UT Southwestern Medical Center

Update in Liver Transplant

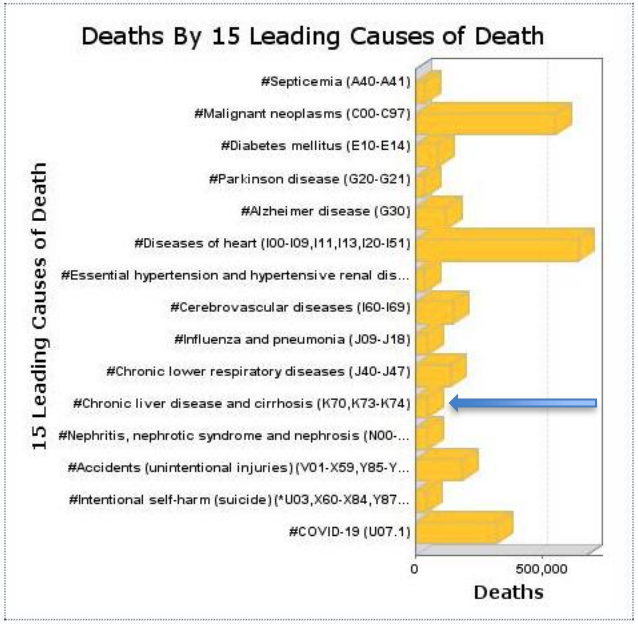
Arjmand Mufti, MD
UT Southwestern Medical Center

Outline

- Outline the state of liver transplant today
- Changing indications for liver transplant
- Allocation policy changes
- Ways to increase the donor pool
- Living donor liver transplantation
- Transplant oncology

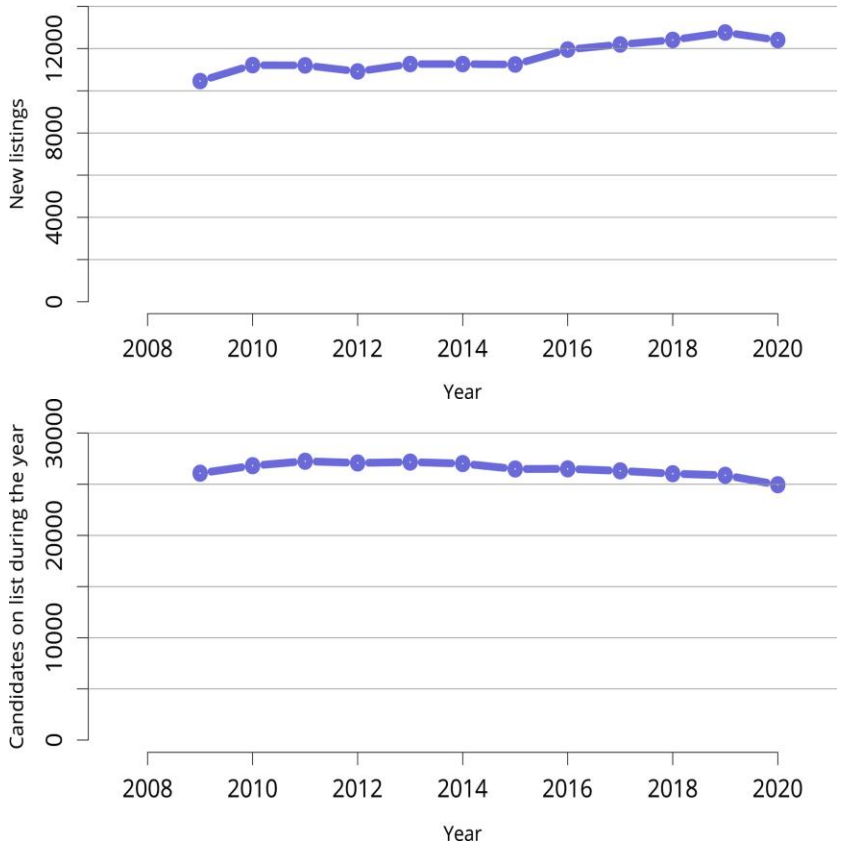
Liver Disease – A Significant Cause of Morbidity and Mortality in the USA

- MORBIDITY
  - Number of adults with diagnosed liver disease: 4.5 million
  - Percent of adults with diagnosed liver disease: 1.8%
- MORTALITY
  - Number of deaths: 51,642
  - Deaths per 100,000 population: 15.7



https://wonder.cdc.gov/controller/datarequest/

Distribution of Candidates Waiting for Liver Transplant

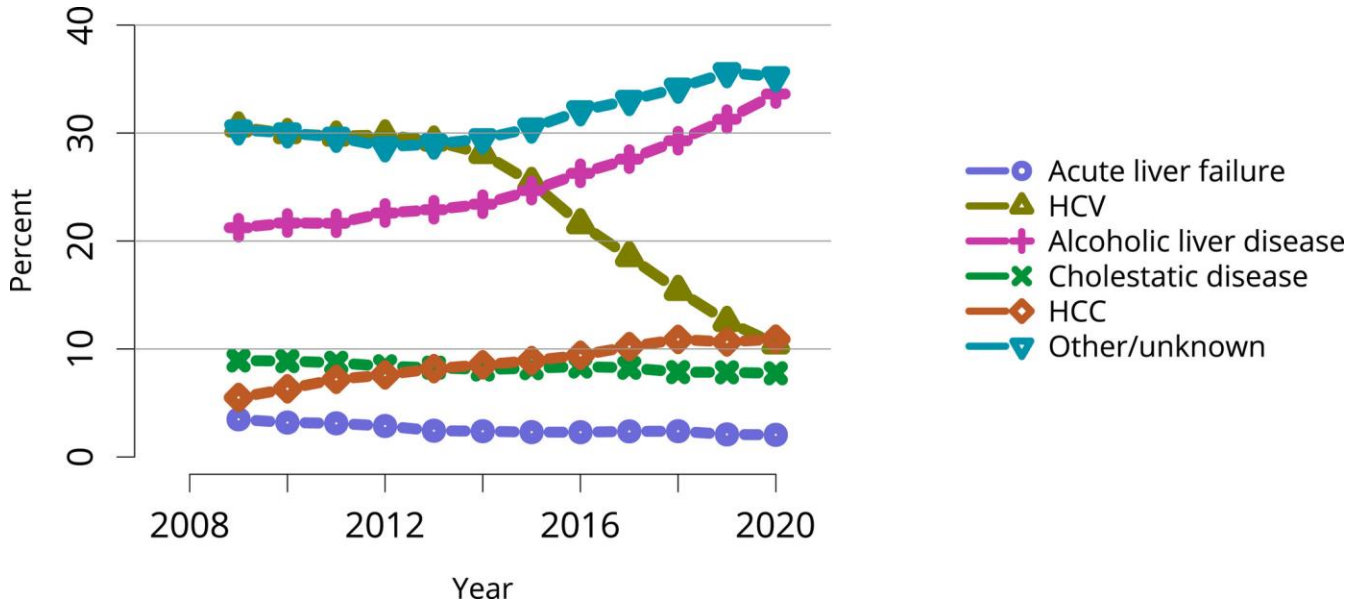


New adult candidates added to the liver transplant waiting list

All adult candidates on the liver transplant waiting list

Kw ong AJ, et al. Am J Transplant 2022

Etiology of Liver Disease at Time of Listing for Liver Transplantation



Kw ong A J, et al. Am J Transplant 2022

A changing landscape of liver transplantation: King HCV is dethroned, ALD and NAFLD take over!

Norah A. Terrault[1,*], Georges-Philippe Pageaux[2,*]

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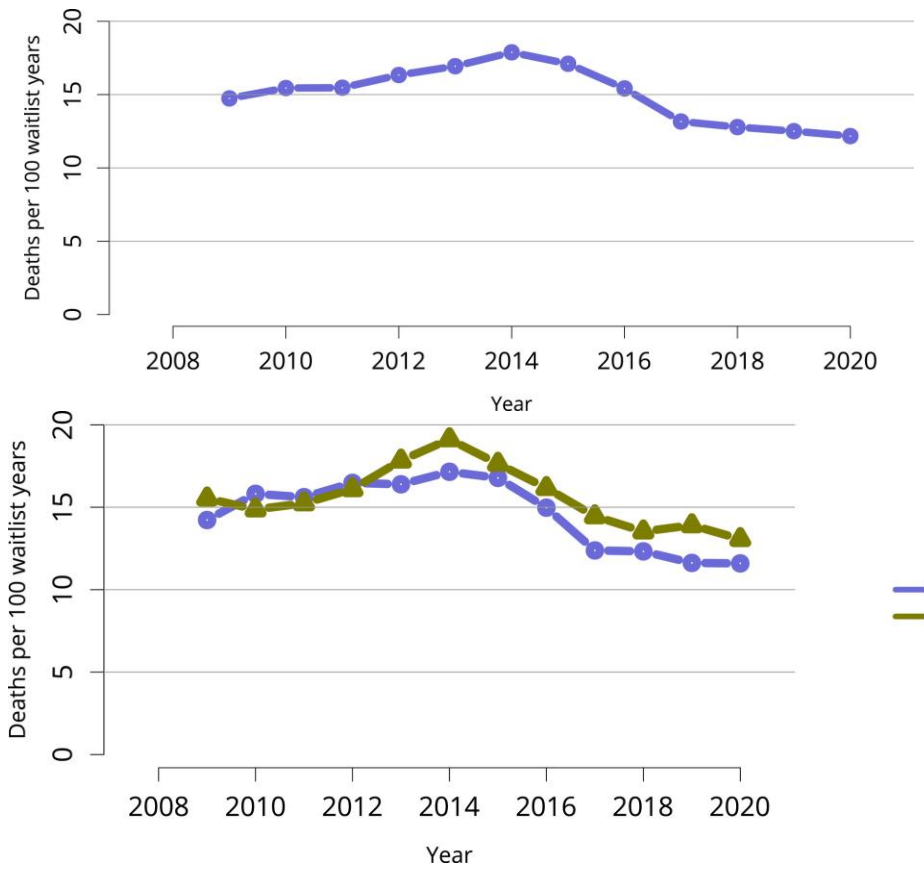
HEPATOLOGY AASLD

Editorial

Obesity and Liver Disease: The New Era of Liver Transplantation

Jorge A. Marrero M.D., M.S., M.S.H.E.

Pre-Transplant Mortality Rates

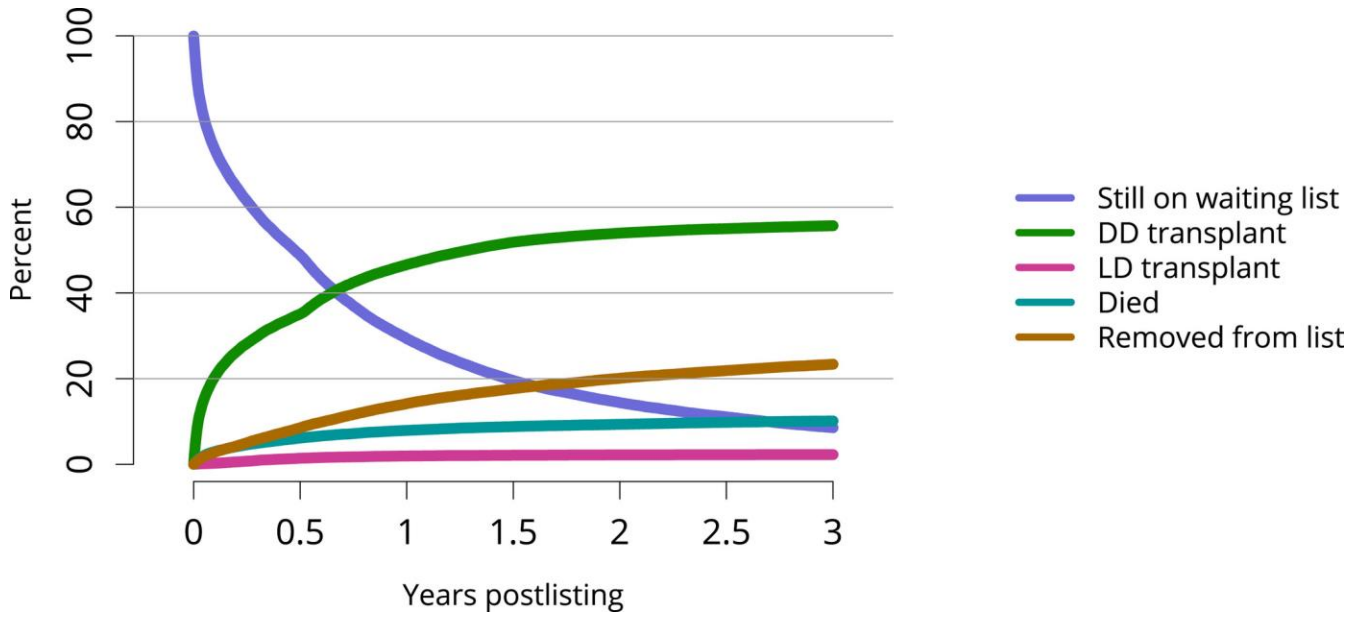


Overall Pre-Transplant Mortality Rate

Higher rates of pretransplant mortality were observed among women than men

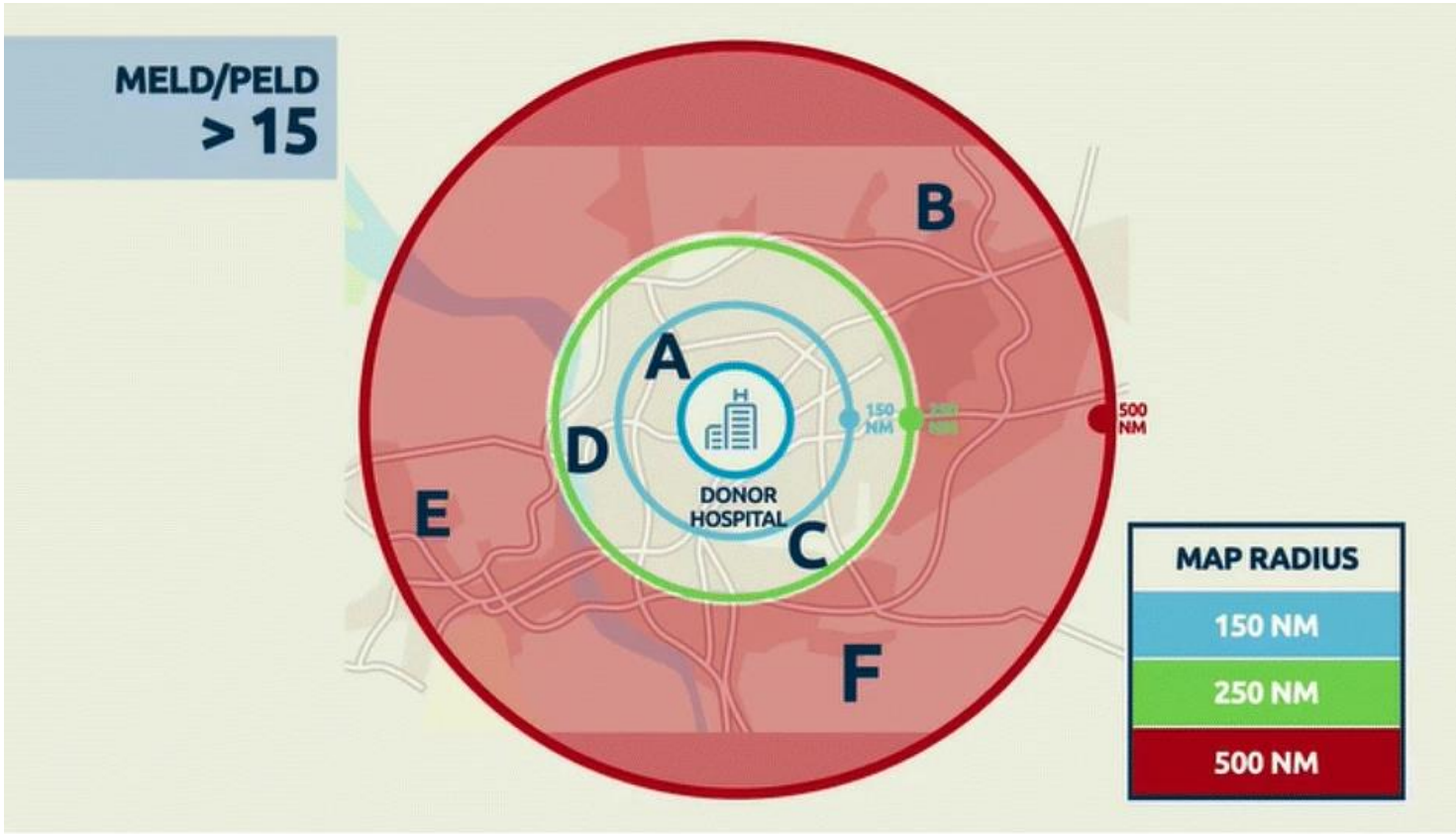
Kwong AJ, et al. Am J Transplant 2022

Three Year Outcomes for Patients Listed in 2017



Kw ong A J, et al. Am J Transplant 2022

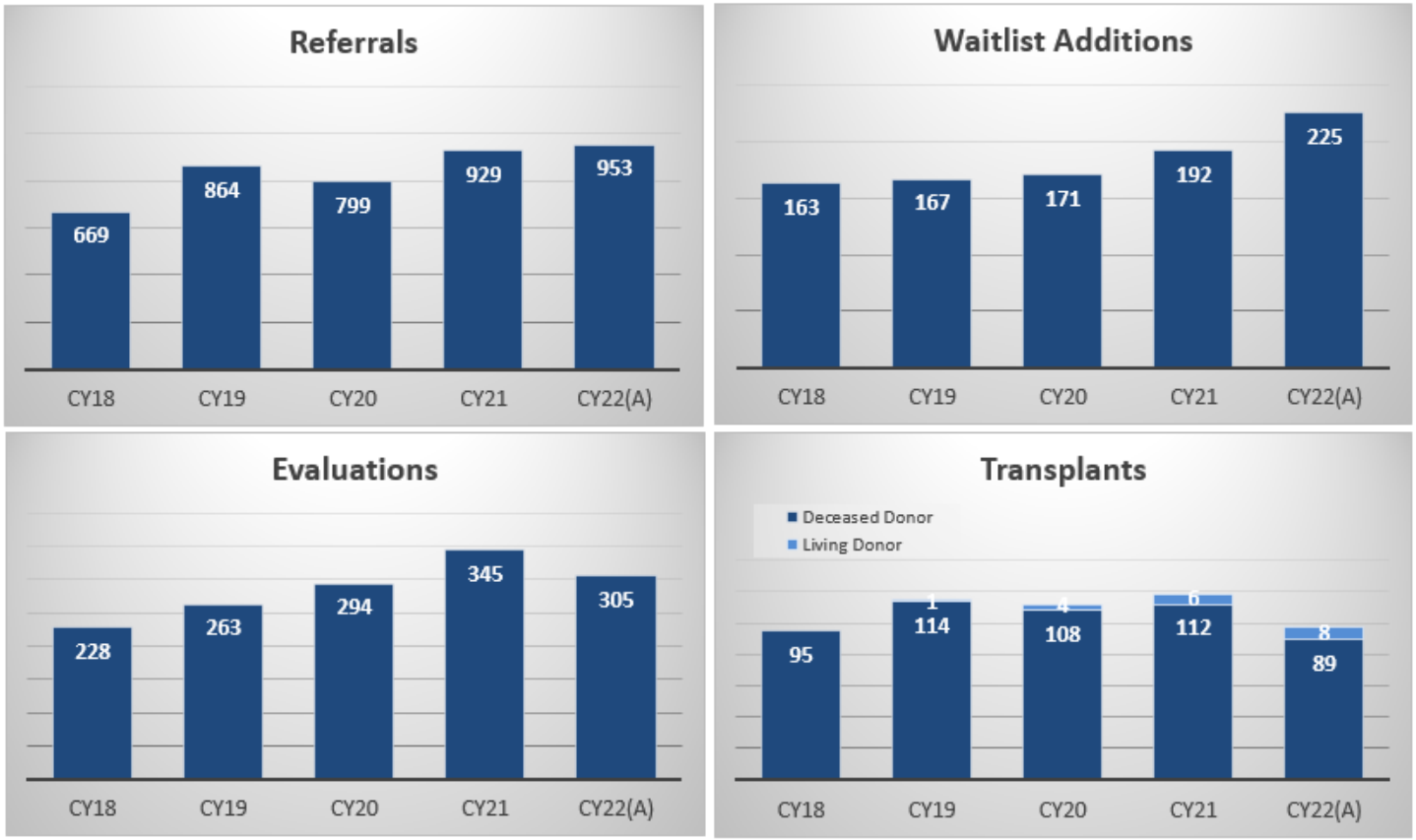
New Acuity Circle Organ Distribution for DCD Donors



Liver Allocation Policy (May 2019)

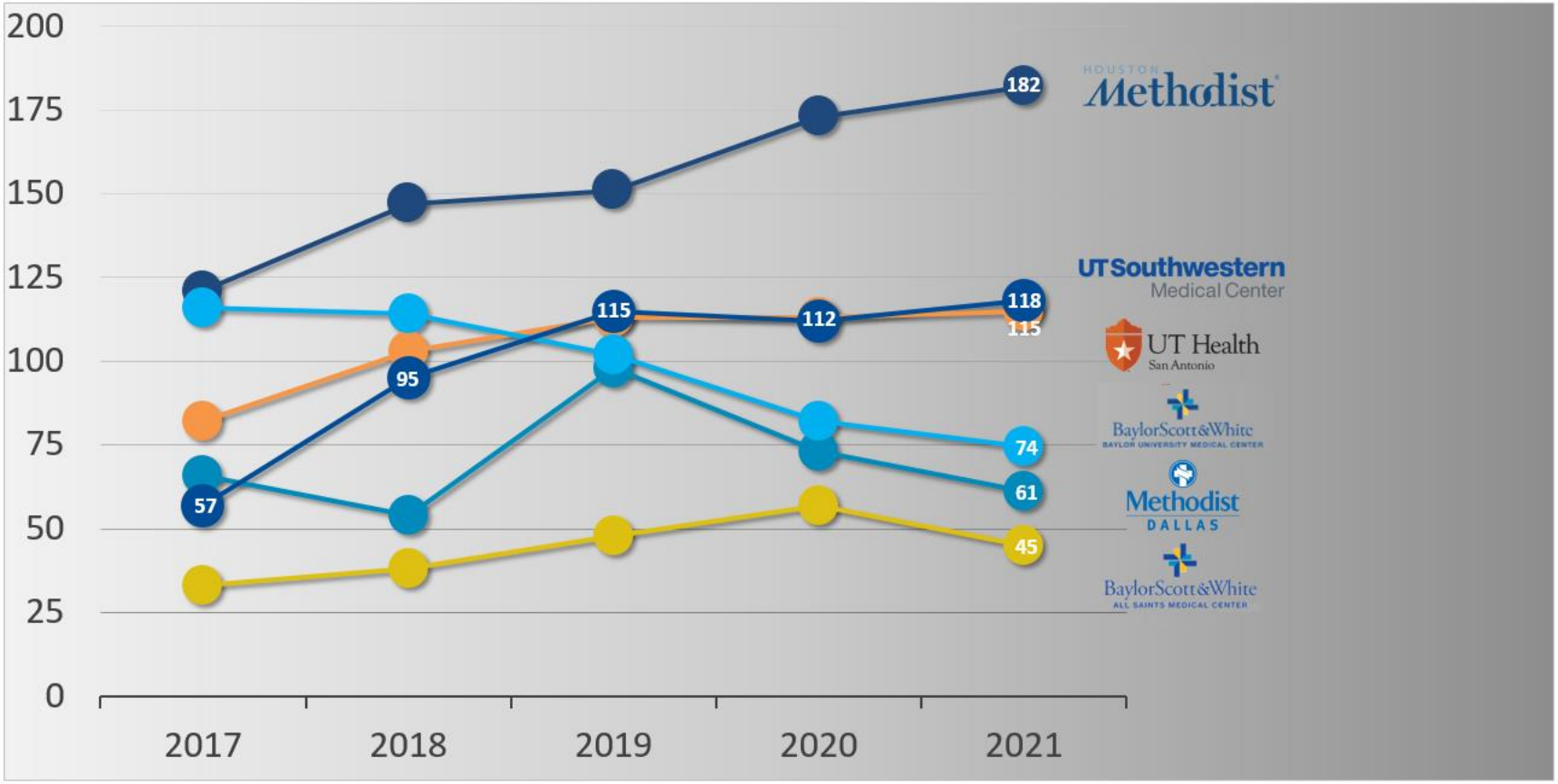
- Candidates with highest medical urgency (**Status 1A and 1B**) listed at transplant hospitals within a radius of 500 nautical miles of the donor hospital
- Candidates with a **MELD or PELD score of 37 or higher** listed at transplant hospitals **within a radius of 150 nautical miles from the donor hospital**
- Candidates with a **MELD or PELD score of 37 or higher** listed at transplant hospitals **within a radius of 250 nautical miles from the donor hospital**
- Candidates with a **MELD or PELD score of 37 or higher** listed at transplant hospitals **within a radius of 500 nautical miles from the donor hospital**
- Repeat for a sequence of progressive offers (candidates at transplant hospitals within 150, 250 and 500 nautical miles of the donor hospital) for candidates with ranges of:
  - **MELD or PELD scores from 33 to 36**
  - **MELD or PELD scores from 29 to 32**
  - **MELD or PELD scores from 15 to 28**

UTSW Liver Transplant: Operational Volumes

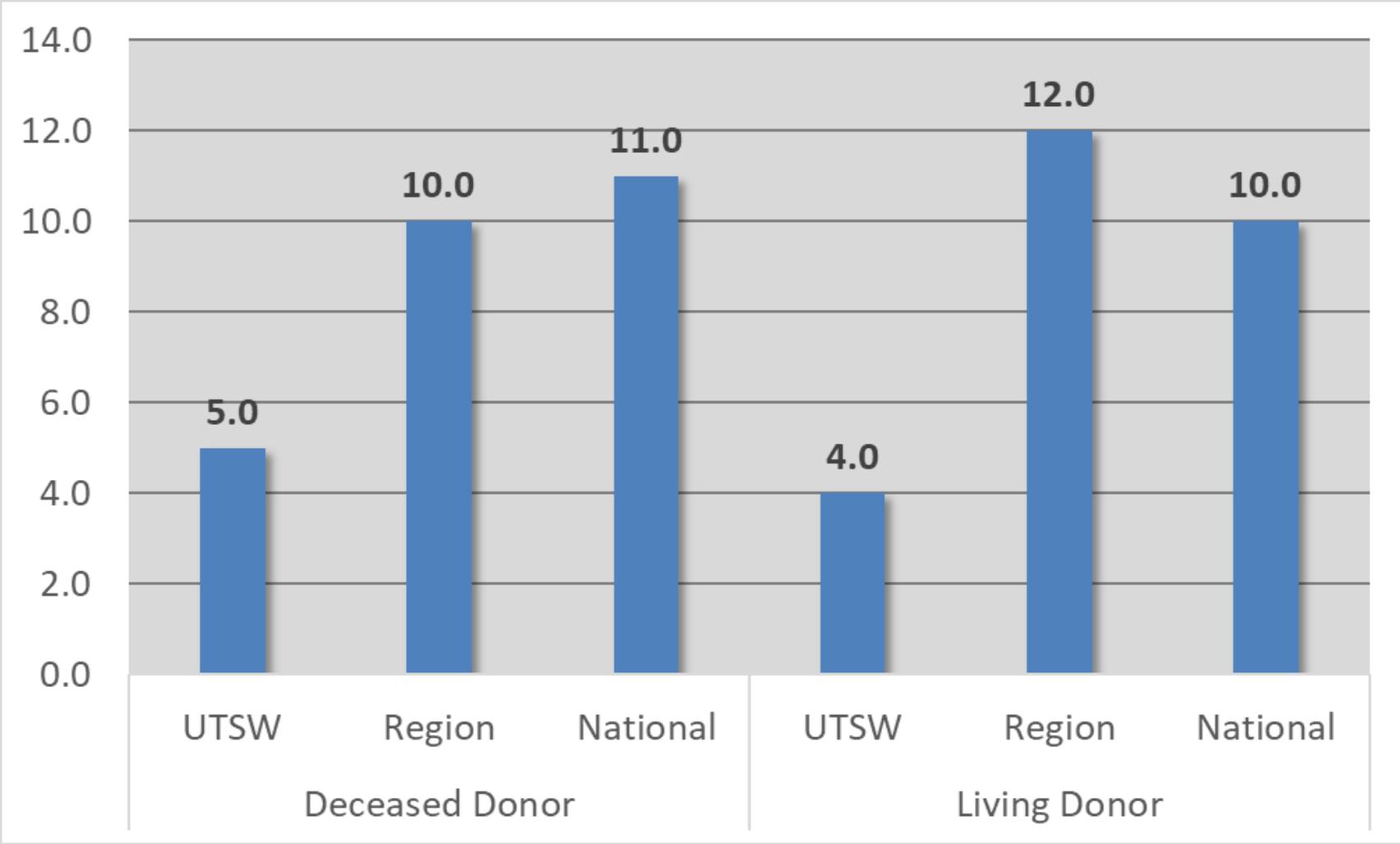


(A) Annualized data through 9/30/22

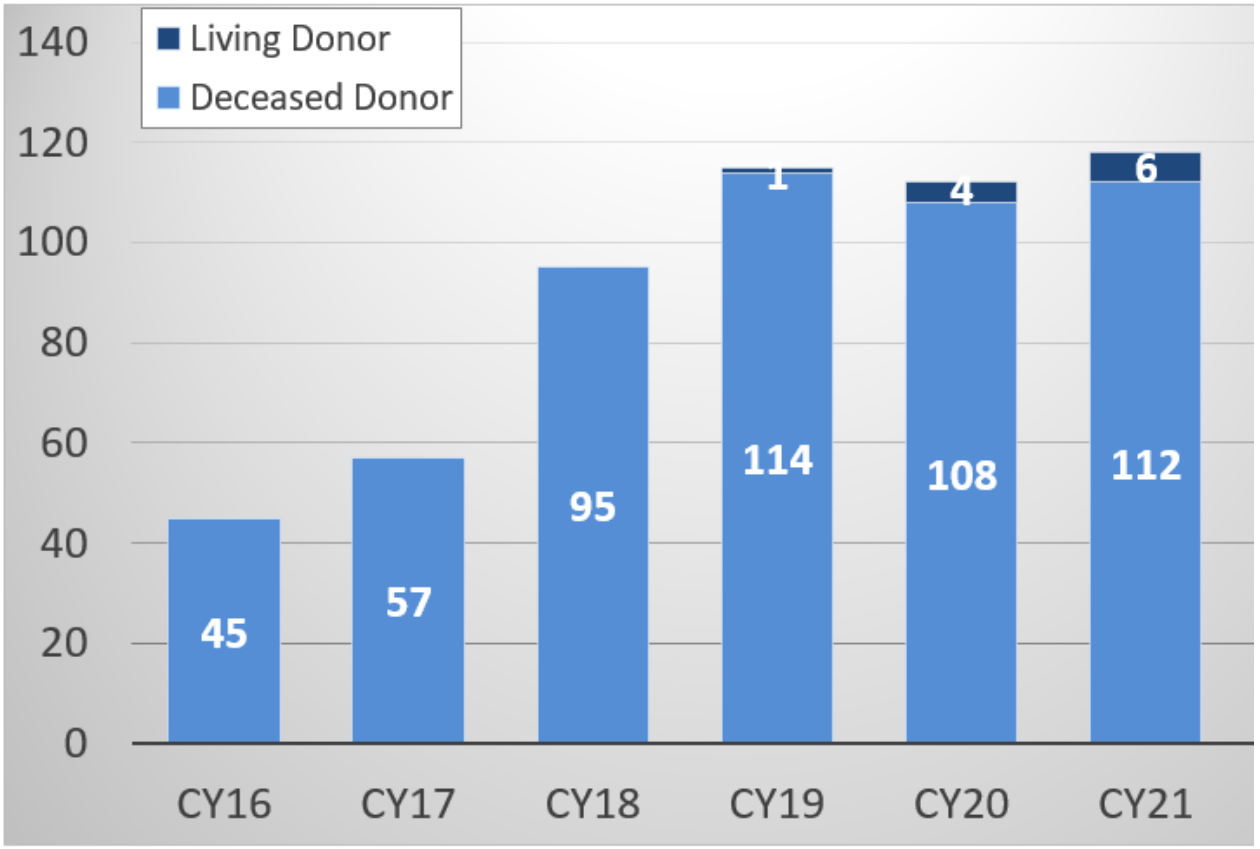
DFW Liver Transplant Trends: Volume



Liver Transplant: Length of Stay



UTSW Liver Transplant: Volumes by Donor Type



Approaches to Expand the Donor Pool

- Living Donor Liver Transplant
- DCD Donors
- Hepatitis C Nat + and Ab + livers
- Older Donors
- COVID positive donors
- HOPE ACT

Transplantation in the USA

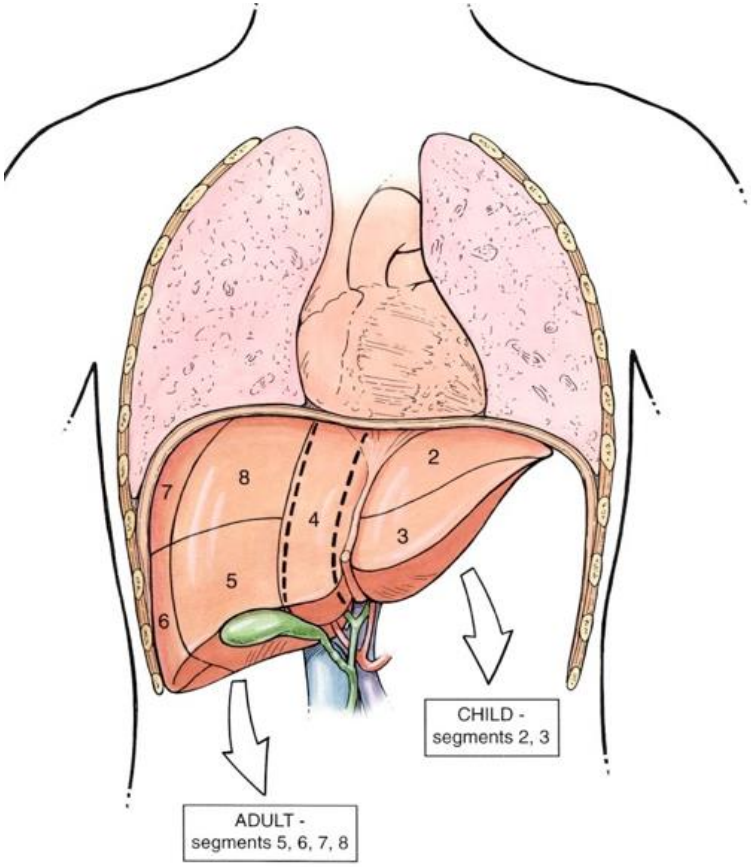
- Is there a need to develop a Living Donor Liver Transplant Program?
  - –Deceased Donor Programs exist
  - –Patient outcomes are excellent

Liver Transplantation – A Limited Resource

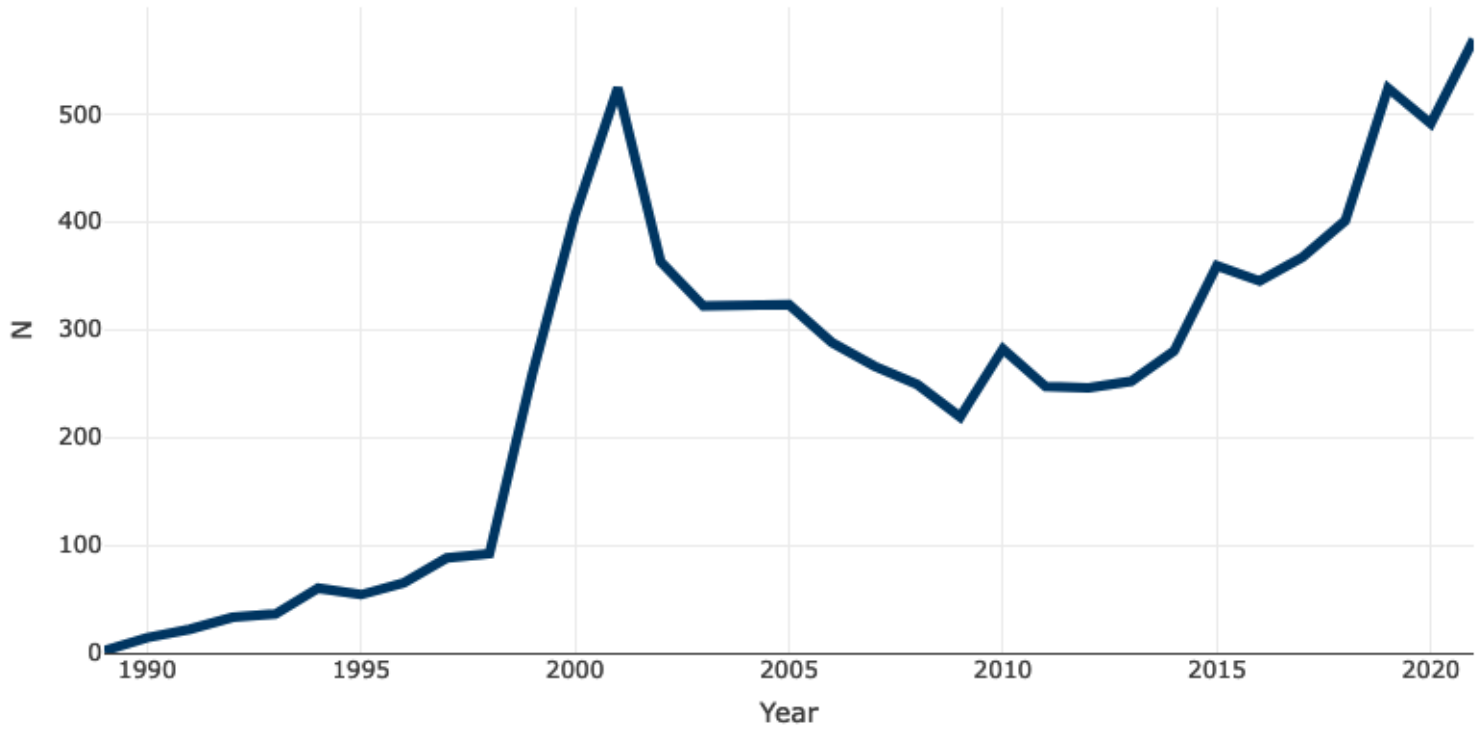
- Consequences
  - About a 25% - 30% chance of never making it to transplant
  - Longer waiting times before receiving a transplant
    - Patients are sicker by the time they receive a liver transplant
    - Increased morbidity post transplant
    - Longer recovery times
  - Not all patients that could benefit reap the rewards of being listed
  - Longer and more difficult recovery time post transplant

Living Donor Liver Transplant

- In healthy individuals, the liver has extra capacity
- Liver segments regenerate
- Transplanting a partial liver restores function in the recipient
- The principles of beneficence, autonomy, and justice provide the ethical foundation of the procedure



Living Donor Liver Transplants by Year



- 569 LDLTs performed in the USA in 2021
- Accounted for ~5% of the total number of transplants

Kw ong A J, et al. Am J Transplant 2022

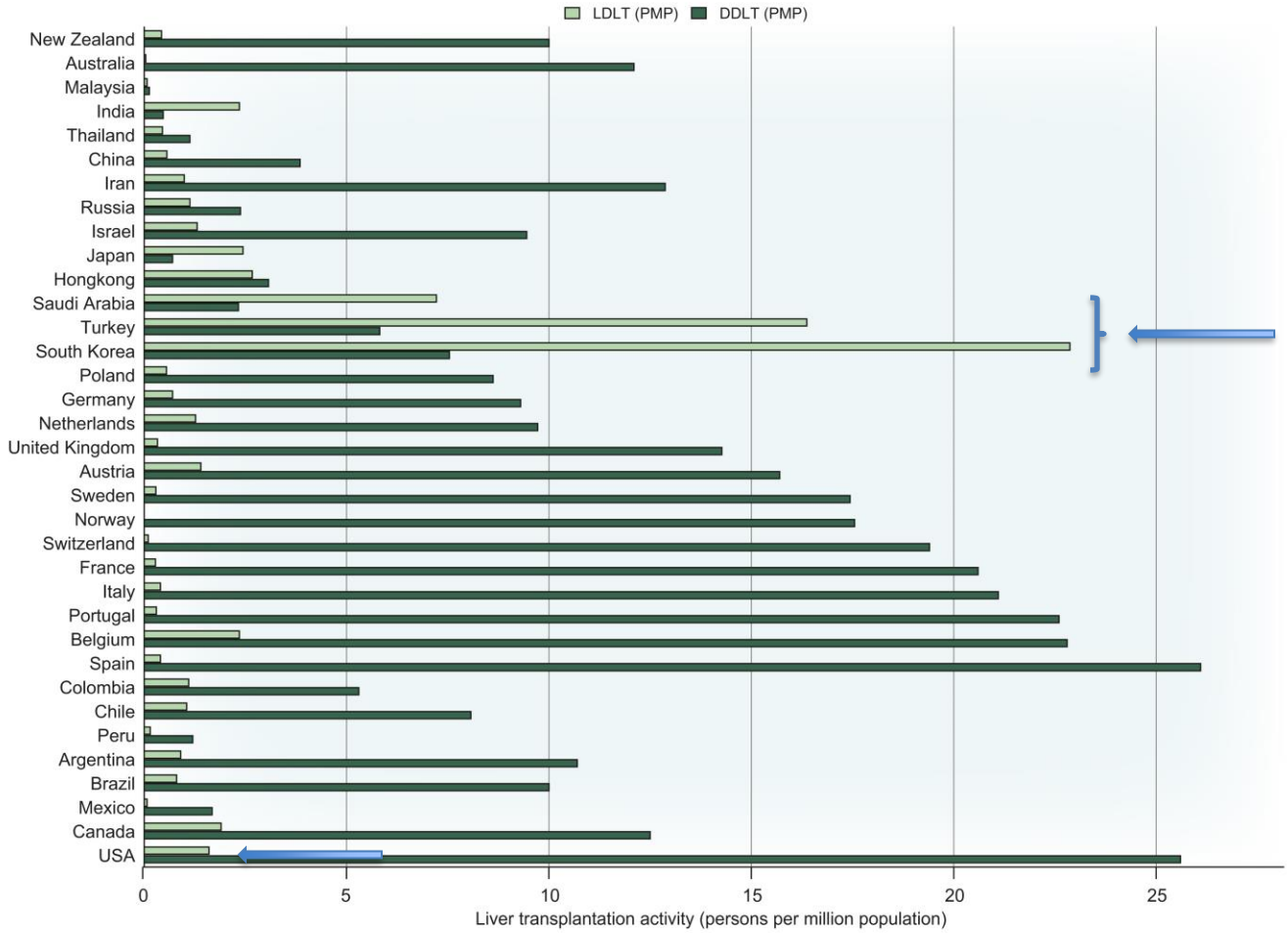
Living Donor Liver Transplantation – An Alternative Option

ADVANTAGES	DISADVANTAGES
Decreased waitlist mortality	Short term risk to donor
Decreased waiting time	Long-term risk to donor
Transplant before being critically ill	Increased risk of biliary complications
Elective, planned surgery	Increased risk of vascular complications
Minimal cold ischemia time	Decreased hepatic reserve
Adds to donor pool	
Long term financial benefit	

Reasons Why LDLT Numbers Remain Low

- Unfamiliarity with the procedure
  - Patients and caregivers
  - Providers
  - Insurance companies have been reluctant to pay in the past BUT no longer true
- Misinformation about the procedure
  - Regarding risks
  - Who can donate
  - Who is eligible for transplant and when to donate
  - Long term consequences of donation
- Fear of a poor outcome
  - Adverse publicity
  - Effect on the transplant program

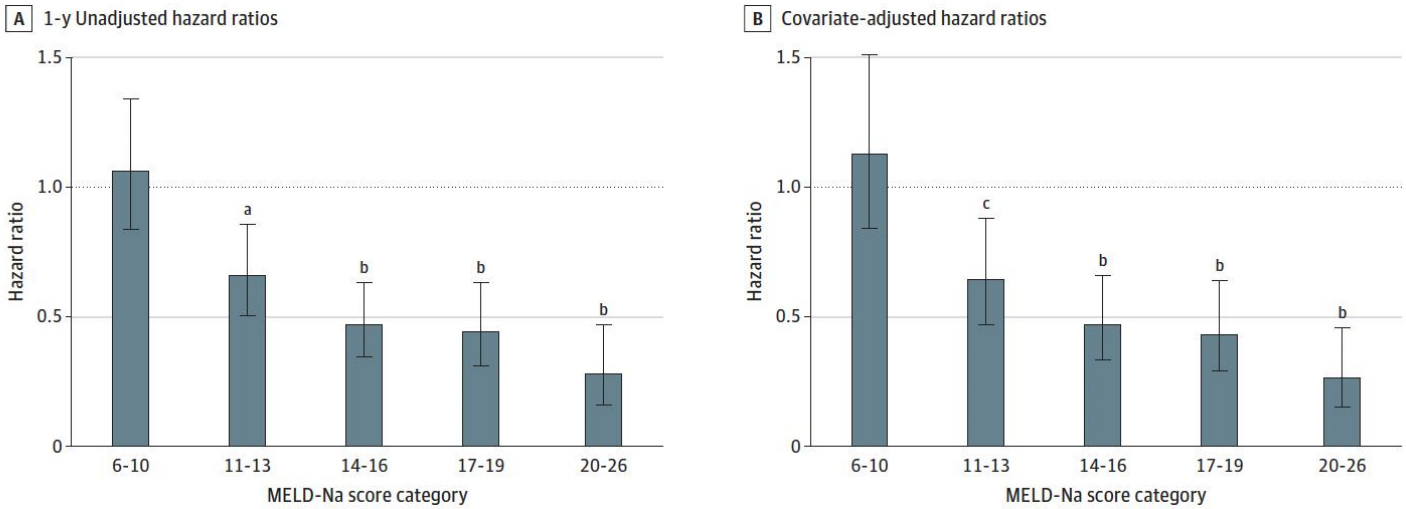
Starkly Different Picture Around the World



Rela M, Rammohan A J Hepatol Volume 75, ISSUE 4, 975-980 , 2021

One year Mortality Risk Across MELD-Na for LD transplant vs Waiting on the List

- Case Controlled Retrospective Study
- SRTR database (2012-2021) – patients who received LDLT vs assigned to the waiting list
- Significant survival benefit at a MELD-Na score as low as 11,with a 34% (95% CI, 17.4%-52.0%)



Jackson WE et al JAMA Surg. doi:10.1001/jamasurg.2022.3327

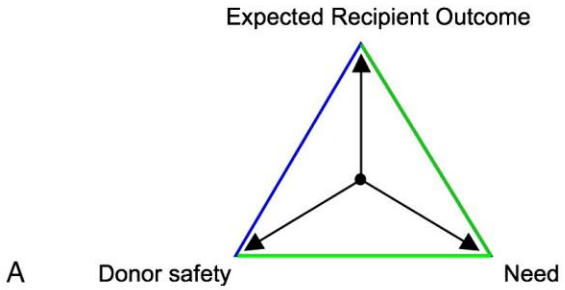
Who is eligible for LDLT

- Anyone who is being considered for transplant
- Patients with any MELD – especially if < 26
- Patients low on the waiting list but with significant decompensation
  - –Patients with liver tumors
- Discussed with all patients at the time of initial evaluation
- Discussed in general hepatology clinic with any patients with cirrhosis and decompensation

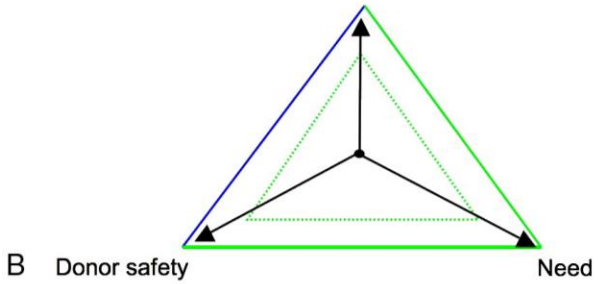
Donor Eligibility

- 18-55
- BMI <30
- No prior hepatic surgery
- No malignancy hx > 5 years
- Able to obtain labs q6 months for 2 years
- FLR >/- 30%
- GWR - at least 0.7

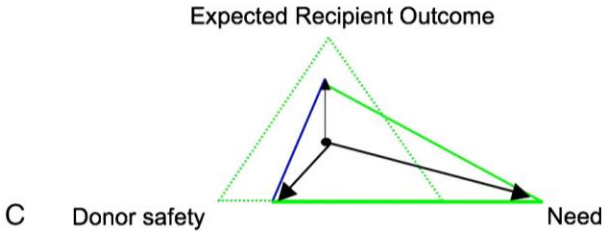
Ethical Considerations in Living Donation



Average Scenario (adult)



Average Scenario (pediatrics)



Scenario where deceased donation is not possible

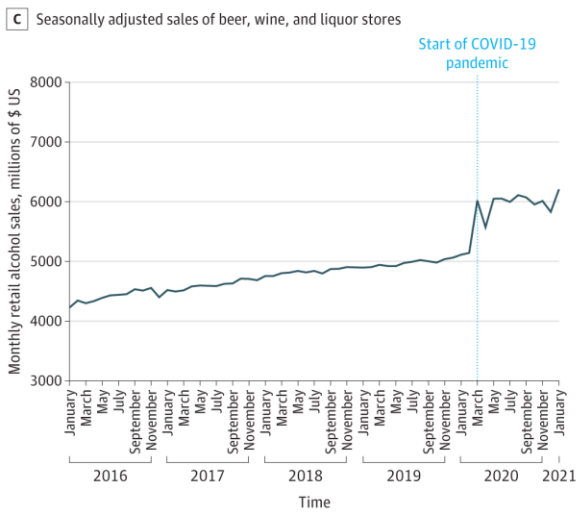
Miller CM Transplantation Reviews Volume 22 (3), 2008, 206-209

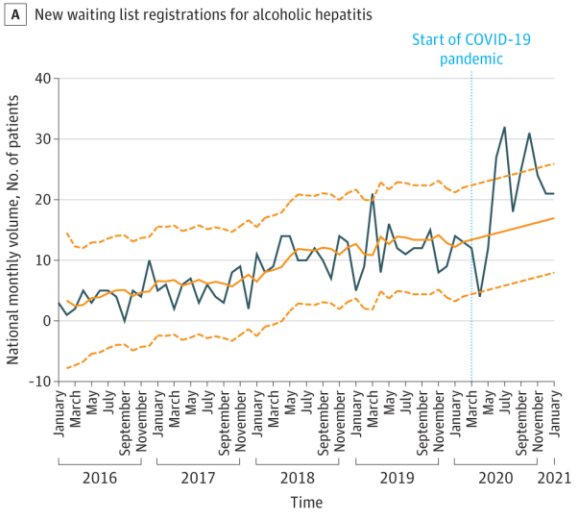
Impact of COVID on MELD-Na Scores at Listing

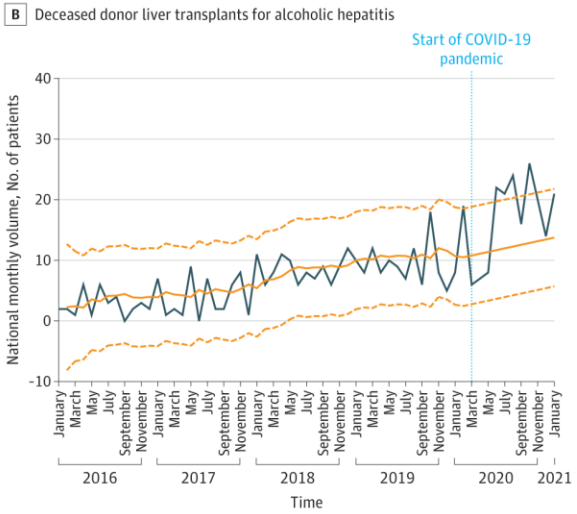
- 40% of listings due to ALD
- Accounted for more listings than NASH and HCV combined during the pandemic
- Over 20% of wait list additions had a MELD-Na of 30 or higher
- Percentage of patients with ALD listed or transplanted with a MELD-Na > 30 significantly increased by over 15% during the pandemic
- ALD had a 50% higher probability of LT rate than patients with other liver disease

Cholankeril et al Hepatology Volume 74 (6)December 2021 Pages 3316-3329

Increased Listing and Transplants for Alcoholic Hepatitis – Impact of COVID



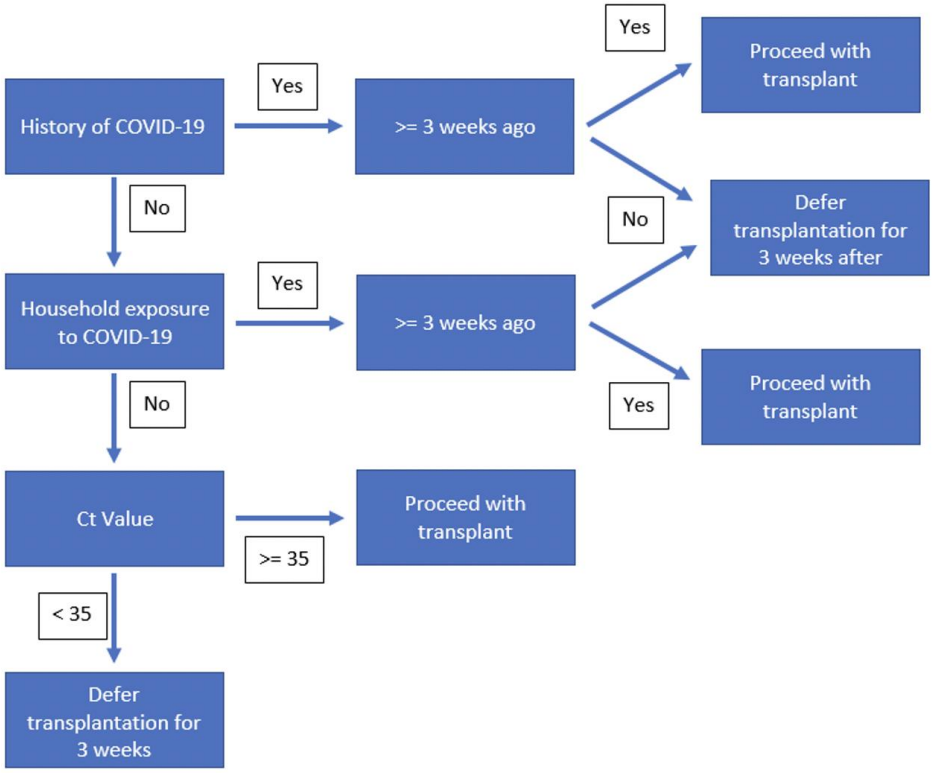




Anderson et al, JAMA Netw Open. 2021;4(10):e2131132

Short-term liver transplant outcomes from SARS-CoV-2 lower respiratory tract NAT positive donors

Ricardo M La Hoz [1], Arjmand R Mufti [2], Parsia A Vagefi [3]

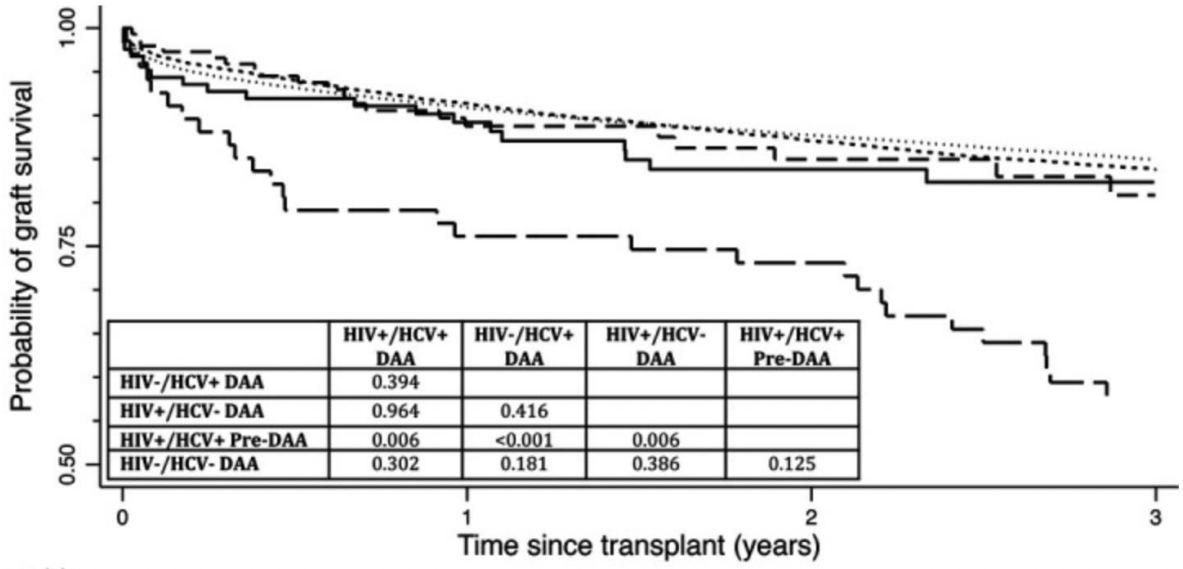


RECIPIENT ALGORITHM

La Hoz et al Transplant Infect Dis. 2022; 24:e13757

HOPE Act

- HIV Organ Policy Equity Act (HOPE Act) in 2013
- Permitted the transplantation of organs from HIV+ donors into HIV+ recipients
- Expanded the donor pool



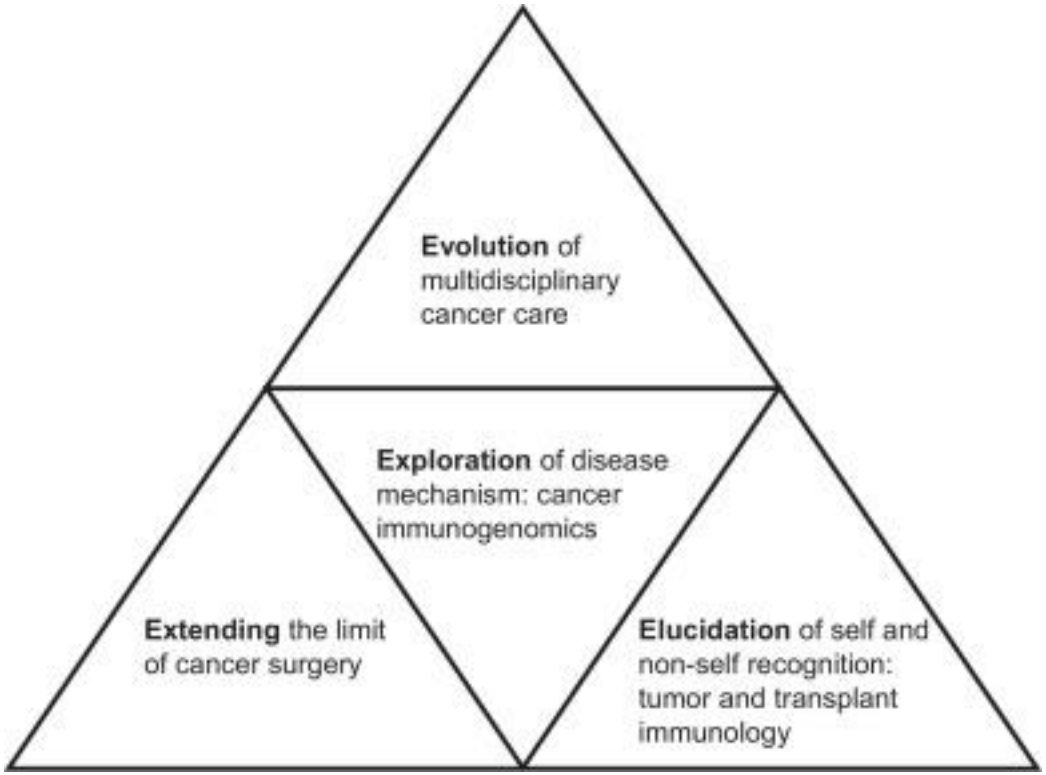
	HIV+/HCV+ DAA	HIV-/HCV+ DAA	HIV+/HCV- DAA	HIV+/HCV+ Pre-DAA
HIV-/HCV+ DAA	0.394			
HIV+/HCV- DAA	0.964	0.416		
HIV+/HCV+ Pre-DAA	0.006	<0.001	0.006	
HIV-/HCV- DAA	0.302	0.181	0.386	0.125

HIV+/HCV+-coinfected LT, 3-year survival **84.0% (DAA era)** and **62.5% (pre DAA era)**

Cotter et al Transplant Direct 2021 Jul; 7(7): e

Transplant Oncology

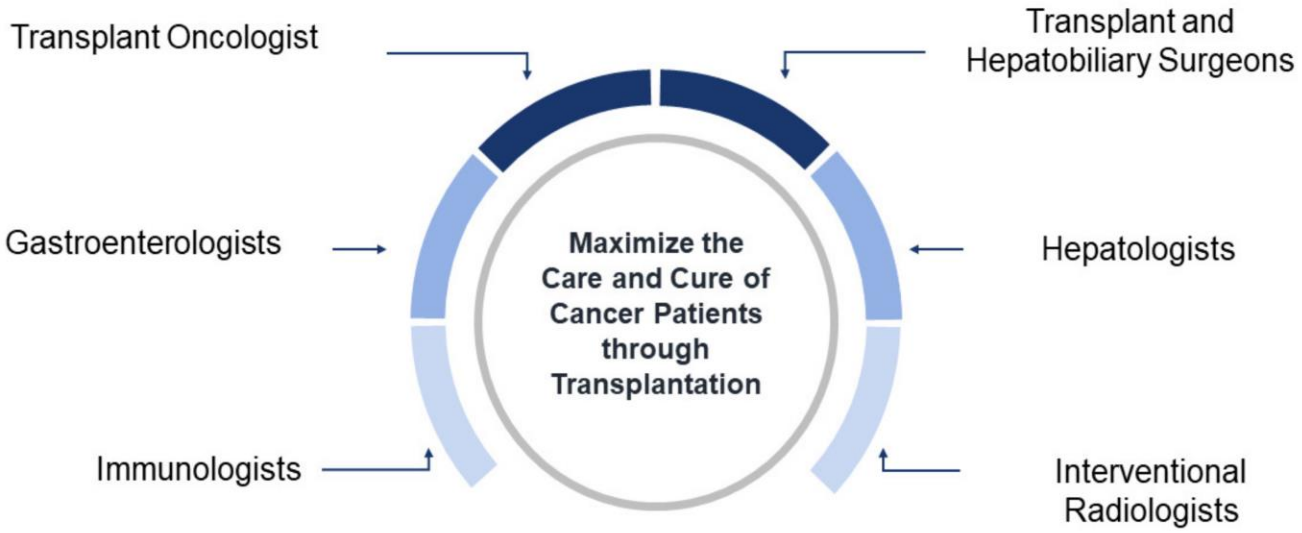
- What is transplant oncology?
- Represents a paradigm shift in the treatment and research of hepatobiliary cancer



Hibi T and Sapisochin G Surgery Surgery, 165 (2); Feb 2019, 281-285

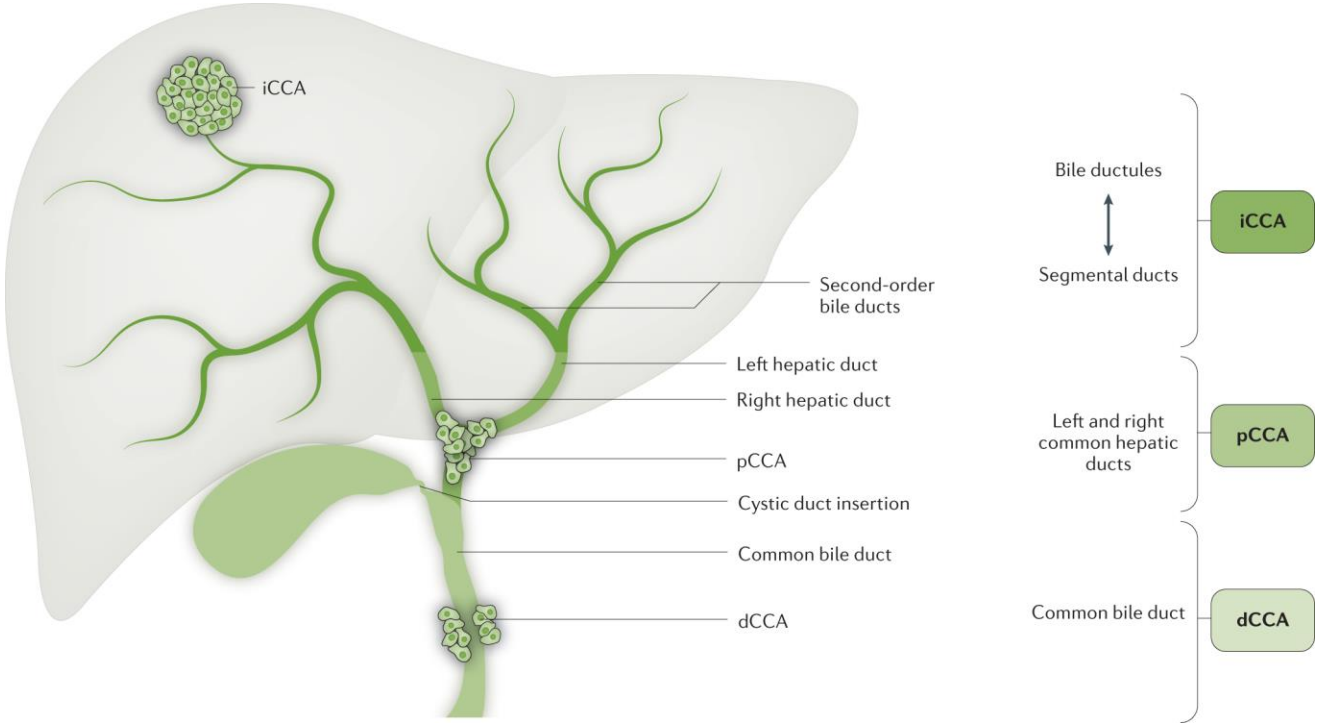
Transplant Oncology

- Multidisciplinary collaborative approach to care



Abdelrahim M et al Cancers 2021, 13(19), 4911

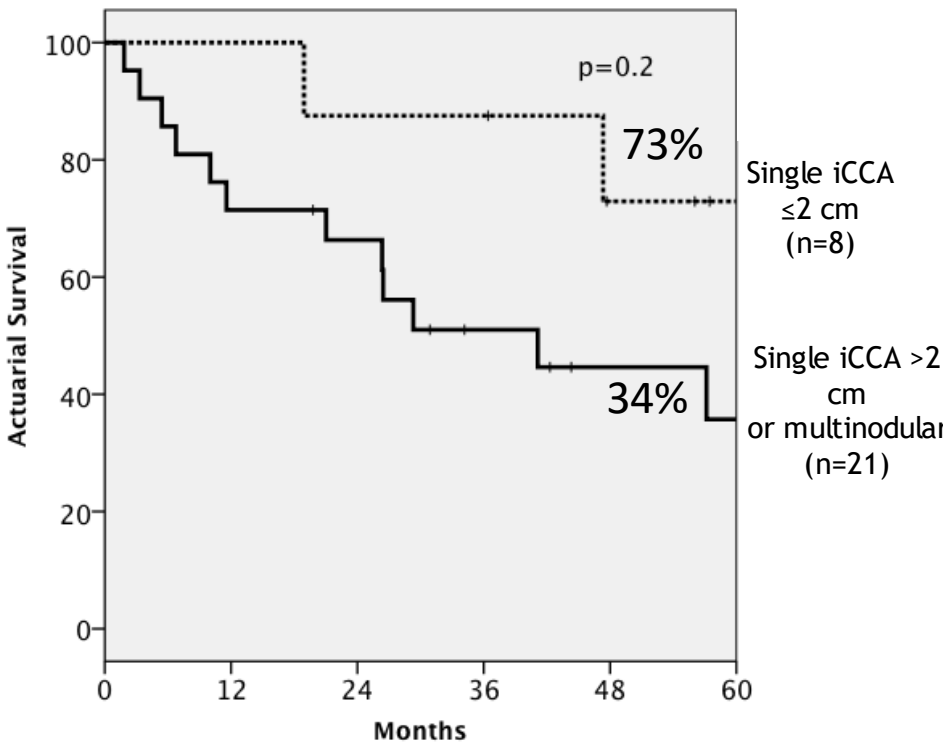
Cholangiocarcinoma

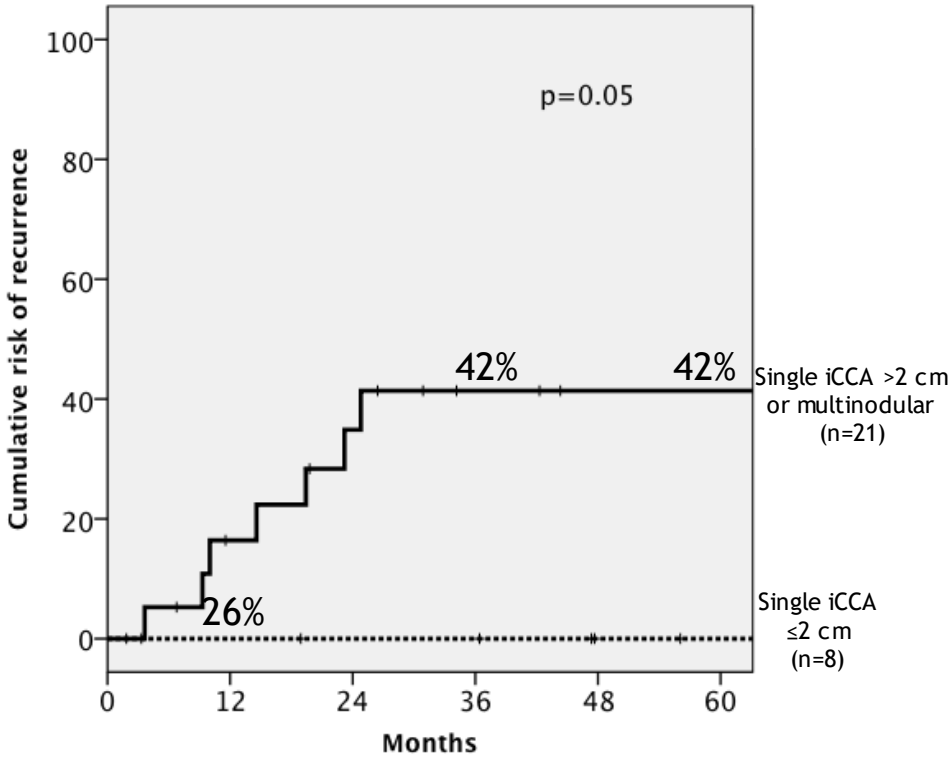


Resection vs Transplantation?

Valle JW et al *Lancet* 2021; 397: 428–44

Liver Transplantation for Intrahepatic Cholangiocarcinoma (iCCa)

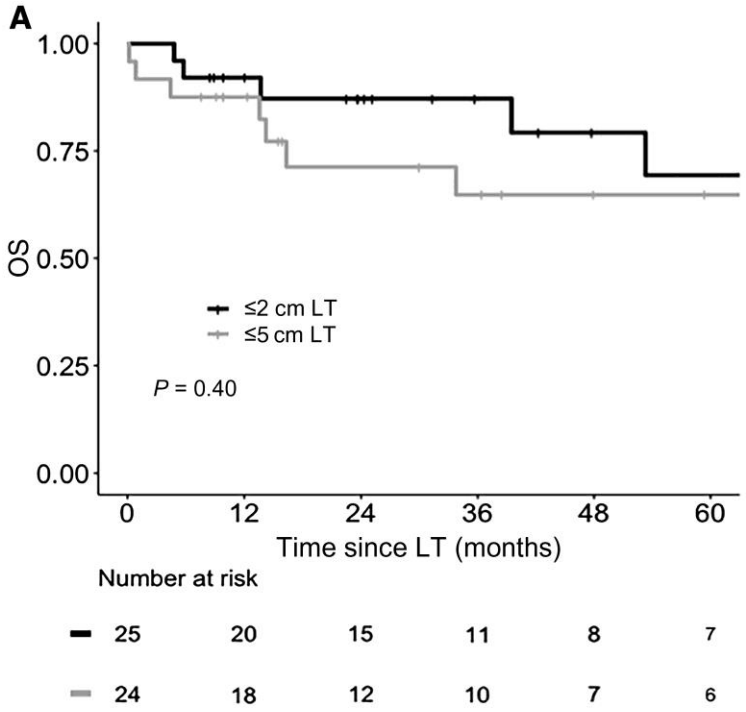




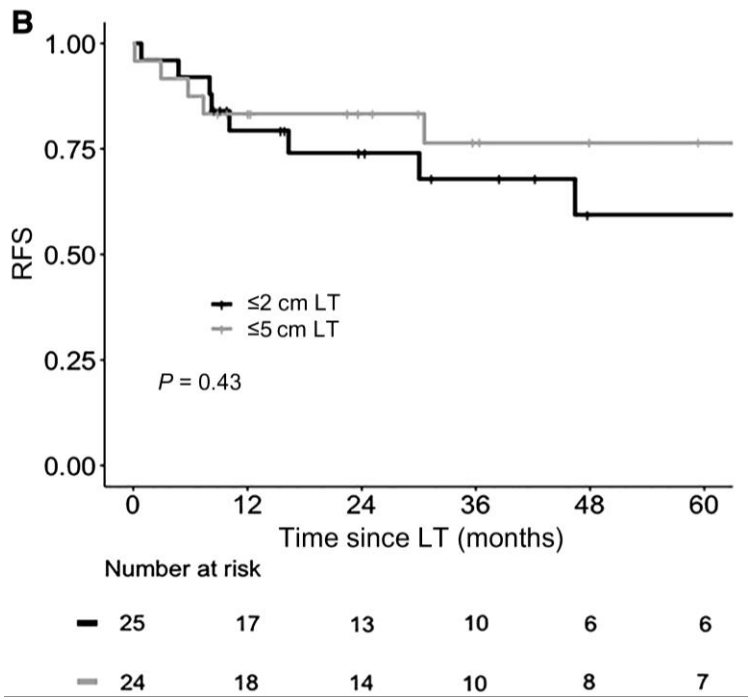
Cirrhotic, unresectable patients

Sapisochin G, et al. Am J Transpl 2014

Liver Transplantation for Tumors < 2 cm and 2-5 cm



Patient Survival



Disease Free Survival

De Martin et al Liver Transpl 26 (6), 785-798

Cholangiocarcinoma Protocols at UTSW

UT Southwestern Medical Center	DEPARTMENT STANDARD OPERATING PROCEDURE

LIVER TRANSPLANTATION FOR UNRESECTABLE HILAR CHOLANGIOCARCINOMA

Liver Transplant – "Very Early (<2cm)" Intrahepatic Cholangiocarcinoma in Cirrhotic, Unresectable Patients Protocol

Liver Transplantation in Locally Advanced, Unresectable, non-Metastatic Intrahepatic Cholangiocarcinoma Treated with Neoadjuvant Systemic Therapy

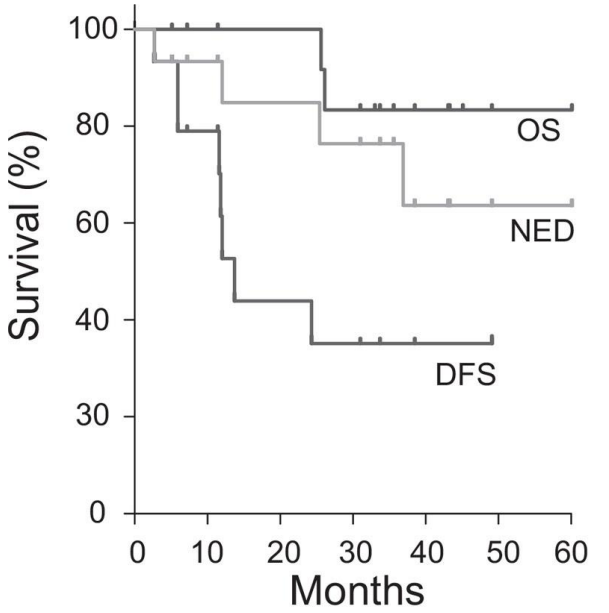
Liver Transplant for Colorectal Cancer with Unresectable Hepatic Metastases

- Colorectal cancer (CRC) - Third most common malignancy worldwide
- ~50% develop hepatic metastases
- Liver resection is considered the only curative treatment option in colorectal liver metastases (CRLM)
- Only 20% of the patients with CRLMs are candidates for liver resection
- BUT 60% to 70% have recurrence within 3 years

Two Prospective Trials

- SECA-1 Trial
  - Estimated 5-year survival 60%
- SECA-2 Trial
  - More stringent Criteria
  - Survival at 1, 3, and 5 years were 100%, 83%, and 83
  - Disease-free survival at 1, 2, and 3 years were 53%, 44%, and 35

Oslo Score	
Largest lesion diameter > 5.5 cm	1
Pre-transplant CEA > 80 µg/l	1
Progression on chemotherapy	1
Time interval: diagnosis to transplant < 24 months	1
Sum score	0-4



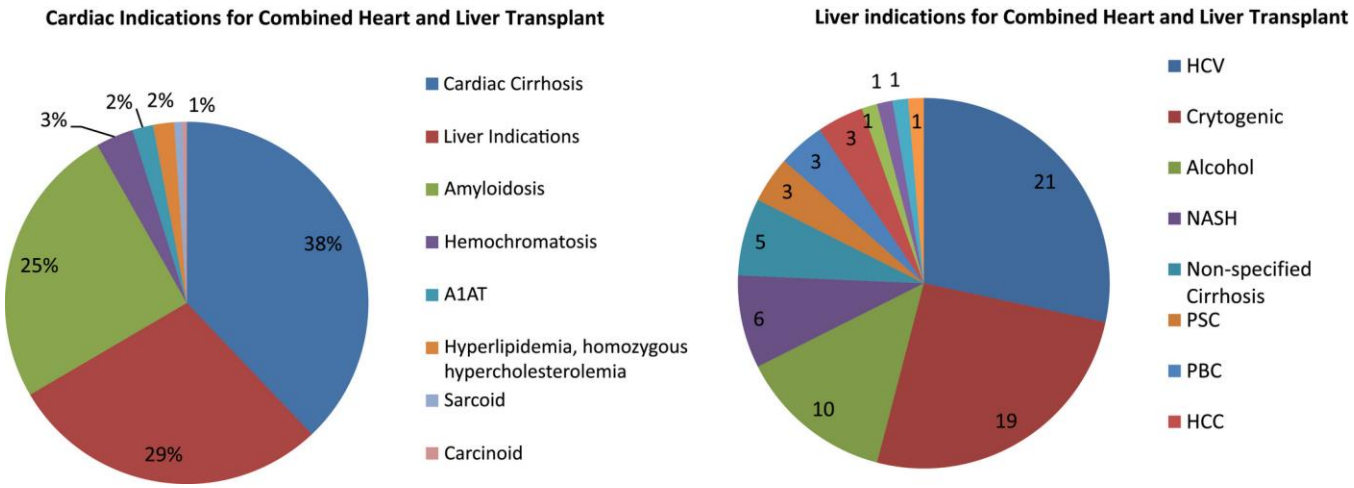
Months	0	6	12	18	24	30	36	42	48	54	60
OS	15	14	12	12	12	10	6	5	2	1	2
DFS	15	11	6	5	5	4	2	1	1	0	0
NED	15	13	11	9	9	9	5	4	2	1	1

Hagness M et al Ann Surg 2013
Dueland S, et al. Ann Surg 2019

UT Southwestern Medical Center	DEPARTMENT STANDARD OPERATING PROCEDURE

LIVER TRANSPLANT – COLORECTAL LIVER METASTASES (CRLM) PROTOCOL

Clinical Indications for CHLT



- Three main indications for CHLT
  - **a) Primary heart disease with cirrhosis secondary to chronic outflow obstruction**
  - b) History of hereditary transthyretin amyloidosis
  - c) Primary liver indication with concurrent heart disease

Zhao et al. Clinical liver Disease 13 (6) June 2019

Etiologies of Congestive Hepatopathy

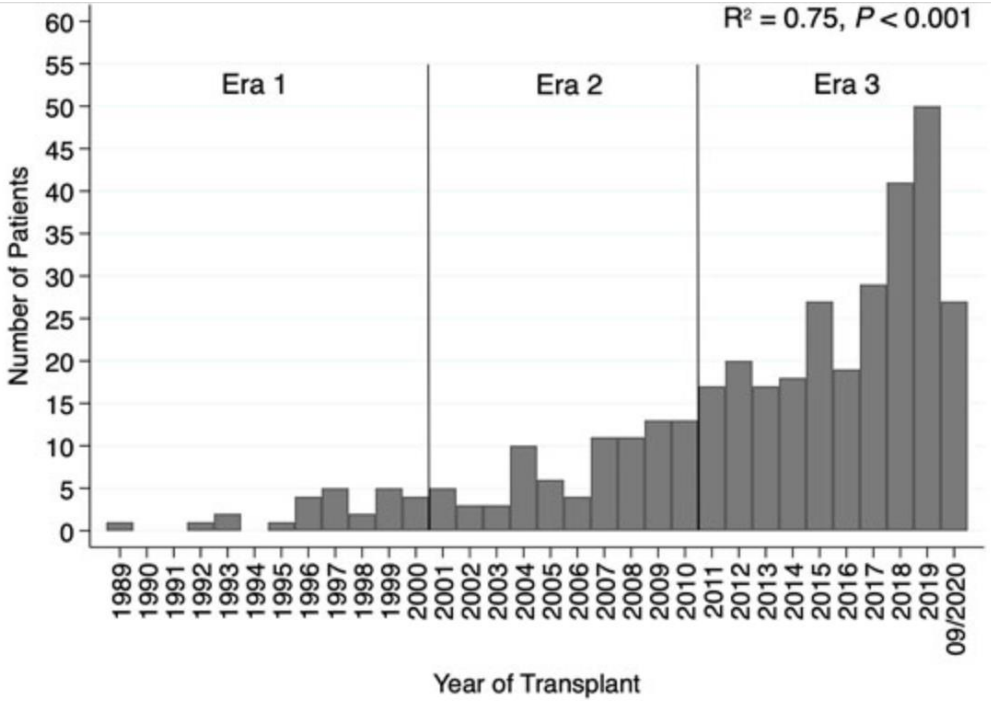
- Burden of congestive cardiac hepatopathy is unknown
- No epidemiological studies
- No recognized definition
- Heterogeneity of etiologies
- Observed in CHD including post Fontan procedure but also in chronic heart failure in elderly

Category	Etiologies
Congenital Heart Disease	**Single-ventricle physiology after Fontan surgery** D-transposition of the great arteries after atrial switch repair Eisenmenger syndrome Repaired tetralogy of Fallot withPR Partial atrioventricular septal defect with TR and/or pulmonary hypertension
Tricuspid Regurgitation	Severe PAH Carcinoid tumor with liver mets
Left Heart Failure	Ischemic / Non-ischemia CM
Constrictive Pericarditis	Idiopathic/Viral Post XRT (e.g., post Hodgkin/breast cancer) Connective tissue disorder Miscellaneous
Right Ventricular Failure	Ischemic CM/Mitral Stenosis /Cor Pulmonale

Prevalence of Patients with Fontan Circulation

- Growing population
  - >1,000 single-ventricle patients undergo a Fontan procedure in the U.S annually
  - Represents 4.1% of all pediatric cardiac surgical procedures performed annually
  - Total of 30K Fontan patients in the US
  - Population is expected to double in the next 20 years conservatively
  - 20-year overall survival was 90.5% in largest North American study
  - 1 in 5 patients with Fontan expected to require a transplant after 20 years

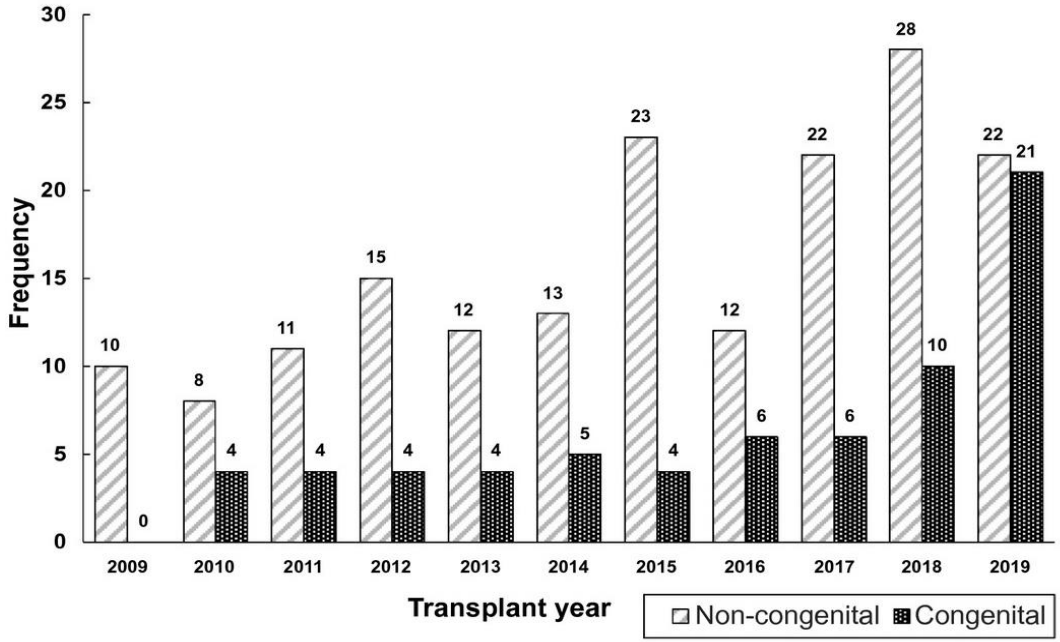
CHLT in different eras



Eras 1 and 2	Era 3
Restrictive/Infiltrative CM	Congenital Heart Disease
Lower median MELD (13.5)	Higher median MELD (16)
Longer Median waitlist time (128 days – era 2)	Shorter median waitlist time (82 days)

Alexopoulos et al. Transpl Int 2022, Vol 35

Annual Trends of Frequency of CHLT (2009-2019)



- Annual increase in all transplanted groups (UNOS Database 2009-2020)
- But disproportionate increase in frequency of the CHD HLT
  - Increased >5-fold over the past decade
  - Average of 4 transplants (2010-2015) → 21 (2019)

Cotter TG Hepatology 2020; 73: 1464-1477
Kenny LA Ann CT Surg 2018; 7: 152-159

Ex-Vivo Normothermic Machine Perfusion

A OCS Liver components

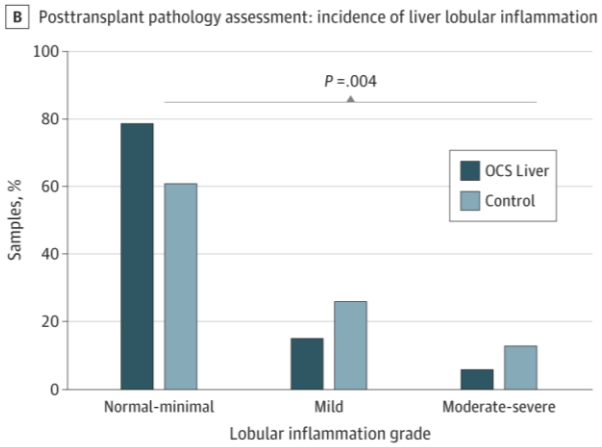
OCS Liver console

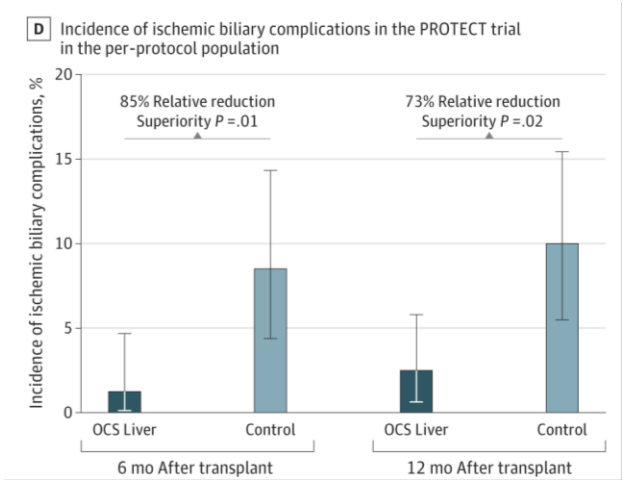
OCS Liver perfusion module

OCS Liver bile salts

Markmann et al *JAMA Surg. 2022;157(3):189-198*

Ex-Vivo Normothermic Machine Perfusion



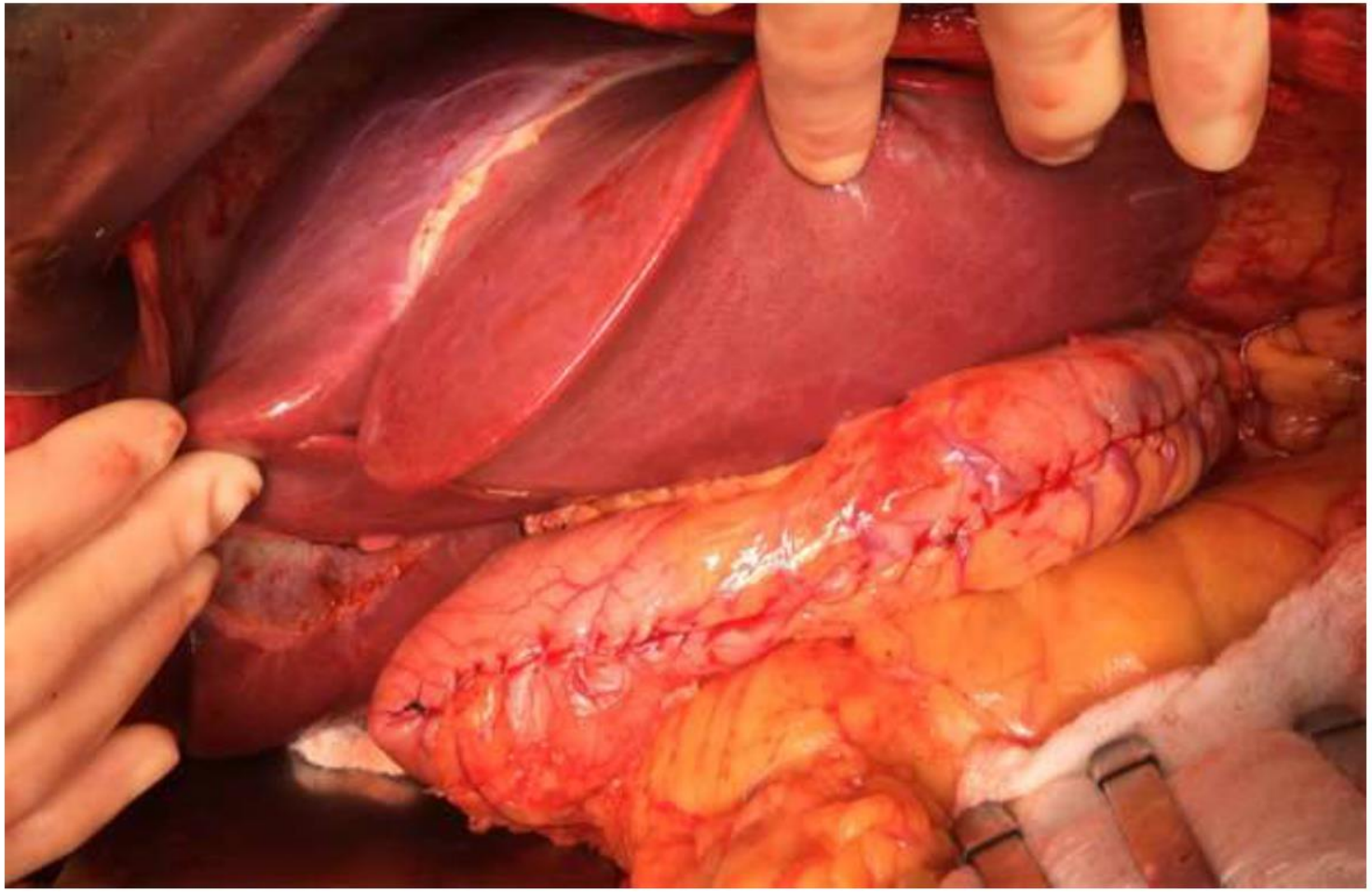


- x2 Rate of DCD donor Liver utilization
- 43% Reduction of severe post transplant complications

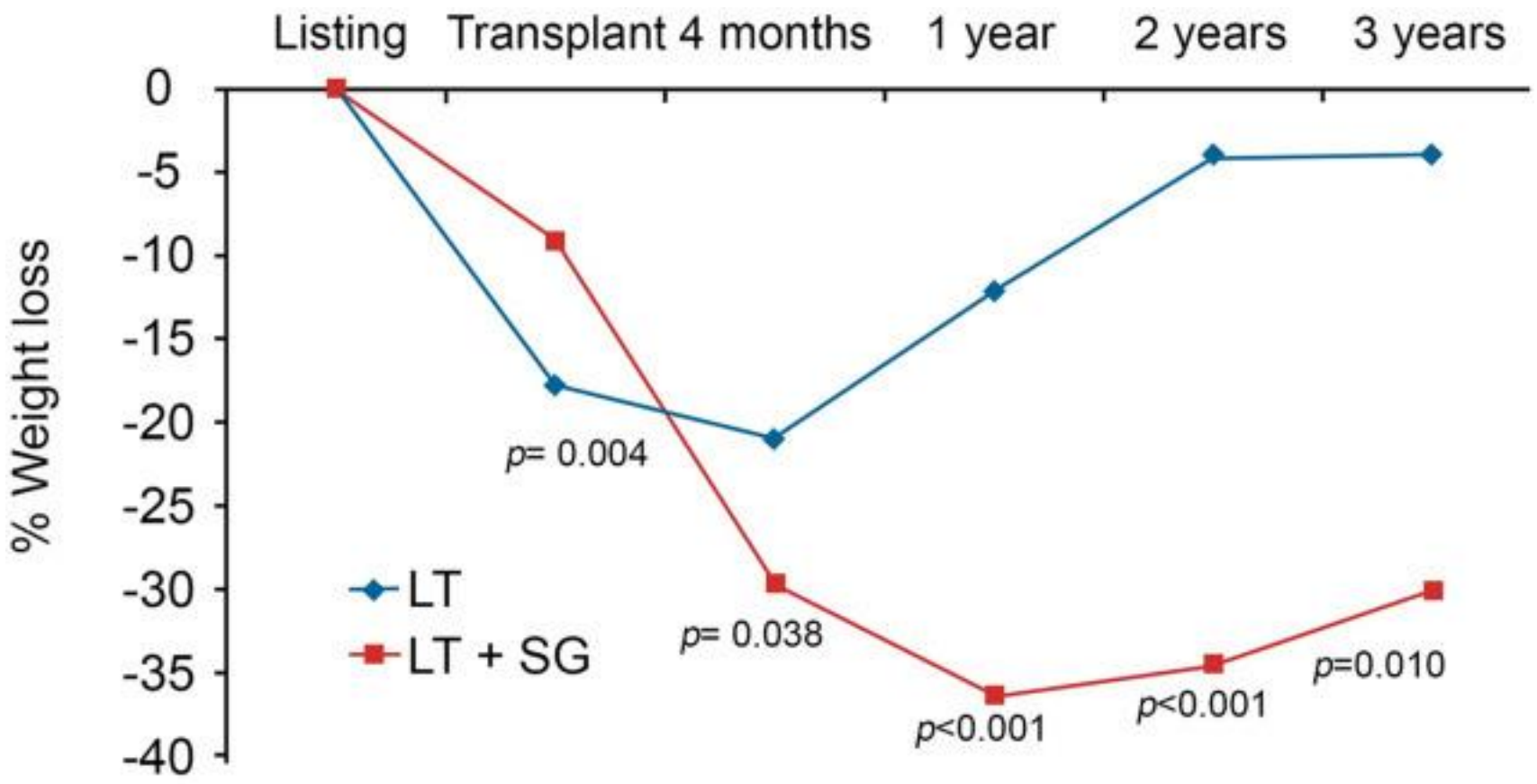
- 84% Reduction in long-term biliary complications

Markmann et al *JAMA Surg. 2022;157(3):189-198*

Long-term Outcomes of Simultaneous Liver Transplant and Gastric Sleeve (LT+SG)



Percentage of total body weight loss for patients undergoing LT or LT + SG



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Long term Outcomes

- In the LT alone cohort, 83.3 percent (30 of 36 participants) achieved > 10 percent loss in total body weight (TBW) before LT
- Three years after transplant, 29.4% of participants in the LT alone cohort maintained > 10 percent loss in TBW vs. 100 percent of the participants in the LT plus SG cohort ($P < 0.001$)
- LT plus SG cohort had a lower prevalence of:
  - hypertension
  - metabolic syndrome
  - insulin resistance
  - hepatic steatosis.
  - also needed fewer antihypertensive medications and lipid agents at last follow-up than did the LT alone
- QOL and Survival not different

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Summary

- Chronic liver disease remains a major cause of mortality and morbidity in the USA
- Changing indications for LT over the last five years since the advent of DAA therapy
- COVID 19 has had an impact on transplantation
- Need to expand the donor pool
- Outcomes remain excellent