Liver Transplantation: Shifting Etiologies of Cirrhosis Brings New Challenges

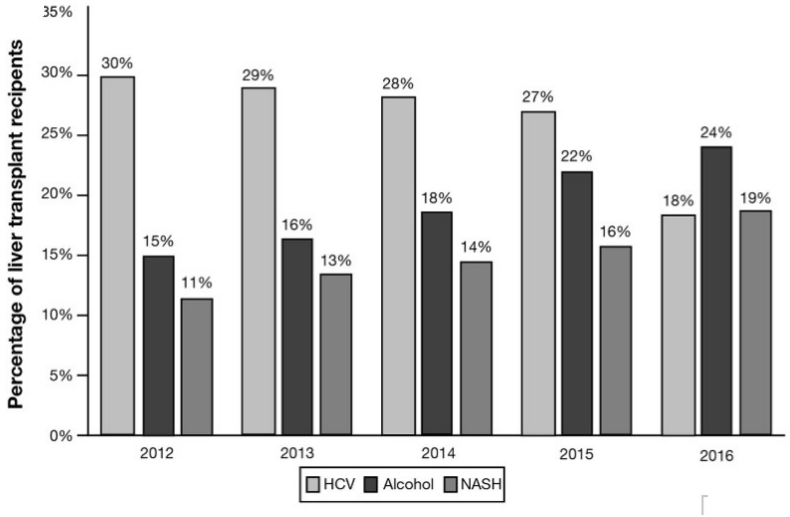
Norah Terrault, MD, MPH
Professor of Medicine and Transplant Surgery
Director Viral Hepatitis Center
University of California San Francisco

Grants/Research Support: AbbVie, Gilead, BMS, Merck, Allergan

Consultant: Genentech, Dova

Liver Transplants in 2019: The Big "3"

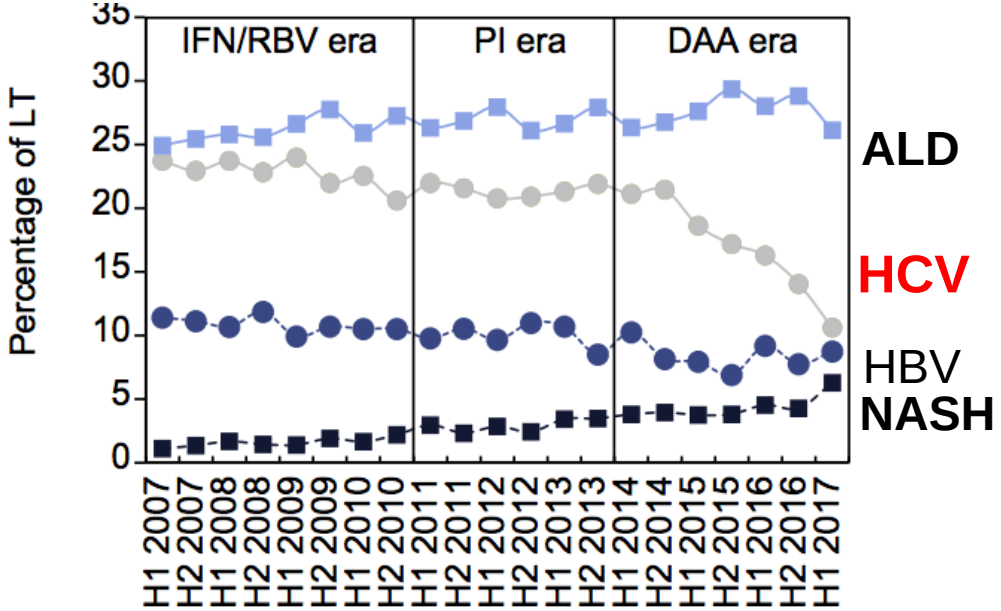
UNITED STATES (UNOS)
HCC excluded



HCV: 30→18%
ALD: 15→24%
NASH: 11→19%

Chonlankeril G CGH 2018;16:1356–1358

EUROPE (ELTR)



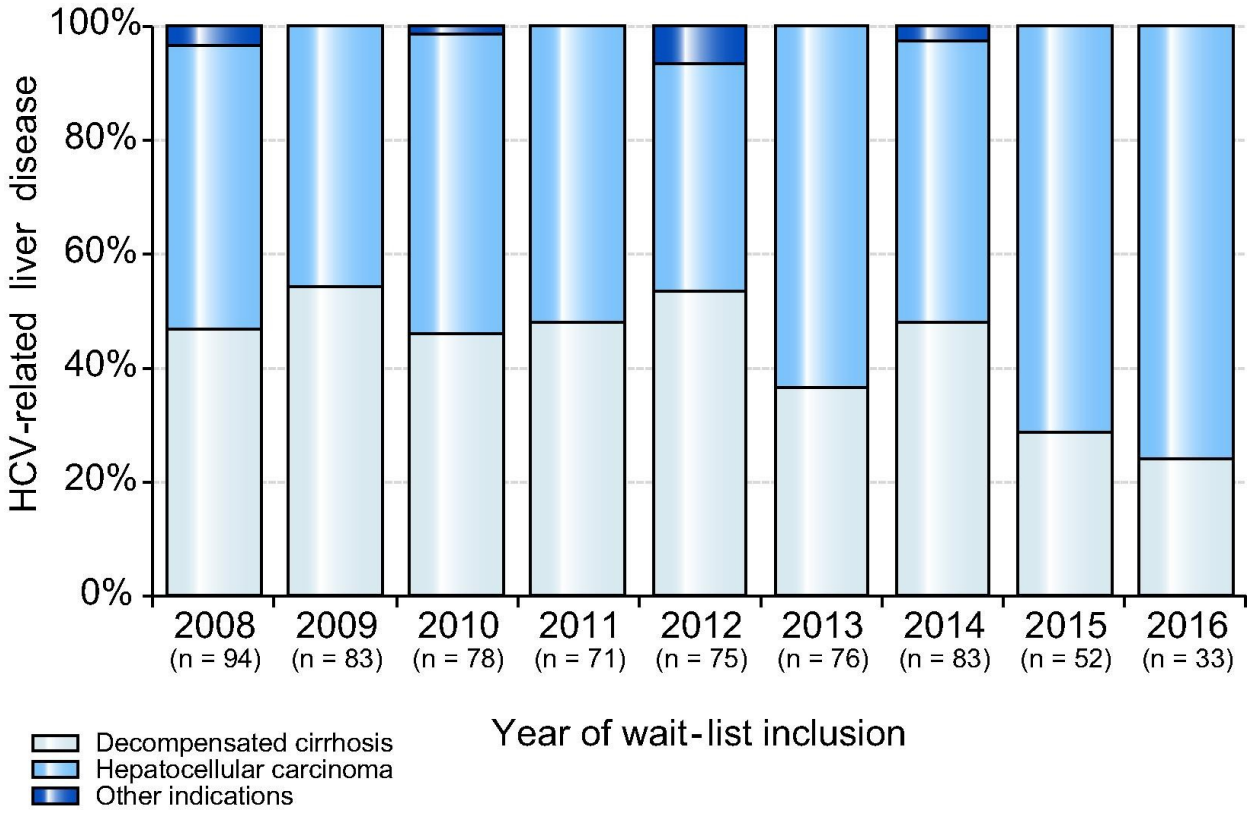
Belli L, J Hepatol. 2018;69:810-817

DAAs and the Impact of LT for HCV

- **SVR associated with less need for LT:**
  - **Lower rates of cirrhosis and HCC**
  - **Reversal of decompensation → delisting (in ~20%)**
- **SVR associated improved outcomes post-LT**
  - **Prevent progression and reverse fibrosis**
  - **Need for retransplantation is disappearing**
- **HCV-positive organs are used more frequently knowing that cure of HCV can be easily achieved post-LT**

Change in Wait-List Composition of HCV Patients in DAA Era

- 3 LT centers in Catalonia Spain
- N=1483 patients



Overall # waitlisted decreased by ~50%

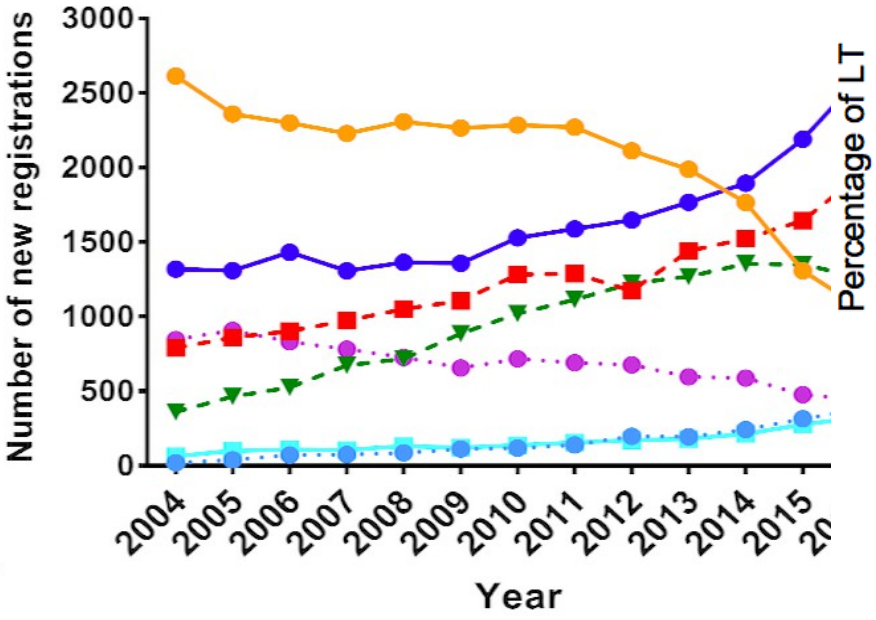
↓ Decompensated cirrhosis

↑ HCC increased

Crespo G, J Hepatol 2018;69(1):11-17

ALD is #1 Indication for LT in U.S. and Europe

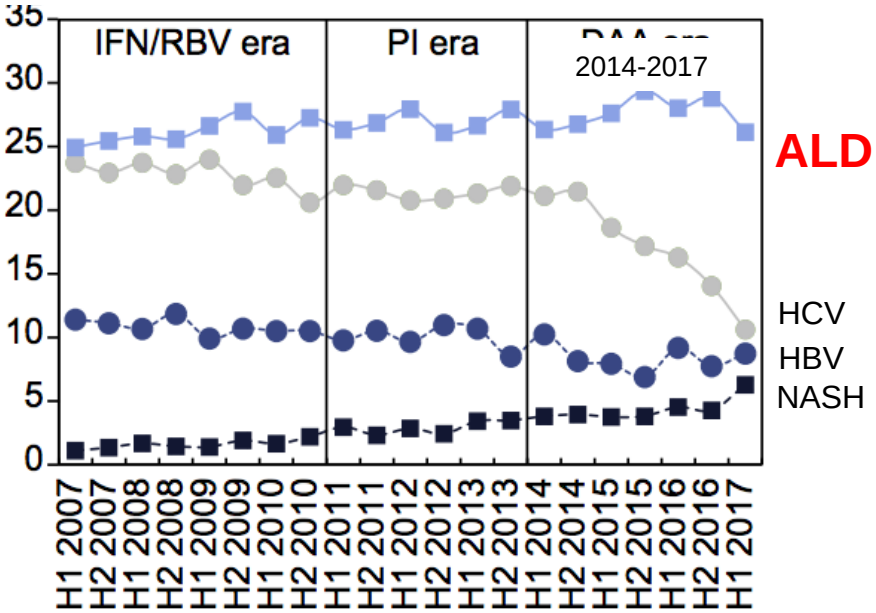
UNITED STATES (UNOS)



Increase by 50% since 2012

Nourredin M, Am J Gastro 2018

EUROPE (ELTR)

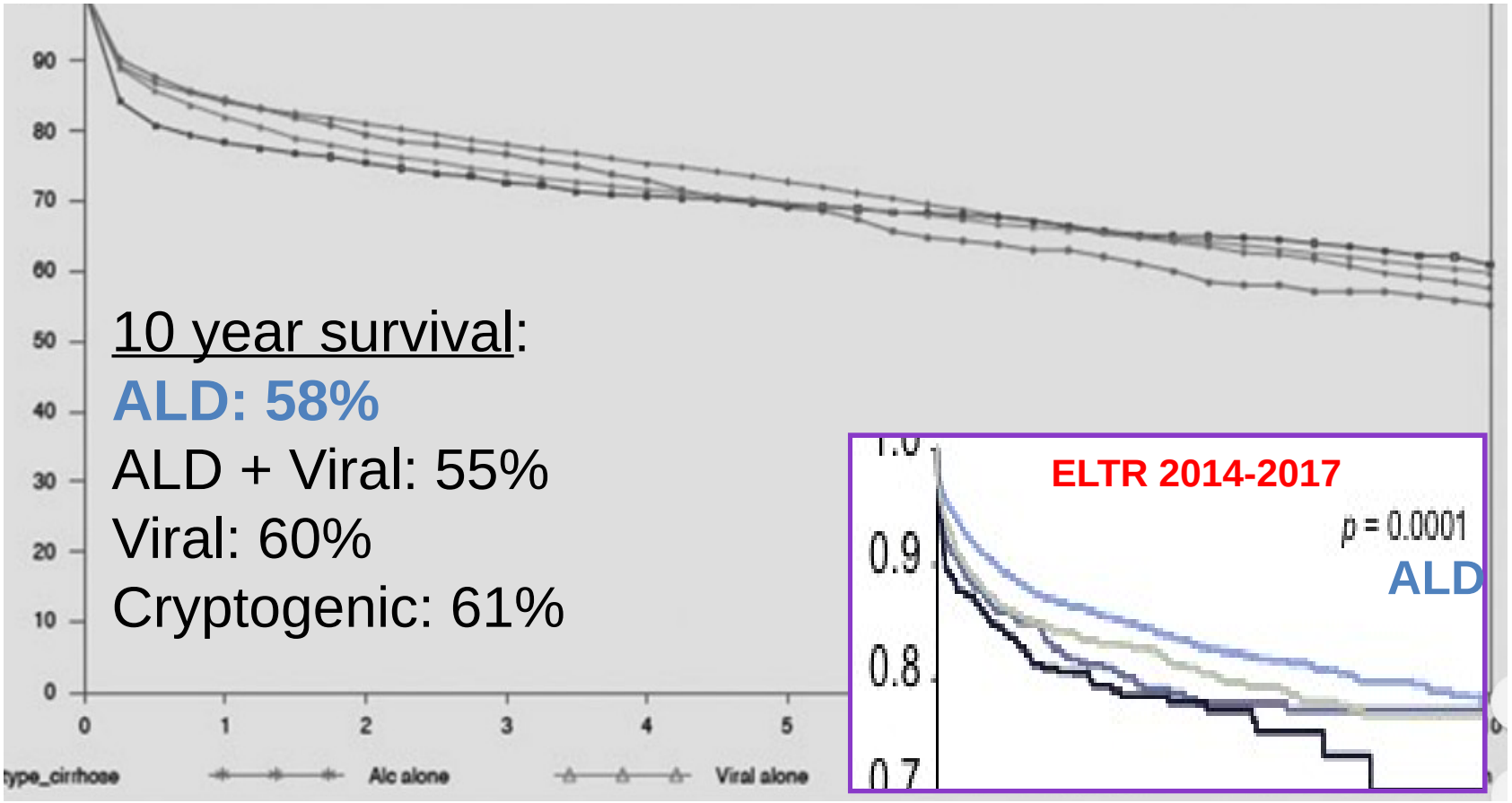


No significant change in past decade = 25% of LT

Belli L, J Hepatol. 2018;69:810-817

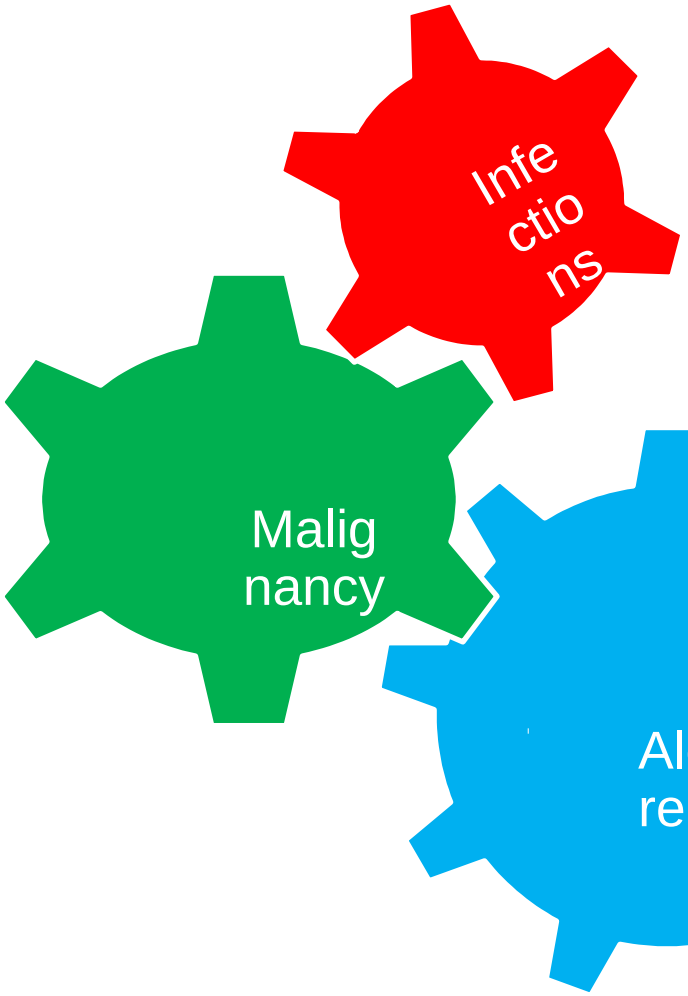
Long-Term Patient Survival in ALD Comparable to Other Etiologies

ELTR 1988-2005, N=9098 LT recipients



Belli L, J Hepatol. 2018;69:810-817
Burra P, Am J Transplant 2010; 10: 138–148

Key Challenges in Optimizing Survival in ALD Post-LT



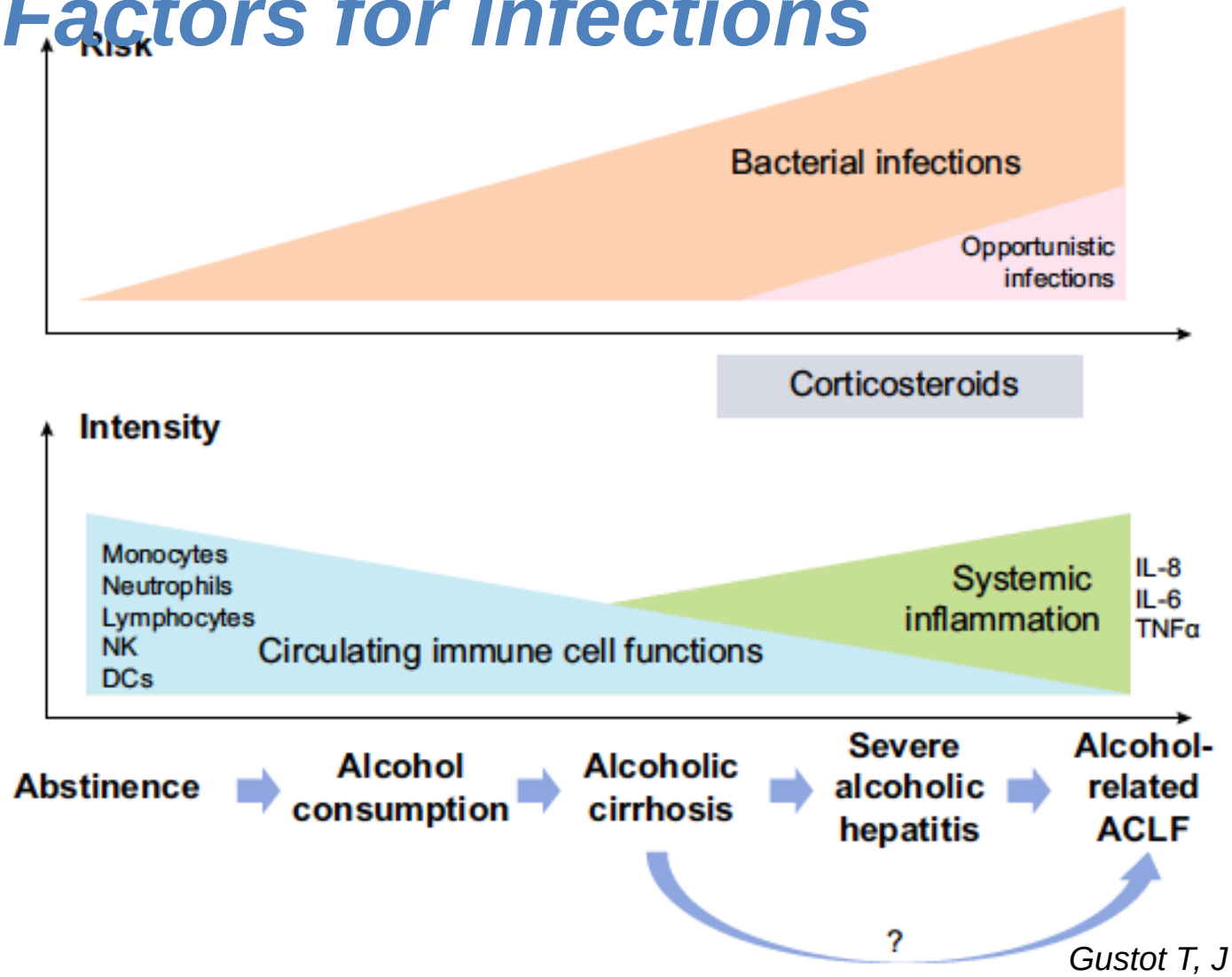
Early, especially among patients with severe AH

High risk of head/neck, larynx, esophageal and lung cancer

Most common cause of graft loss

Immune Dysfunction and ALD Patients

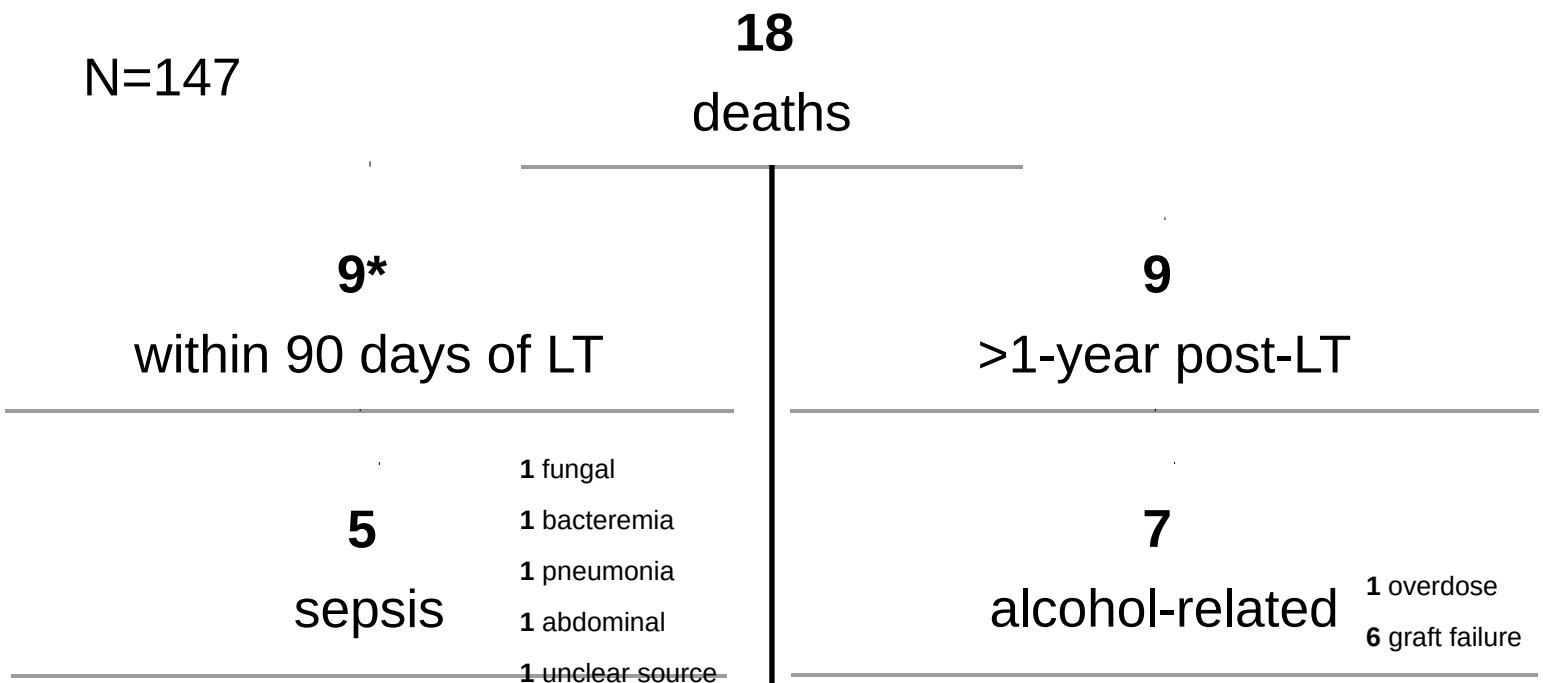
Risk Factors for Infections



Gustot T, J Hepatol 2017

Infections and Post-LT Mortality in Severe AH: Link with Prednisone Use?

ACCELERATE-AH: Multicenter US study of LT for severe acute alcohol-associated hepatitis

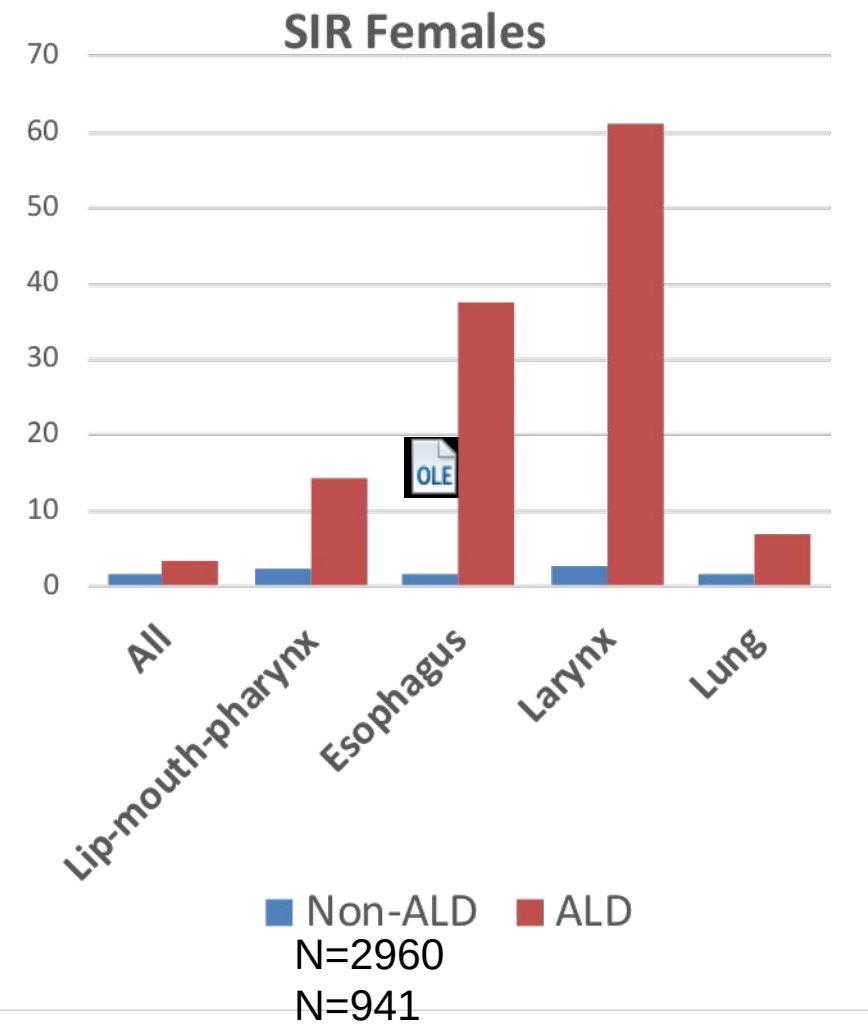


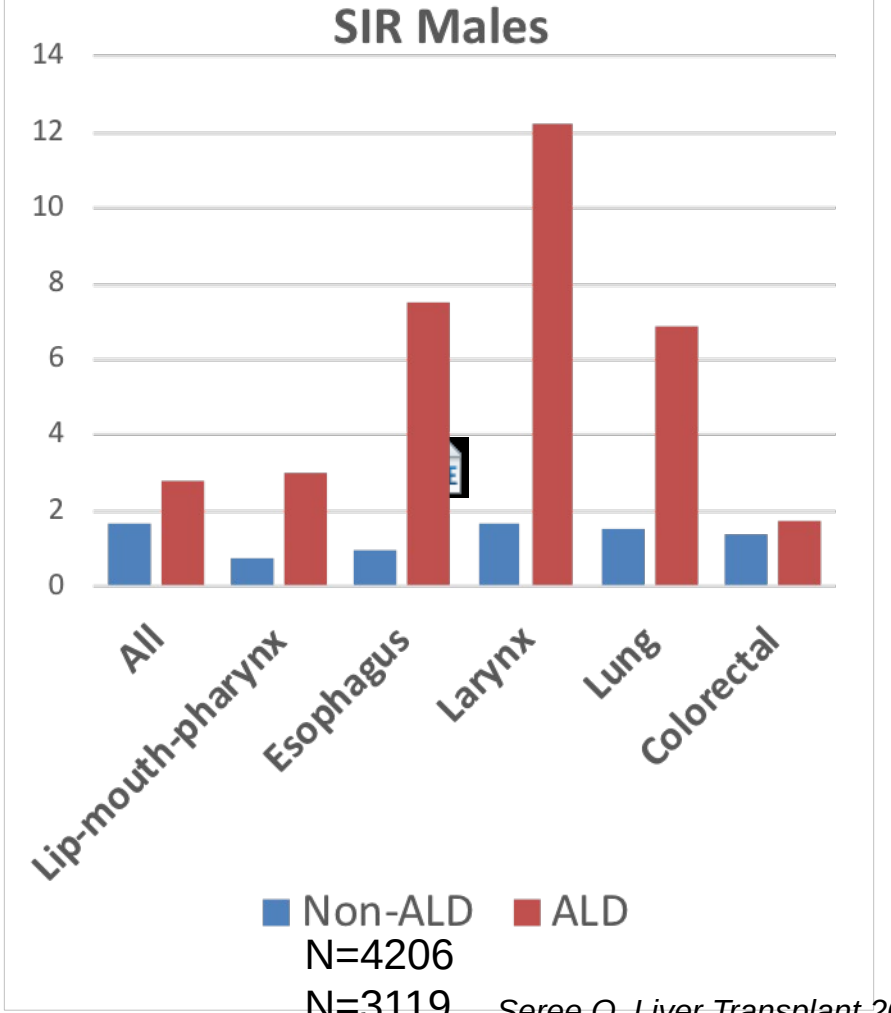
*8 of 9 received steroids pre-LT for AH (p=0.04)

Lee B, AASLD 2018, San Francisco

ALD Associated with Higher Risk of Post-LT Malignancy

- **French National Database of LT recipients 1993-2012**

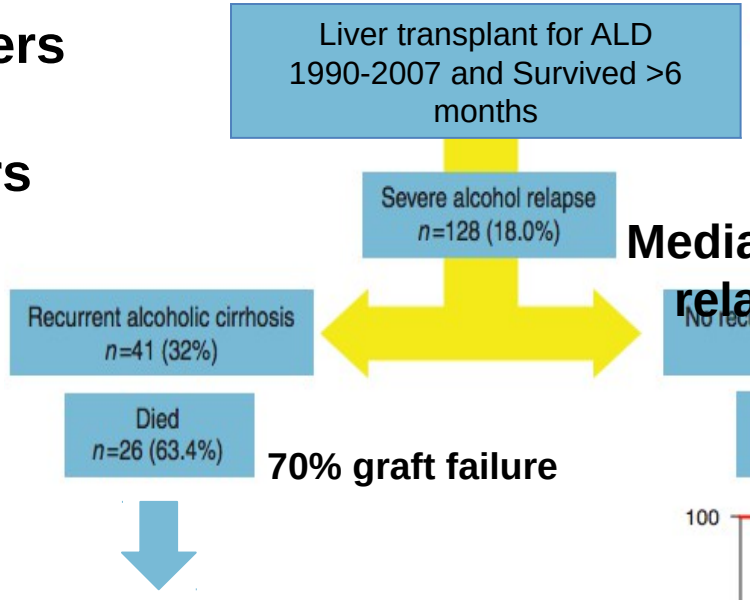




Seree O, Liver Transplant 2018

Incidence and Consequences of Alcohol Use Post-LT

3 French Centers
N=712
Mean f/u = 9 yrs

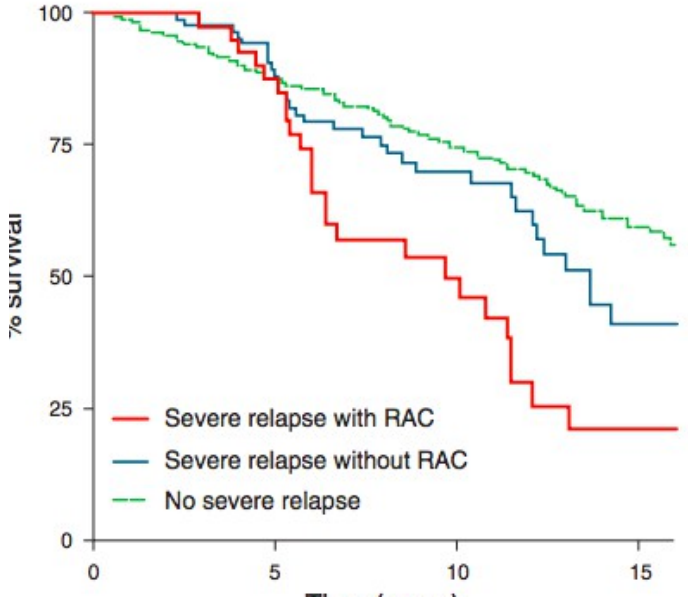


Median time from LT to relapse = 1.1 years

70% graft failure

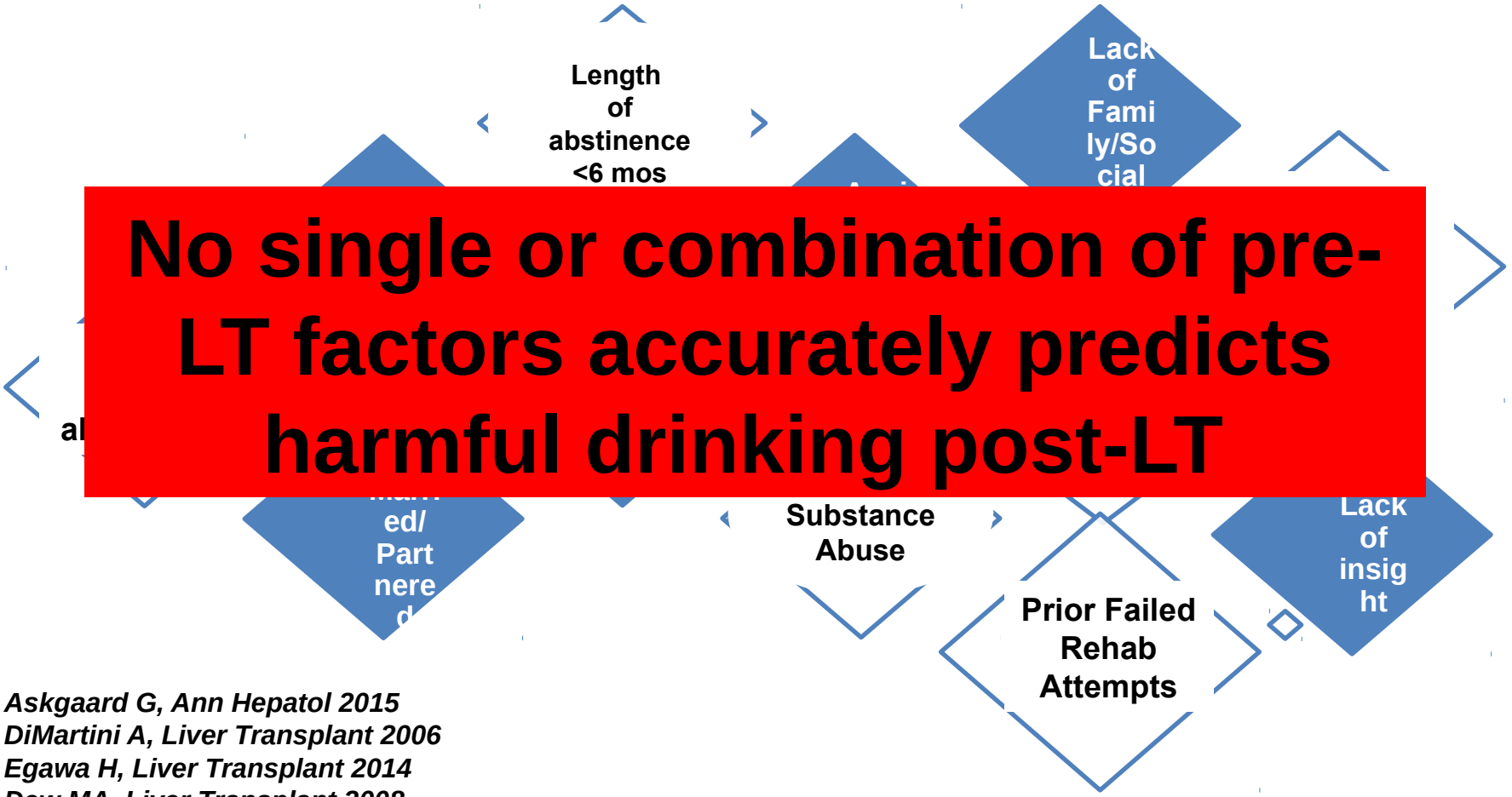
6% graft failure (CR)

- **Median time LT to recurrent cirrhosis= 4.4 yrs**
- **Median time from diagnosis recurrent ALD cirrhosis to death = 1.1 yrs**



Dumortier J, AJG, 2015

Pre-Transplant Factors Associated with Harmful Alcohol Use Post-LT

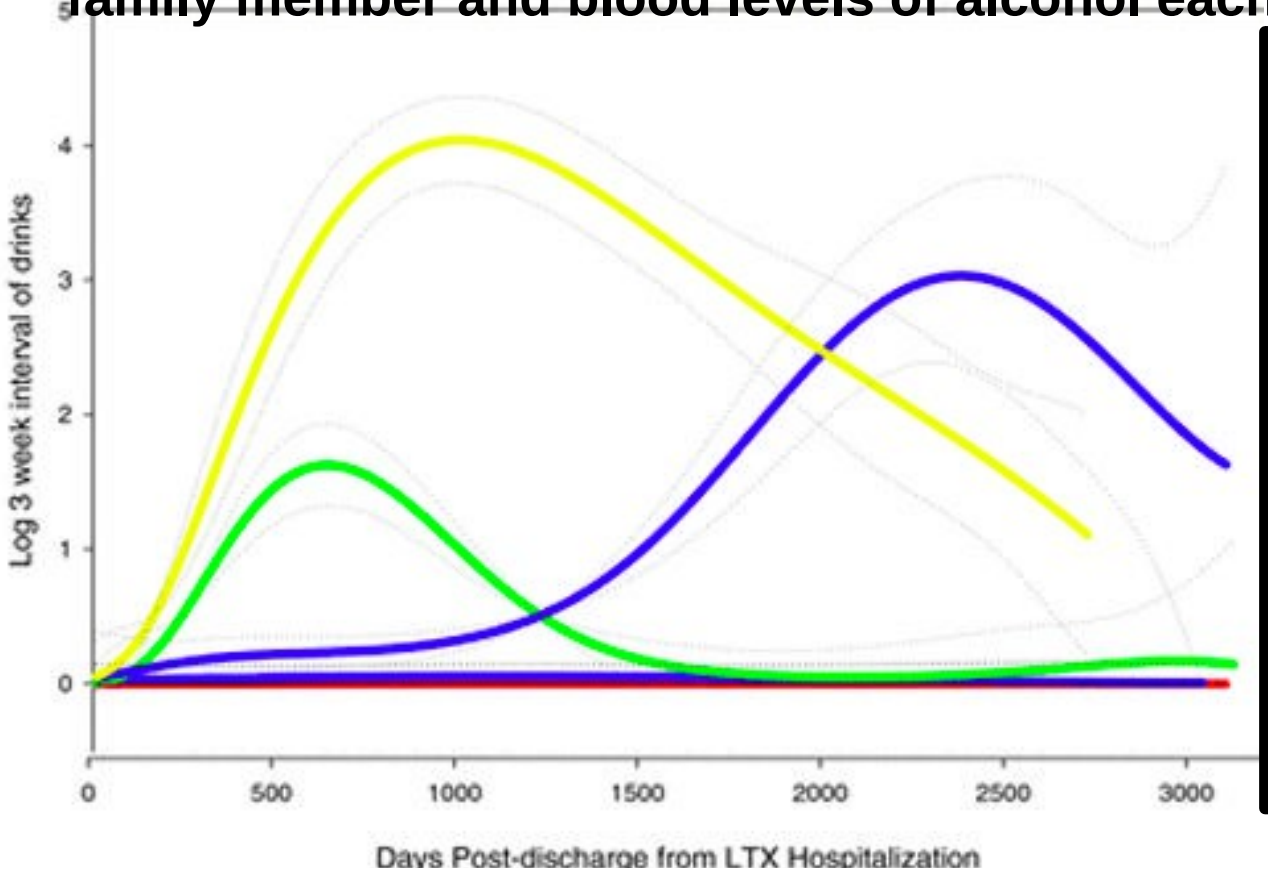


No single or combination of pre-LT factors accurately predicts harmful drinking post-LT

Askgaard G, Ann Hepatol 2015
DiMartini A, Liver Transplant 2006
Egawa H, Liver Transplant 2014
Dew MA, Liver Transplant 2008
Lee B, Hepatology 2019

Patterns of Alcohol Use Post-LT Among Patients with Prior ALD

- **Single center, 265 LT recipients with primary or secondary diagnosis of ALD**
- **TLFB and interviews of LT recipients, freq/quant questionnaire by family member and blood levels of alcohol each clinic visit**



Five distinct trajectories of alcohol use post-LT:

-- Abstinent
-- Low level, fluctuating
-- Late onset to moderate
-- Early onset, rapid progression to moderate
-- Early and rapid progression to heavy

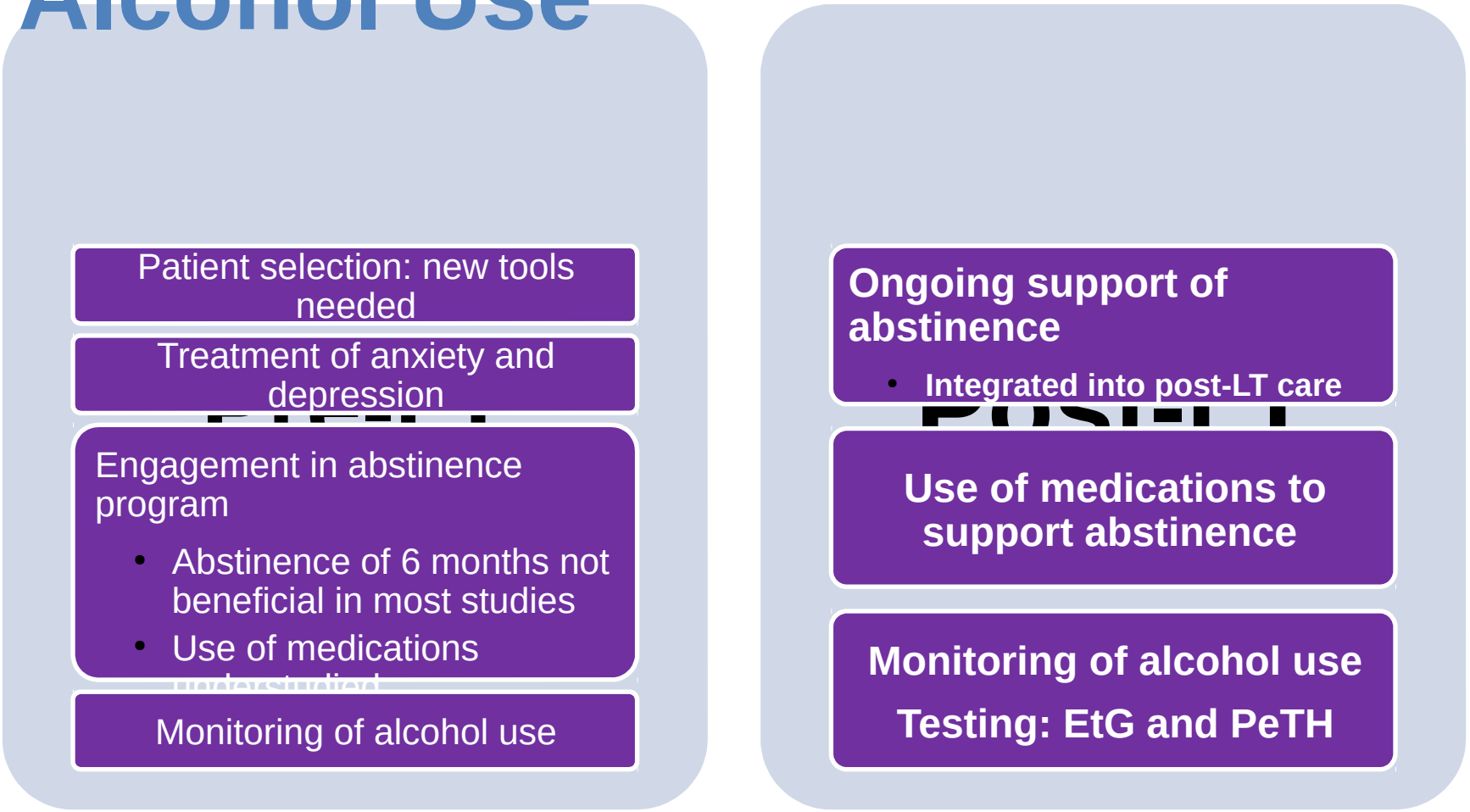
DiMartini, Am J Transplant, 2010

Early Return to Harmful Drinking Impacts Patient/Graft Survival

Outcomes	Early onset groups	All others	P value
≥20% of biopsies with steatohepatitis	**23%**	**9%**	**0.05**
≥40% of biopsies with acute rejection	**41%**	**18%**	**0.02**
Graft failure	**73%**	**37%**	**0.04**
Cause of death			
ALD	**46%**	**0%**	**<0.001**
Malignancy	0%	21%	0.19
Cardiac	18%	10%	0.60
Infection/sepsis	9%	12%	1.00

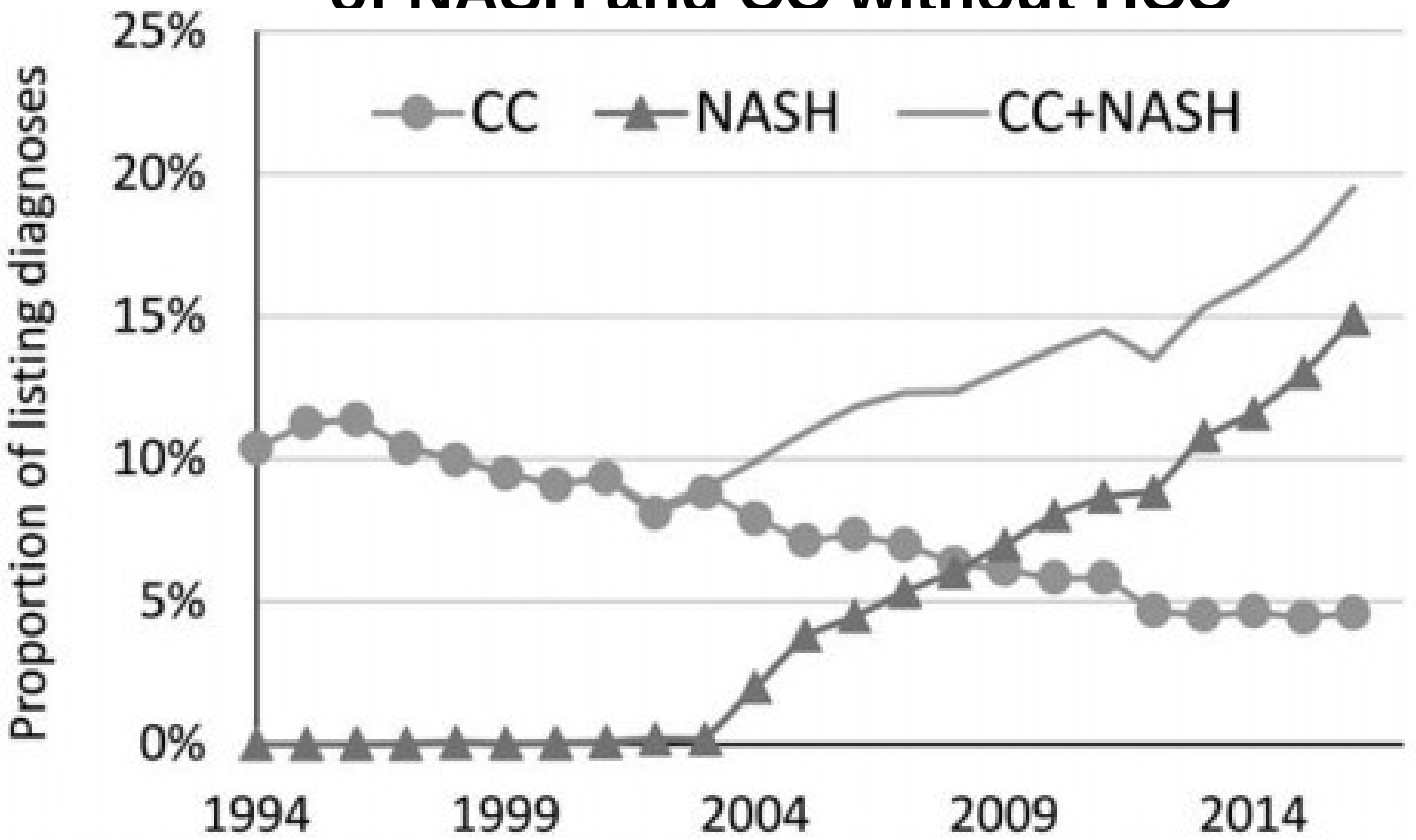
DiMartini, Am J Transplant, 2010

Strategies to Reduce Graft Losses Related to Harmful Alcohol Use



NASH is Rapidly Rising Indication for LT in the U.S.

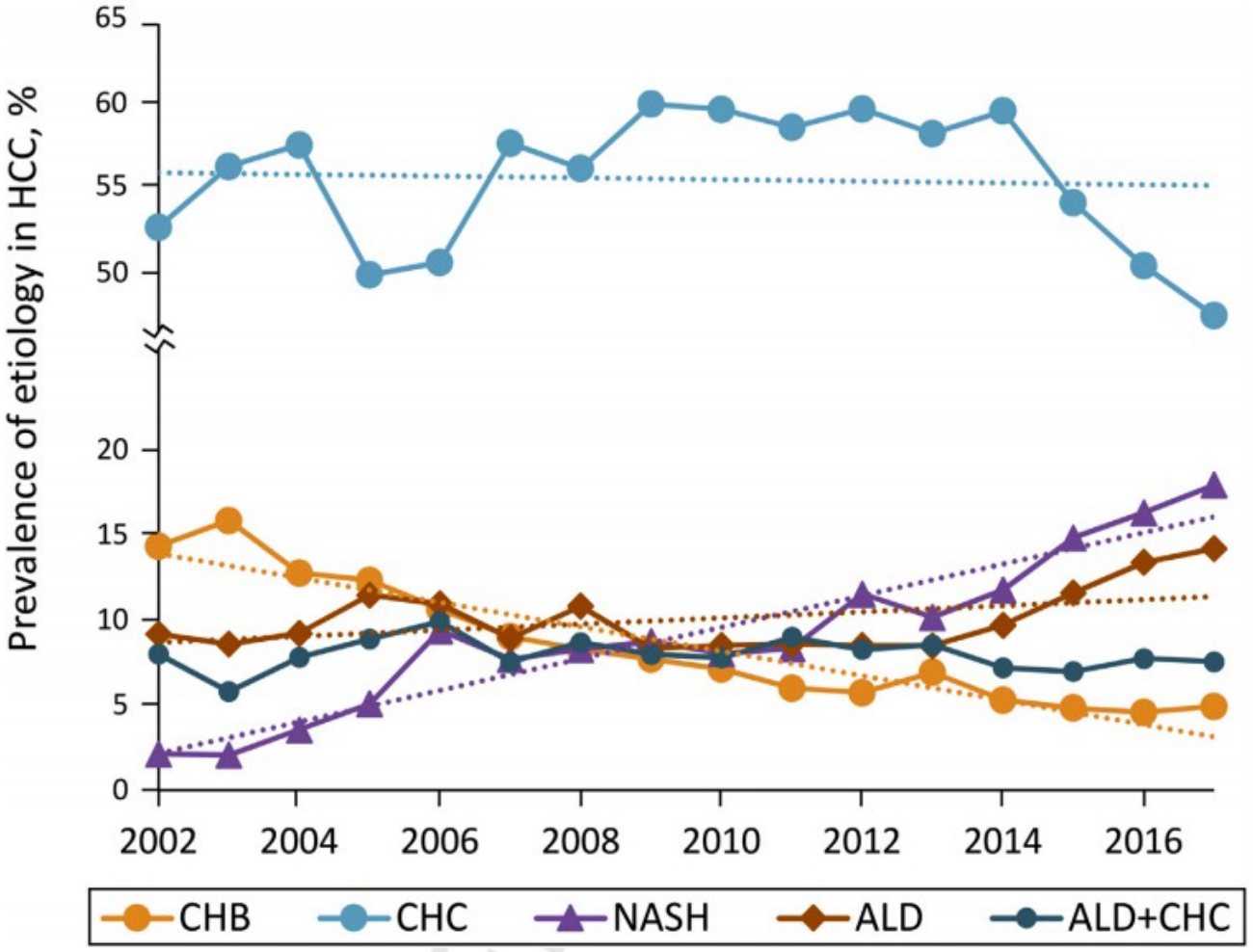
U.S. LT 1994–2016 LT candidates with primary diagnoses of NASH and CC without HCC



- **NASH is the 2nd most common indication for LT in U.S.**

Golabi P Medcine 2018

Changing Etiologies of HCC Among Wait-Listed Patients



HCV #1 by declining

NASH most dramatic rise

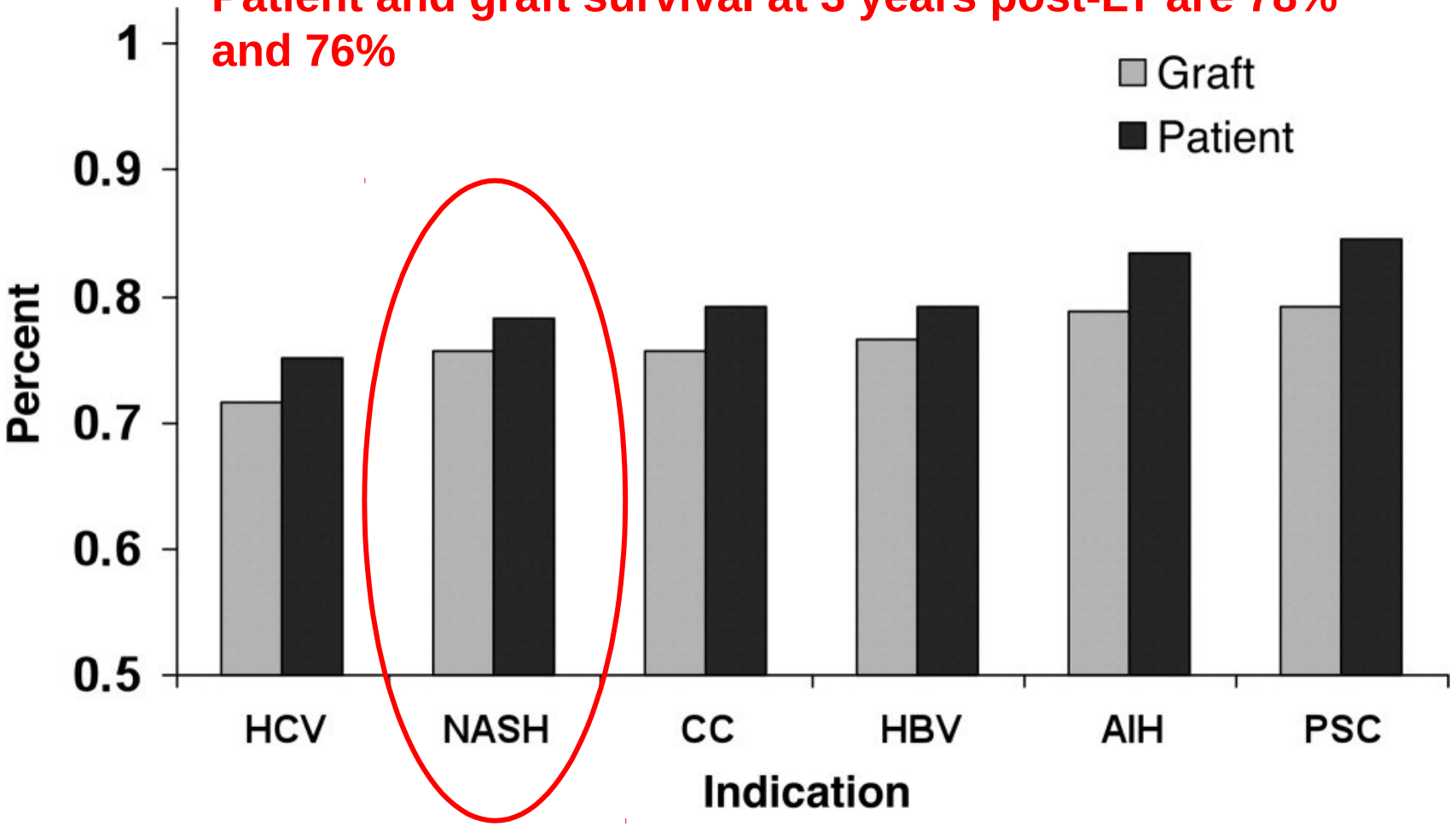
ALC no change

HBV declining

Younossi Y, CGH, 2018

Overall Patient Survival for NASH is Similar to Other Indications

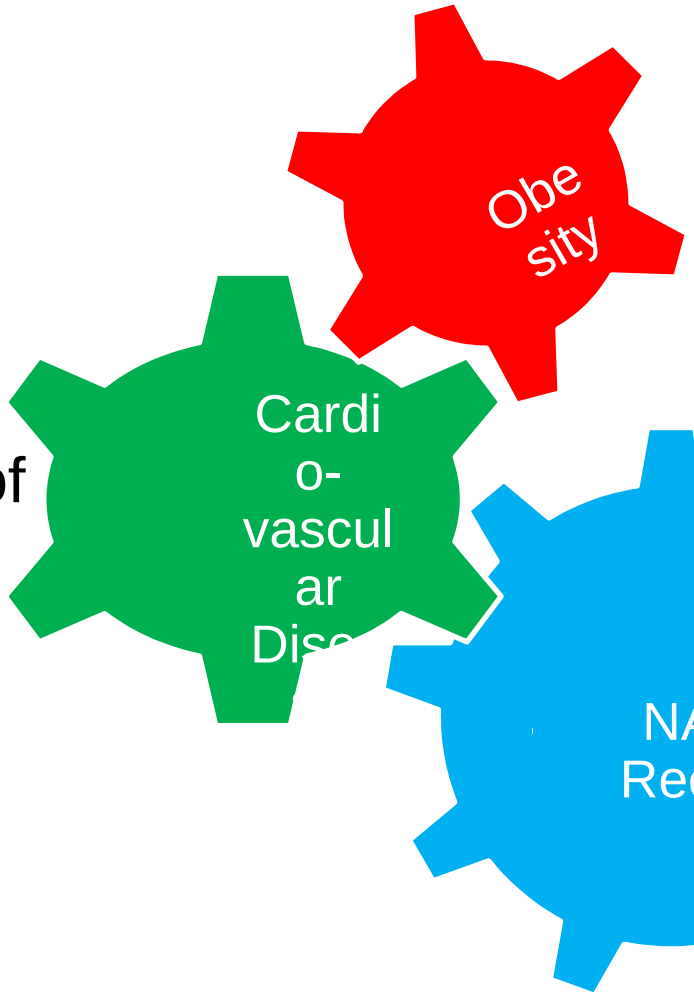
Patient and graft survival at 3 years post-LT are 78% and 76%



NASH patients older, higher BMI and % diabetes, female

Charlton et al. Gastroenterology. 2012

Key Challenges in Optimizing Survival in NAFLD Patients Post-LT



Key driver of metabolic and liver disease risks

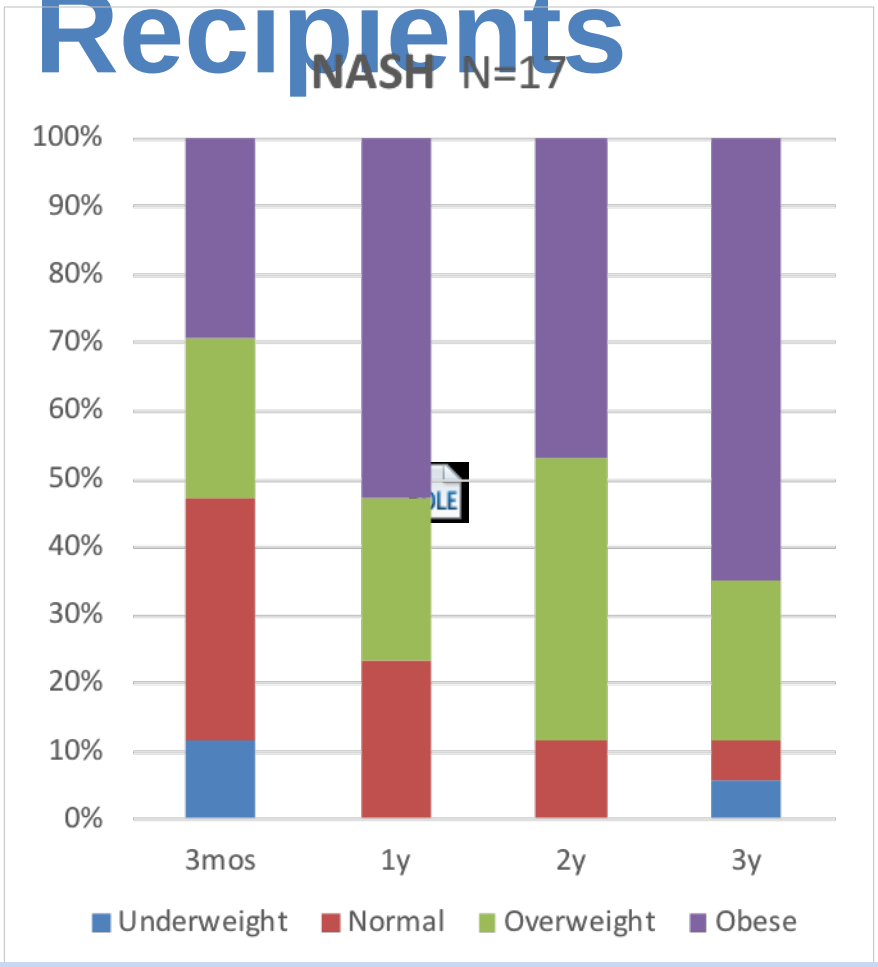
As pre-LT is a competing risk of short and long-term survival

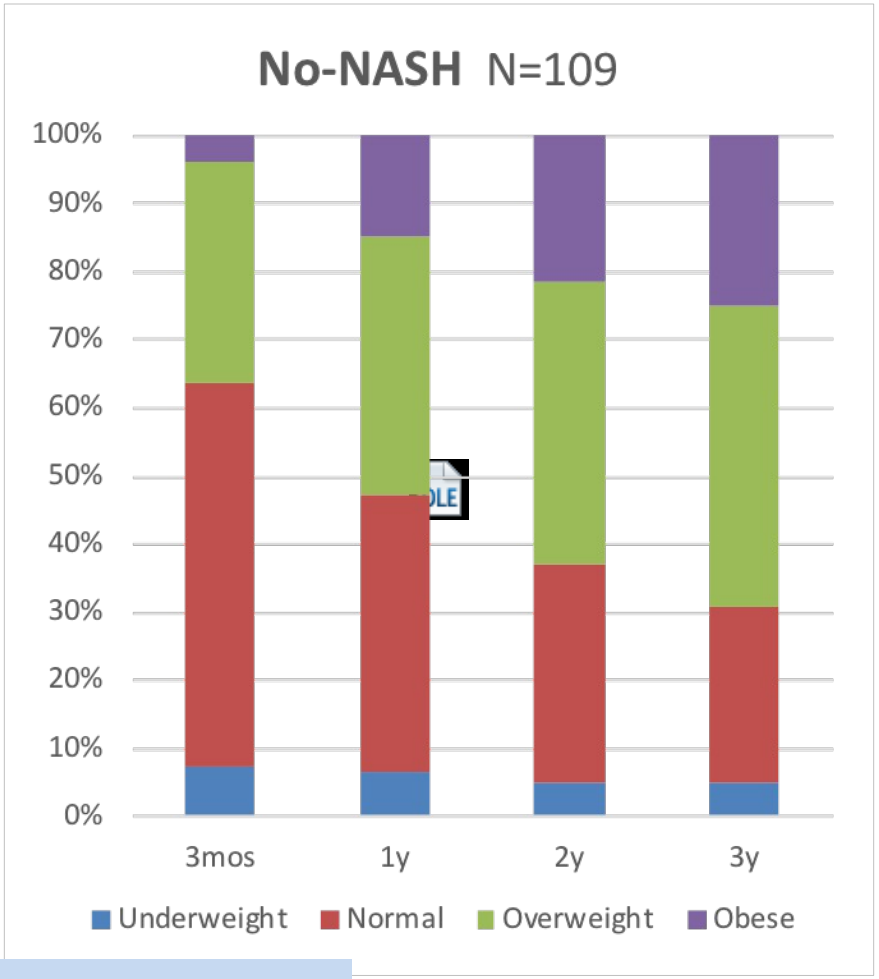
Risk for graft loss

Immunosuppressive Drugs Amplify Metabolic Risks

	Calcineurin Inhibitors	Mycophenolate Mofetil	mTOR inhibitors	Steroids
Diabetes	↑	Potential Benefit	Potential Benefit	↑
Dyslipidemia	↑	Less than CNI	↑*	↑
Hypertension	↑	Less than CNI	↑	↑
Malignancy	↑		↓	
Renal Injury	↑	Less than CNI & mTOR inhibitors	Less than CNI	
Weight	↑	Less weight gain than CNI	Less weight gain than CNI	↑

Weight Gain Post-LT Greater in NASH Transplant Recipients



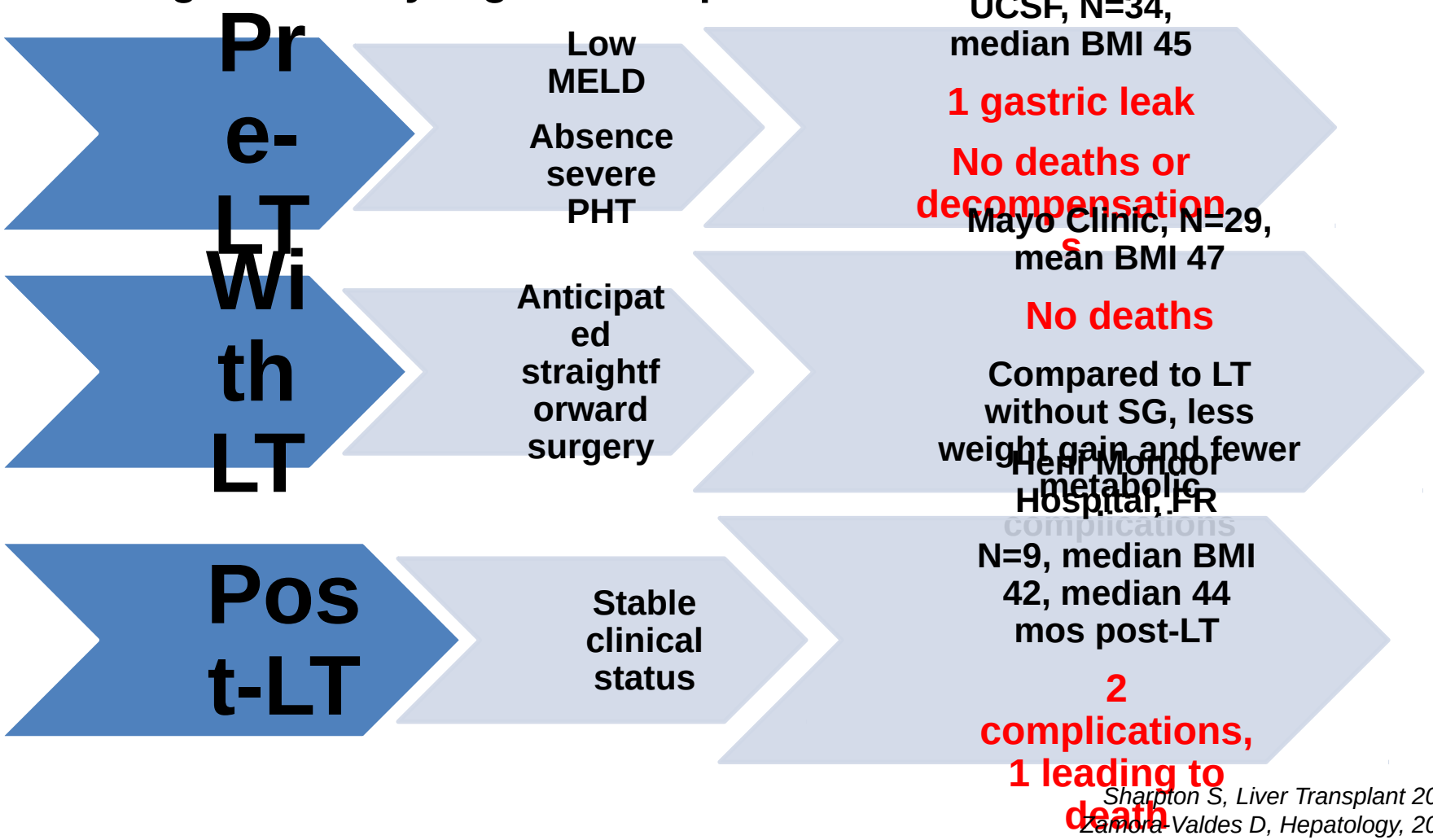


- **Weight is earlier and greater in NASH patients**
- **>60% obese after 3 yrs follow-up**

Kouz J. Liver Transpl 2015

Bariatric Surgery in the Transplant Setting

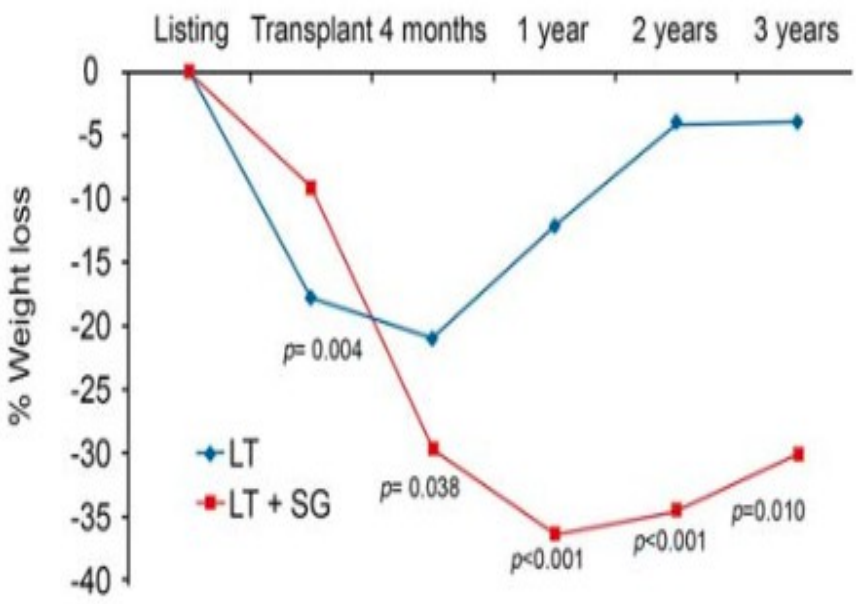
- **Sleeve gastrectomy regarded as procedure of choice**



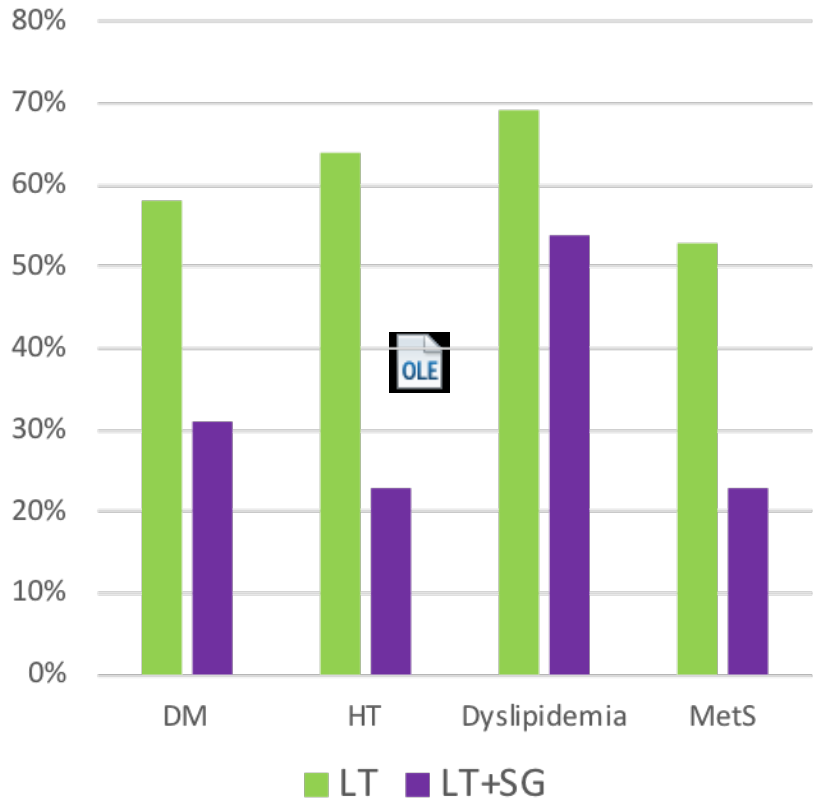
Sharpton S, Liver Transplant 2018
Zamora-Valdes D, Hepatology, 2018
Osseis M, Obes Surg 2018

3-Year Post-LT Outcomes in Patients with and without SG

Weight Loss Post-LT



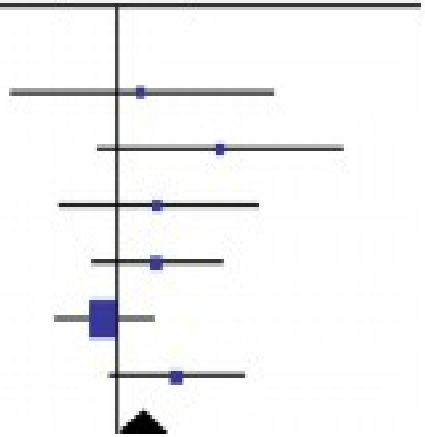
Metabolic Comorbidities



Zamora-Valdes D, Hepatology, 2018

More CV Deaths Among NASH versus Non-NASH LT Recipients

Study or subgroup	NASH Events	NASH Total	Non-NASH Events	Non-NASH Total	Weight	Odds ratio M-H, random, 95% CI
Cardiovascular events						
Barritt 2011	1	21	3	97	4.5%	1.57 [0.15, 15.85]
Bhagat V 2009	5	71	1	83	3.8%	6.21 [0.71, 54.48]
Houlihan DD 2011	4	48	2	48	8.1%	2.09 [0.36, 12.00]
Kennedy C 2012	4	129	12	775	14.6%	2.03 [0.65, 6.41]
Malik SM 2009	6	98	52	686	53.8%	0.80 [0.33, 1.90]
Vanwagner LB 2012	10	115	4	127	15.3%	2.93 [0.89, 9.61]

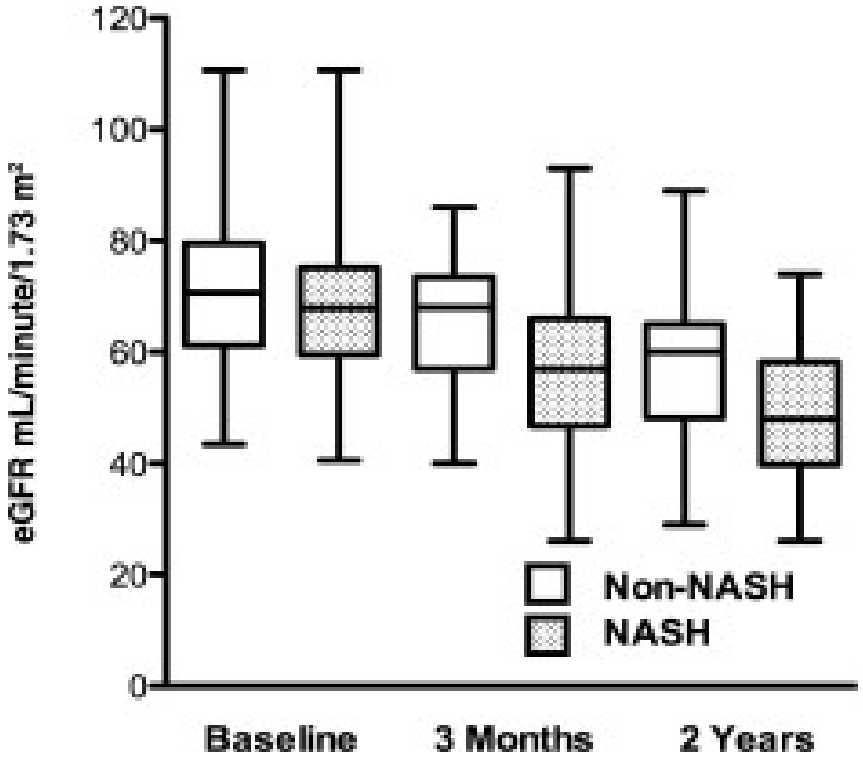


VanWagner L, Hepatology 2012

Event	NASH (N=115)	ALD (N=127)	OR (95% CI)
Any CV within 1 yr of LT	**26%**	**8%**	**4.12 (1.9-8.9)**
Cardiac arrest	**8%**	**1%**	**5.37 (1.1-25.4)**
CV Mortality	**9%**	**1%**	**2.72 (0.83-8.95)**

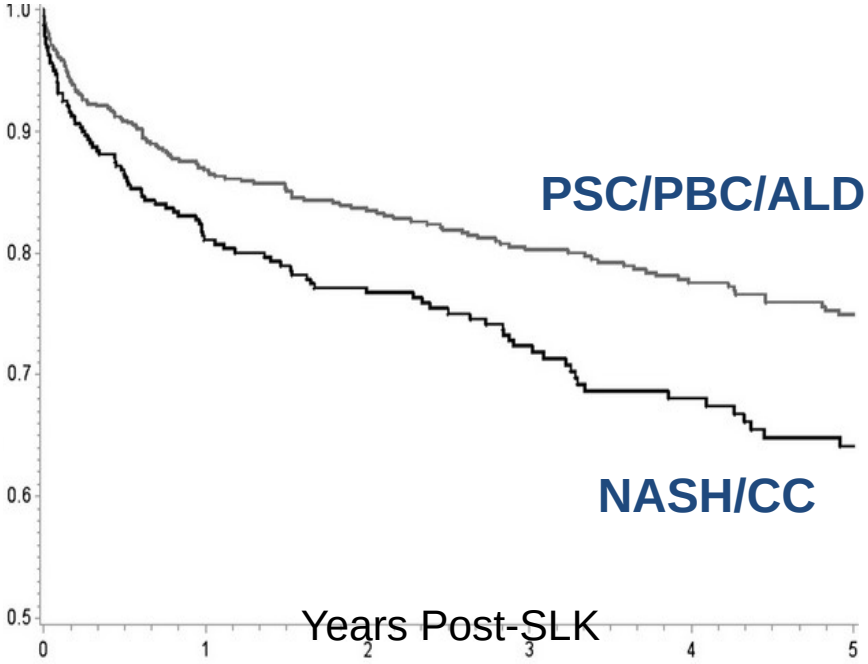
Patients Transplanted for NASH/CC at Higher Risk of Renal Complications

Changes in GFR Post-transplant



Houlihan et al. Liver Transpl 2011

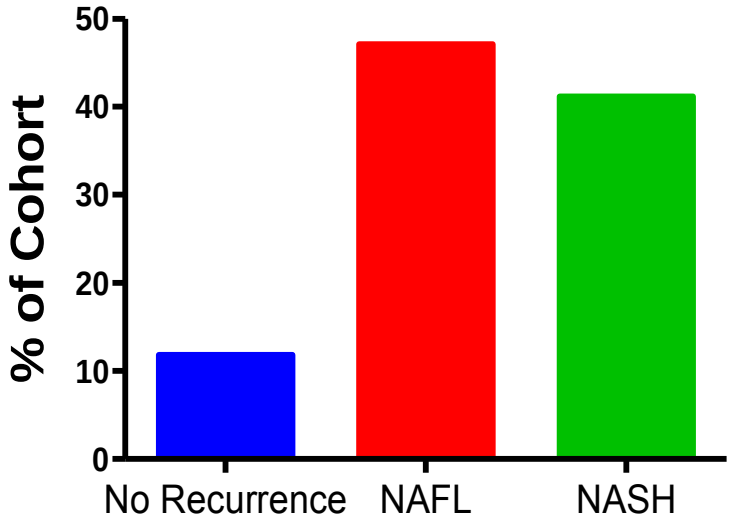
Kidney graft survival in SLK Patients

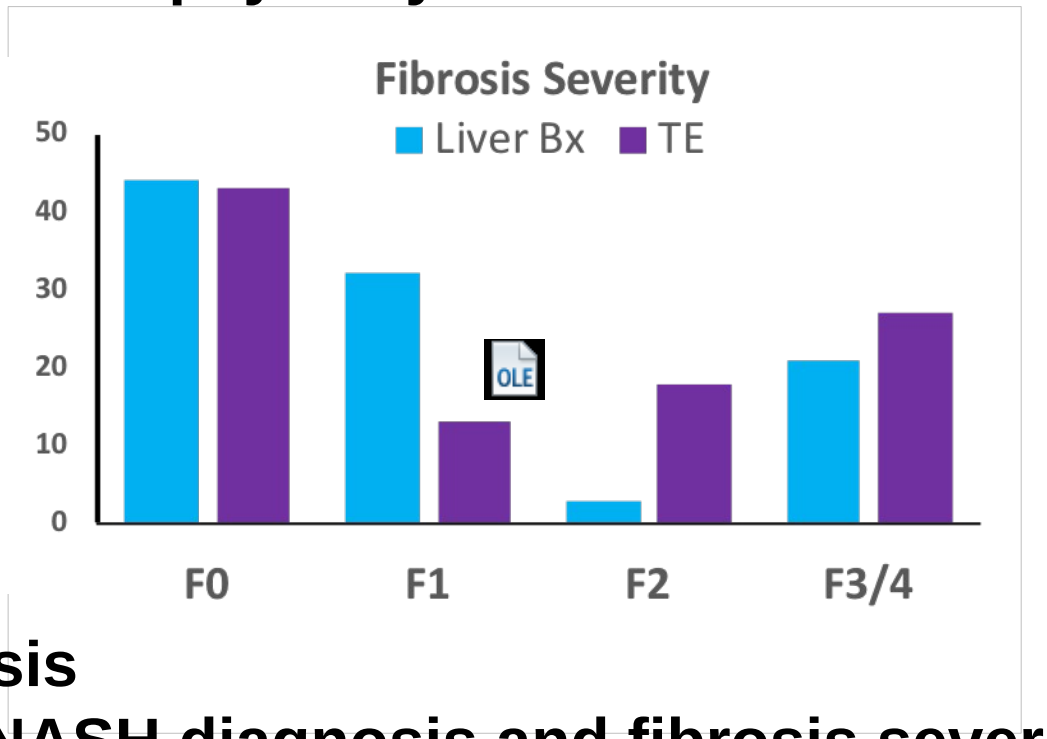


Singal A, Transplantation 2016

Recurrence of NAFLD Post-Transplant Among those NASH Pre-LT

- **Single U.S. center, non-protocolized liver biopsy, N=30 biopsy and N=76 with TE**
- **Median time from LT to biopsy = 4 years**





~25% had significant fibrosis

Poor correlation between NASH diagnosis and fibrosis severi

Bhati et al. Transplantation 2017;101: 1867–1874

Recurrent NASH: The Emerging Picture

- **Steatosis develops more frequently and rapidly in NASH vs. non-NASH patients**
  - **60% at 1 year**
- **NASH present in 40-60% within 3-5 years**
  - **Advanced fibrosis in 5-10% at 5-10 years**
- **No association of steatosis with post-transplant outcomes**
- **Overall, no difference in survival is apparent (yet)**

Charlton MR, et al. Gastroenterology 2011;141:1249-53, Wong RJ, Hepatology 2014;59:2188-95, Maor-Kendler Y, et al. Transplantation 2000;70:292-297, Wang X, et al, Clin Gastro Hepatol 2014;12:394-402, VanWagner LB, et al. Hepatology 2012;56:1741-50

Optimizing the Outcomes in Patients Transplanted for NASH

Pre-Transplant

- Patient Selection
- BMI management plan
- CVD evaluation and risk management

Transplant

- Steroid free/reduced steroid use
- Renal protective protocols
- Management of hyperglycemia

Post-Transplant

- **Long-term BMI management**
- **Aggressive management of hyperglycemia, hypertension and dyslipidemia**
- **Reducing disease recurrence**
  - Protocol liver biopsies
  - Need for novel drug therapies

Adapted from Siddiqui and Charlton Gastro. 2016

Changes in LT Indications and Challenges

Summary

- **HCV continues to decline as indication**
  - More for HCC than for decompensated cirrhosis
- **ALD on the rise in US likely related to LT for AH and changing attitudes regarding sobriety requirements**
  - Infections, malignancy and relapse of alcohol are main areas to focus on for improving outcomes
- **NASH shows largest increases – both for cirrhosis and HCC**
  - Management of obesity and metabolic complications are main challenges (as they are pre-LT)
  - Recurrent NASH – need better natural history data