0.32)
- **Sustained** alcohol use = still drinking at last follow-up + duration of alcohol >100 days
  - 4.6-fold higher risk of death (p=0.01)

Lee BP *et al*, Gastroenterology

Early Liver Transplantation for Severe Alcoholic Hepatitis
Mathurin et al. N Engl J Med 2011; 365:1790-1800

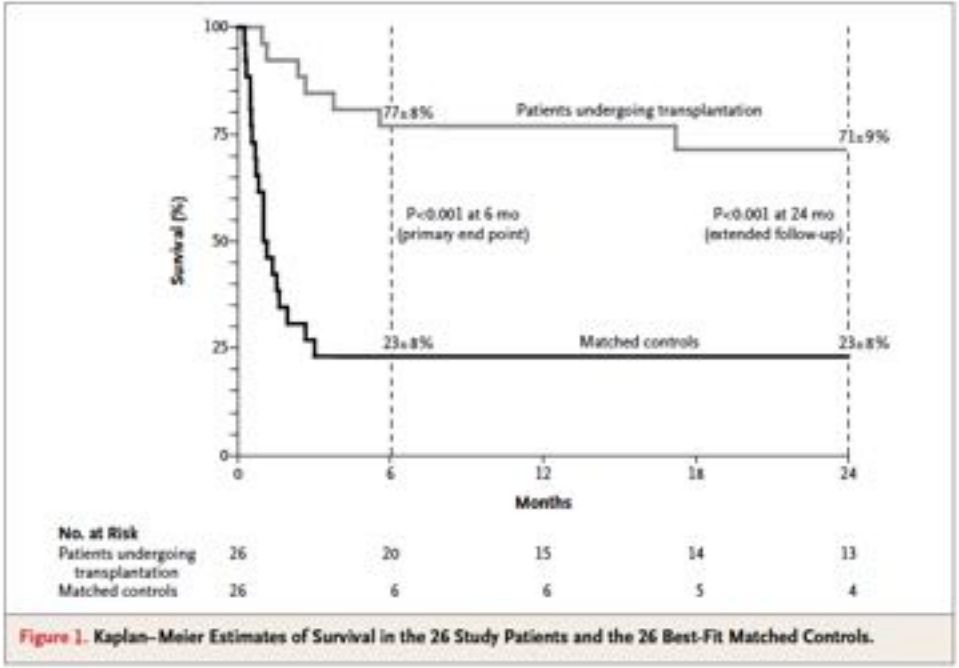


Figure 1. Kaplan–Meier Estimates of Survival in the 26 Study Patients and the 26 Best-Fit Matched Controls.

#9. Predicting Low-Risk for Sustained Alcohol Use after Early Liver Transplant for Severe Alcoholic Hepatitis: The Salt Score

- Given the impact to long-term outcomes, there is need for objective tools to guide patient selection, with the goal to minimize the risk of sustained alcohol use after transplant.

- To leverage our large, multi-center cohort to develop a prognostic score from pre-transplant variables to predict low-risk for sustained alcohol use post-transplant

Study population: ACCELERATE- AH

- Inclusion criteria
  - LT recipients with clinician-diagnosed AH
  - Maddrey's Score ≥ 32
  - Liver Bx not required
  - NO prior AH episodes
  - No prior Dx of chronic liver disease
- LT without minimum period of abstinence

Statistical Analysis

- Unadjusted logistic models
- LASSO (Least Absolute Shrinkage and Selection Operator) to produce a point score to predict sustained alcohol use after transplant
- Internal cross-validation of overall LASSO model

Results

- 12 centers
- N=129
- Median post-LT follow up=1.6 years (IQR 0.7-2.8)
- Complete records of per LT assessment of alcohol use disorder by an addiction specialist or medical social worker were available in all patients

Baseline and Clinical Characteristics

Age , yrs. (median)	**42 (34-51)**
Male	72%
Caucasian	82%
Employed	65%
Private Medical Insurance	66%
Married/Stable Companion	58%
Co-morbid psychiatric disease	31%

Maddrey's Score	**78(58-102)**
Na-MELD	34(29-39)
Days Listed before LT	6(3-11)
Days from last drink to LT	54(36-88)

Alcohol Related Characteristics

History of Failed Rehab Attempt **1 prior attempt** **≥ 2 prior attempts**	 **22%** **18%**
History of non-THC related Illicit drug use	12%
History of alcohol related legal issues	30%
Family history of alcohol use disorder	37%
Pre-abstinence alcohol consumption-units/day	9(6-15)
Years of heavy drinking	15(9-25)
High-Risk alcohol relapse (HRAR) score ≥ 4	14%

Predictors of Sustained Alcohol use Post-LT (univariate)

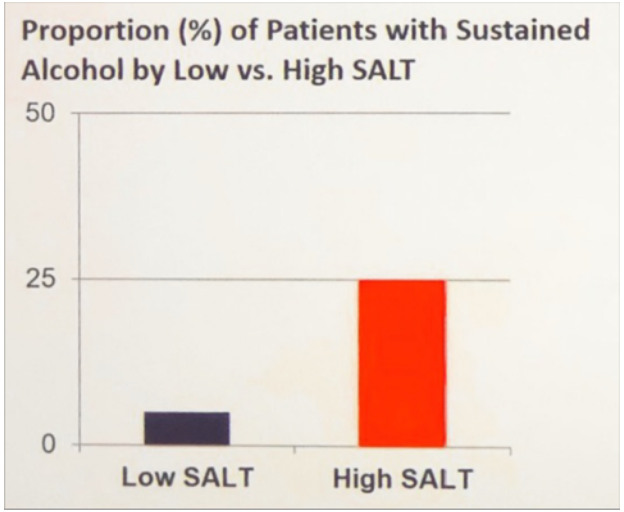
	OR (95% CI)	p
Hx of multiple ≥2 failed Rehab attempts	6.9(1.7-28.2)	0.007
> 10 drinks/day at presentation	5.4(1.1-25.9)	0.04
Any history of alcohol related legal issues	3.2(1.0-10.2)	0.05
History of non-THC illicit substance use	3.8(1.0-14.4)	004

- NOT associated
- Length of pre-LT abstinence
- Age, Race, medical insurance, psychiatric disease, employment, marital status
- Family history, years of heavy drinking

Predictors of Sustained Alcohol use Post-LT (univariate)

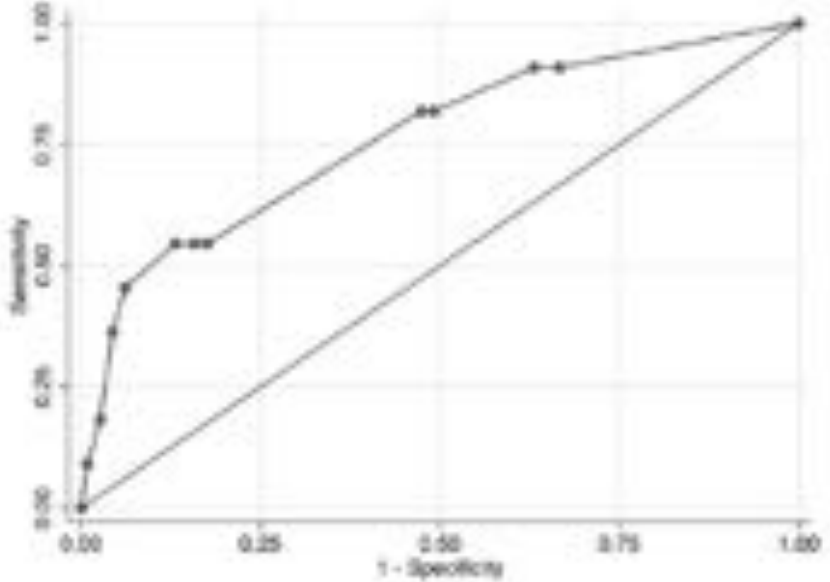
	OR (95% CI)	p	SALT Points
Hx of multiple ≥2 failed Rehab attempts	6.9(1.7-28.2)	0.007	+4
> 10 drinks/day at presentation	5.4(1.1-25.9)	0.04	+4
Any history of alcohol related legal issues	3.2(1.0-10.2)	0.05	+2
History of non-THC illicit substance use	3.8(1.0-14.4)	004	+1

Predicting Sustained Alcohol use post-LT : SALT Score



- Low SALT score 0-4
  - 95% NPV (95% without sustained alcohol use after LT
- High SALT score 5-11
  - 25% PPV (25% with sustained alcohol use after LT
- Maximal score 11, PPV 50%

Figure 1. AUROC Curve of Full LASSO Model for Sustained Alcohol Use Post-LT



A LASSO logistic model for sustained alcohol use post-LT, which incorporated greater than 10 drinks per day at initial hospitalization, history of illicit substance abuse, history of any alcohol-related legal issues, and history of multiple rehabilitation attempts had a c-statistic estimate of 0.76 (95% CI, 0.68-0.83).

Thank You