Optimizing Living Donor Liver Transplantation: Risks and Benefits

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Disclosures

- This study was supported by the National Institute of Diabetes & Digestive & Kidney Diseases through cooperative agreements
  - Grants U01-DK62444, U01-DK62467, U01-DK62483, U01-DK62484, U01-DK62494, U01-DK62496, U01-DK62498, U01-DK62505, U01-DK62531, U01-DK62536, U01-DK85515, U01-DK85563, and U01-DK85587
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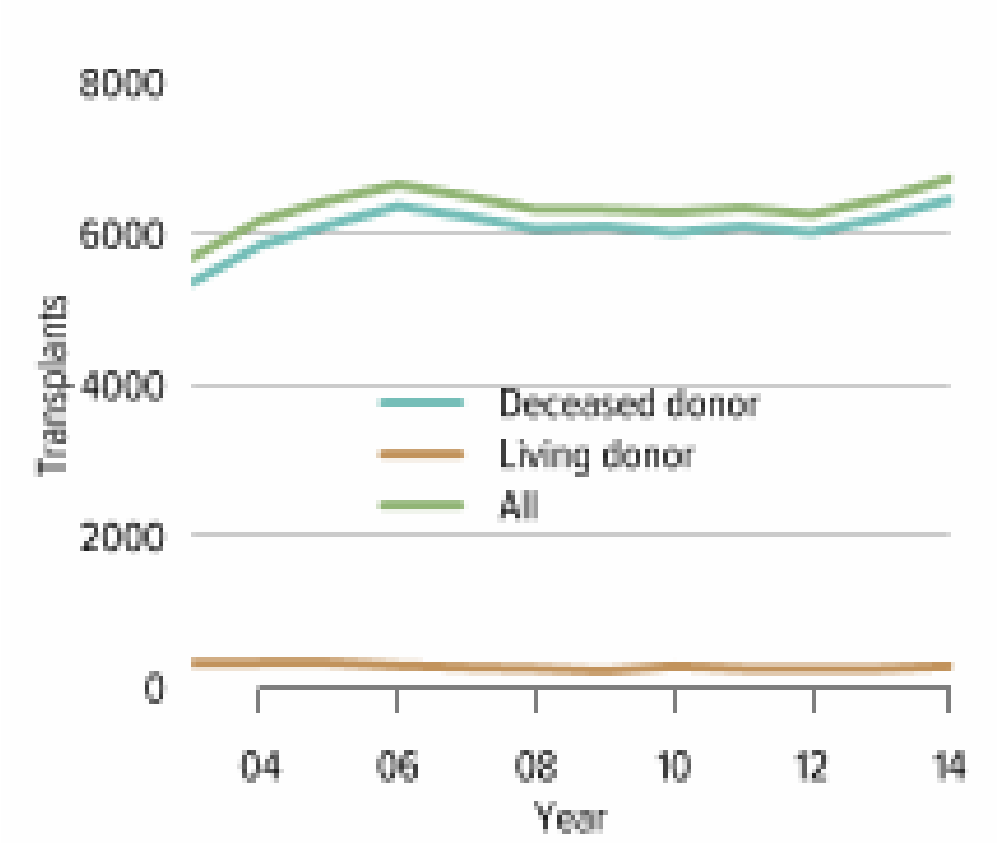
- No conflicts of interest were declared by the authors

Total Number of Adult Transplants

AJT 2016: OPTN/SRTR 2014 Annual Report



2004: 273, 4.9%

2014: 228, 3.8%

Adult LDLT Outcomes

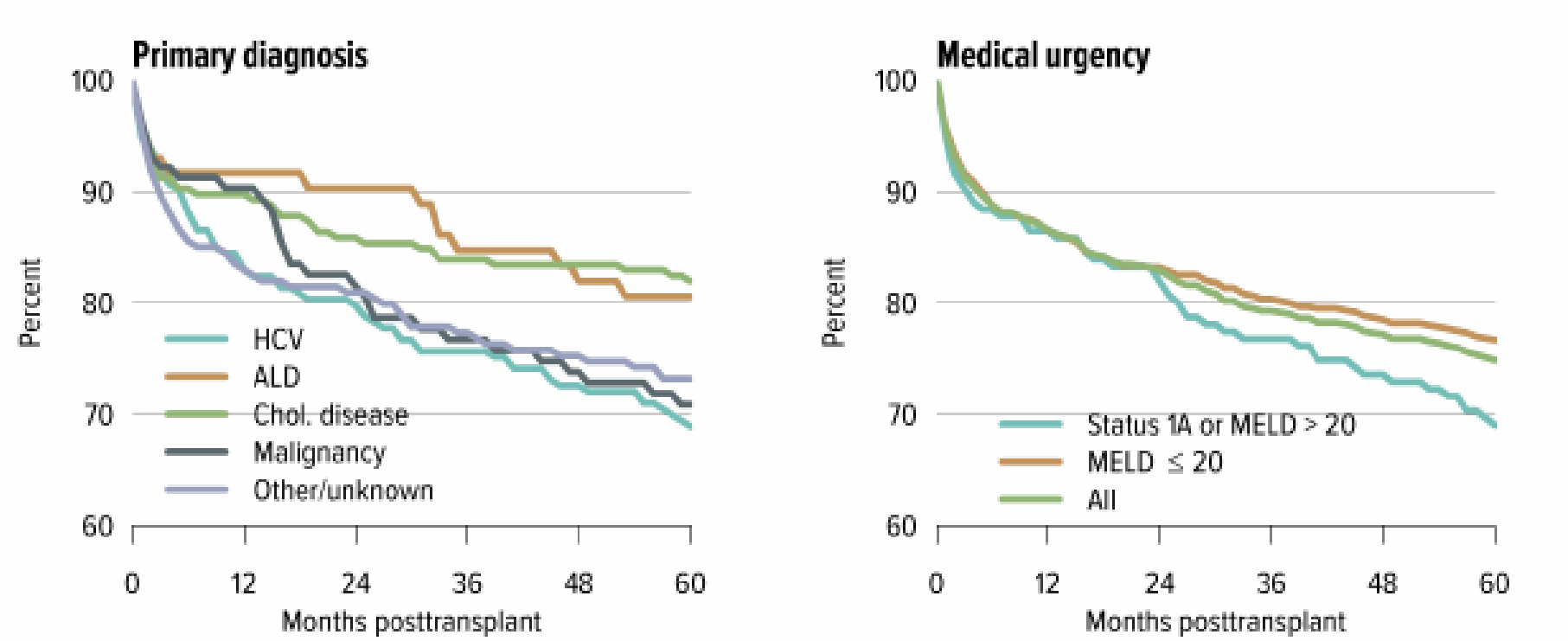
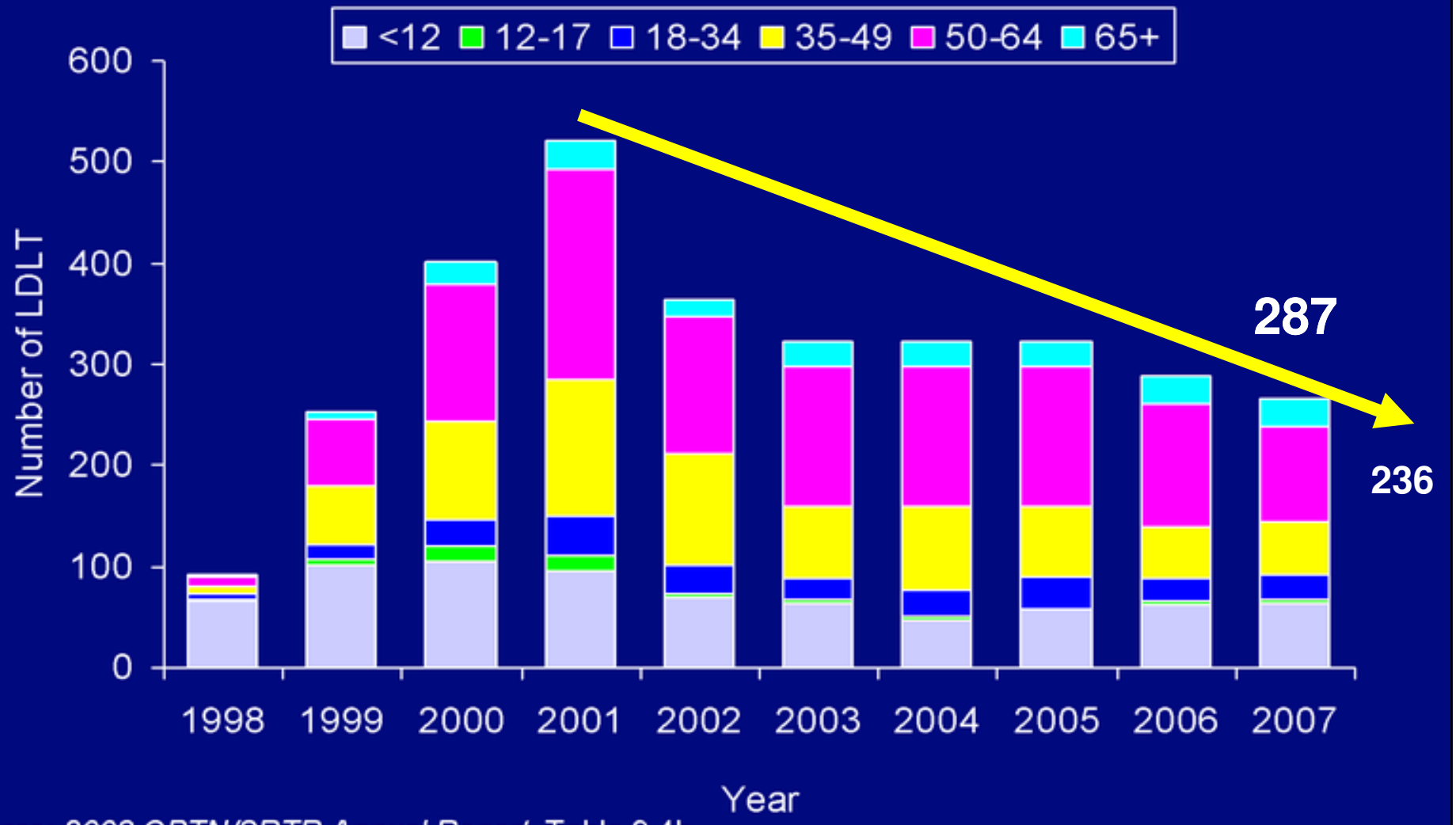


Figure LI 5.4 Graft survival among adult liver transplant recipients, 2006-2009: living donors

AJT 2016: OPTN/SRTR 2014 Annual Report

Figure IV-8. Number of Living Donor Liver Transplants by Age, 1998-2007



Source: *2008 OPTN/SRTR Annual Report*, Table 9.4b.

SRTR

American Journal of Transplantation 2010; 10: 2577–2581
Wiley Periodicals Inc.

doi: 10.1111/j.1600-6143.2010.03341.x

Personal Viewpoint

When Disaster Strikes: Death of a Living Organ Donor

WORLD NEWS WITH DIANE SAWYER
abc NEWS

Organ Donor Death Raises Questions About Living Donors

THE HUFFINGTON POST

Live Donor Deaths Beg the Question: Does the Benefit Outweigh the Risk?

PAULINE ARRILLAGA | 11/14/10 10:28 PM ET | AP

Montefiore live-donor transplant program shut down after donor mom dies during surgery

By SUSAN EDELMAN, FREDRIC U. DICKER and DAN MANGAN
Last Updated: 7:24 AM, June 6, 2012
Posted: 1:21 AM, June 6, 2012

Slide: Courtesy of Daniela Ladner

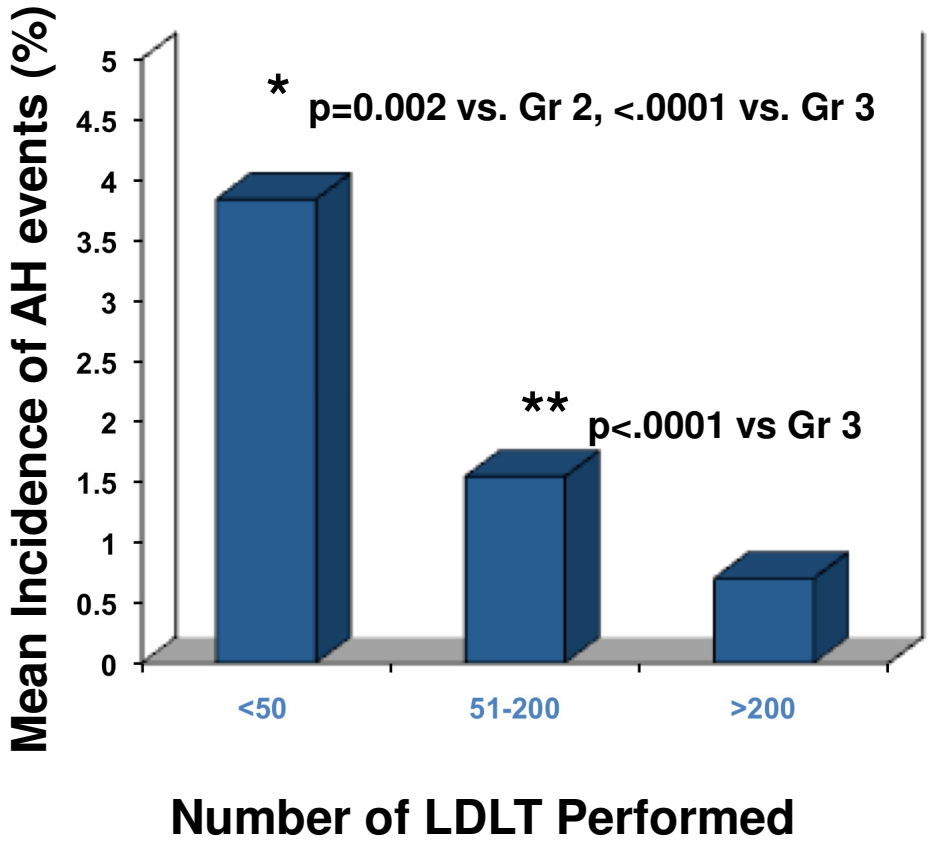
Factors Influencing Donor Surgery: Extent of Donor Hepatectomy

- The **amount of remnant hepatic parenchyma** in the donor after hepatectomy has been repeatedly identified as the **single most important predictive factor for donor outcome**.

- Individuals with **larger remnant volumes** consistently display **fewer adverse events**, shorter lengths of stays, and faster return to pre-donation activity levels

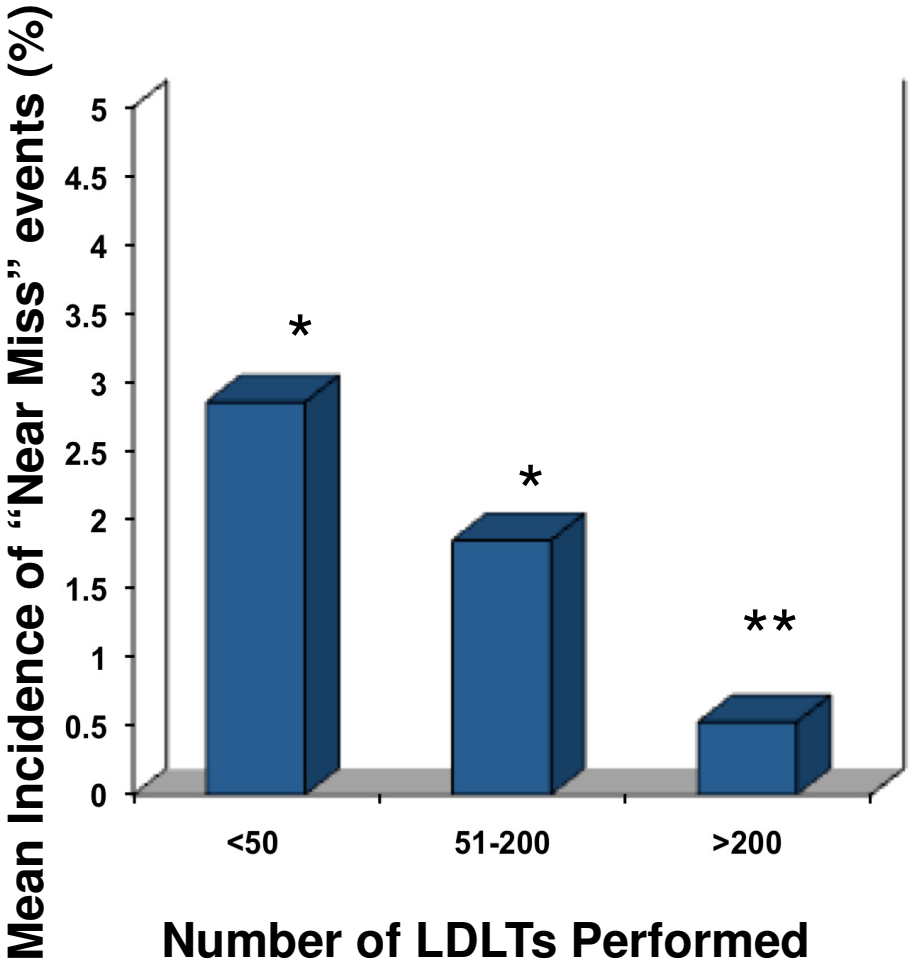
Program Volume and Aborted Hepatectomy

Cheah YL et al., Liver Transpl. 2013;19:499–506.



- 11,553 completed donor hepatectomies reported
- 136 donor hepatectomies were aborted
- 1.16% overall risk of aborted hepatectomy
- However, high volume programs experience significantly fewer AHs (>200 = 62/8860, 0.7%)

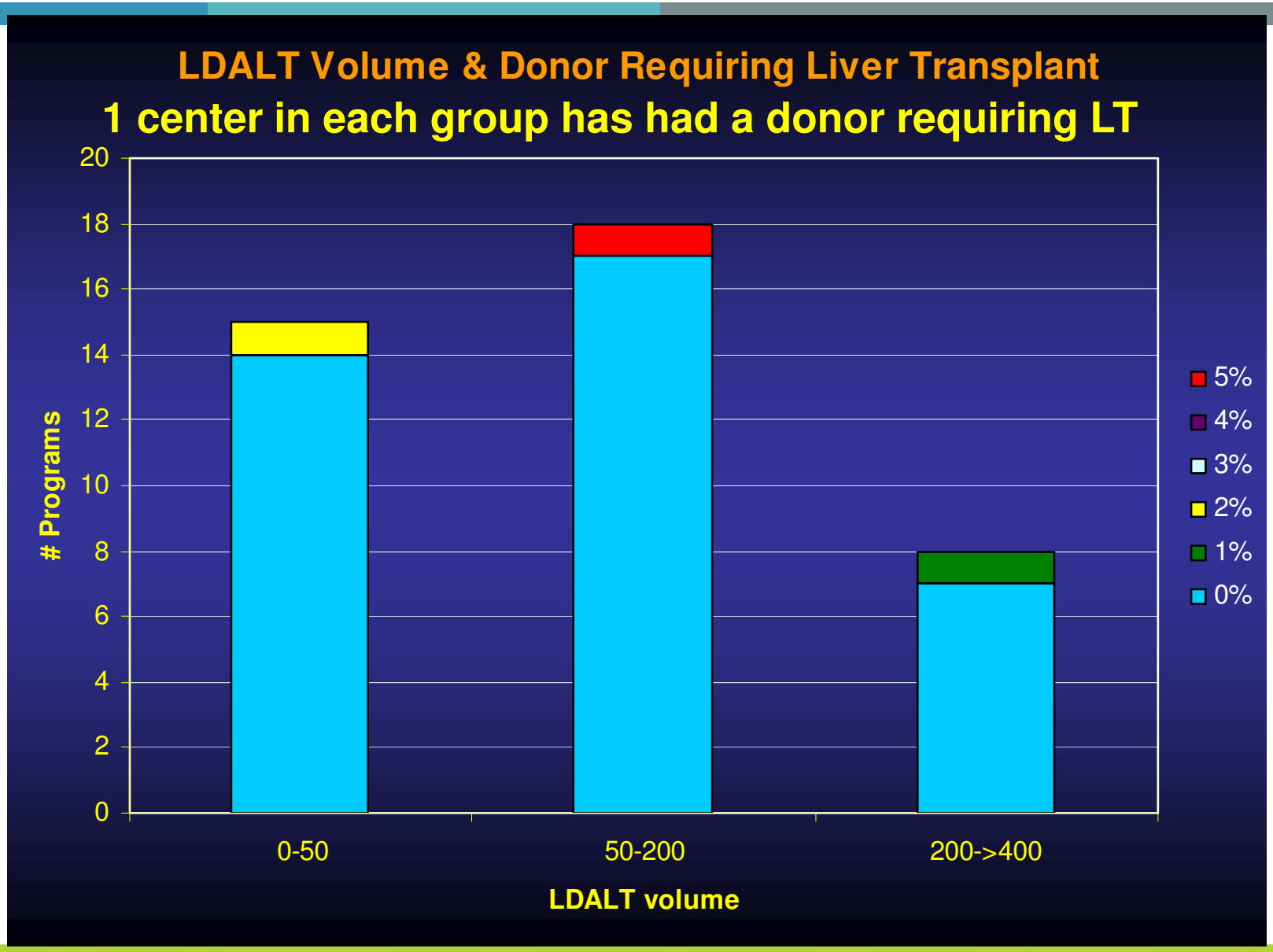
Program Volume and "Near Miss" Events



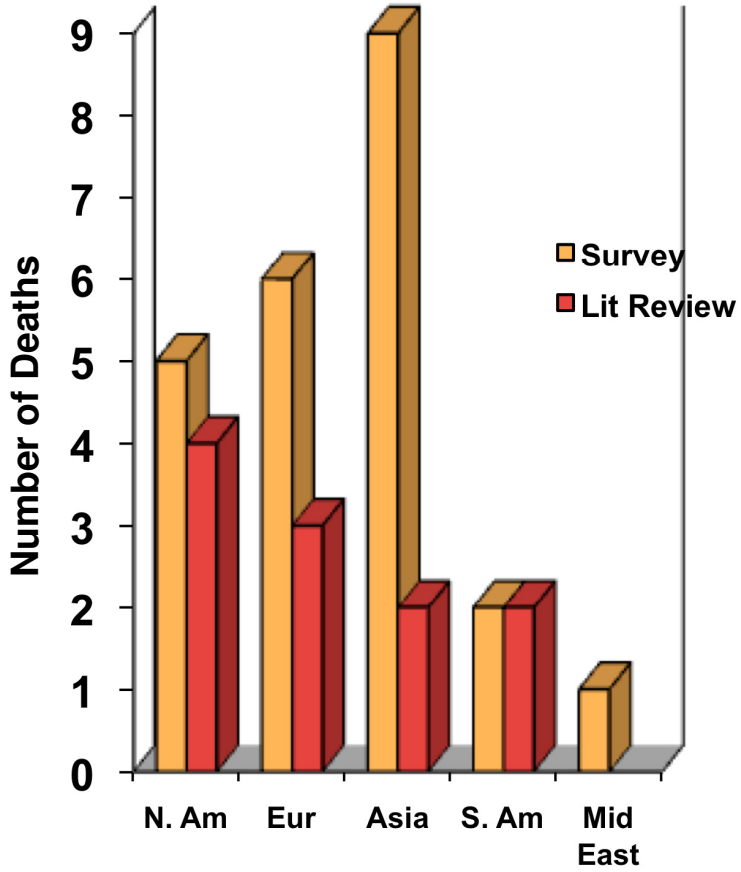
- "Near Miss" events decreases with experience
- Both low and medium volume programs have higher incidence of near miss events compared to high volume programs (**p<0.001, both groups)

Cheah YL et al., Liver Transpl. 2013;19:499–506.

Cheah YL et al., Liver Transpl. 2013;19:499–506.



36 Total Donor Deaths by Geographic Region



Cheah YL et al., Liver Transpl. 2013;19:499–506.

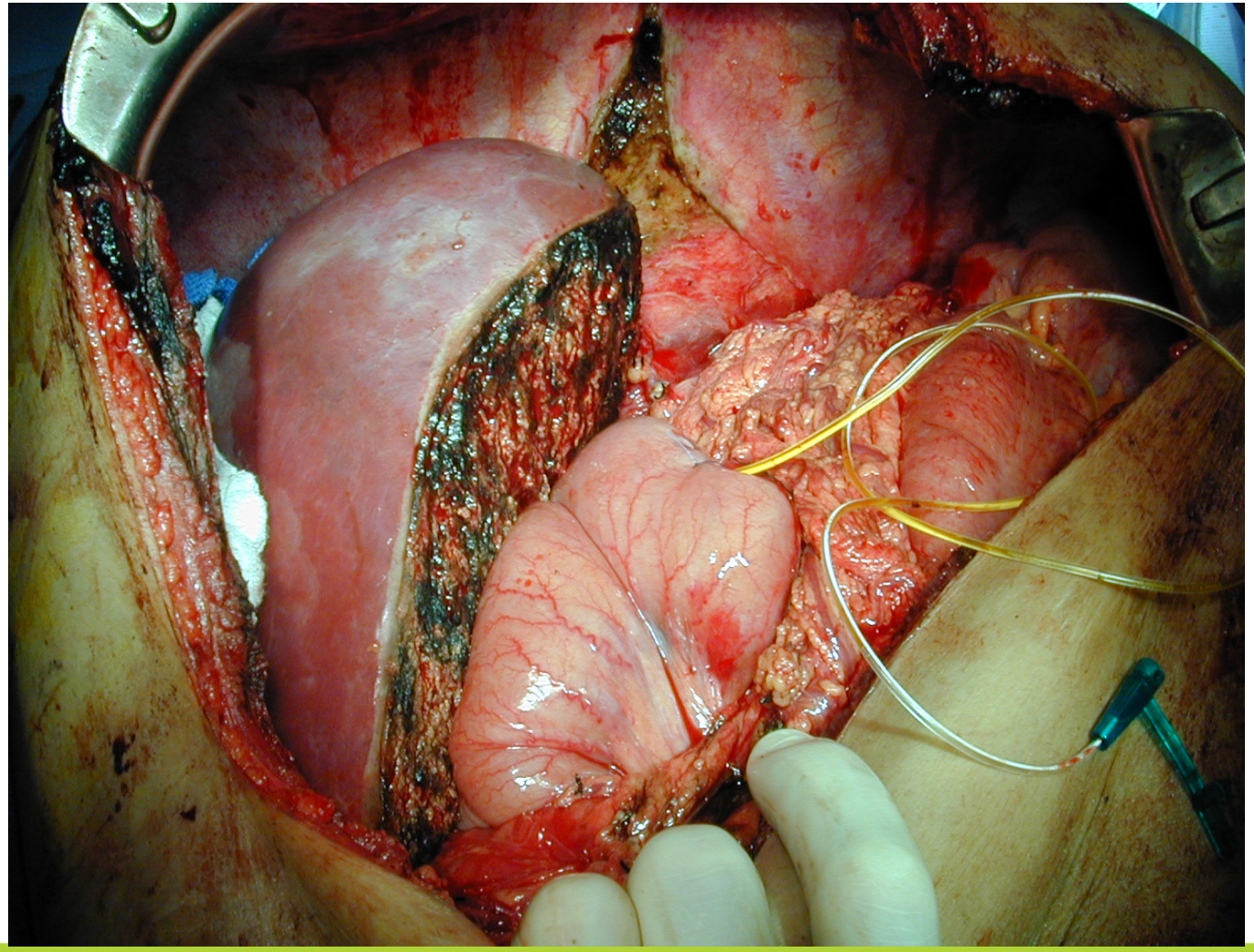
- Deaths reported in survey (n=23)
  - 15 ≤ 60 days Post Op
  - 8 >60 days Post Op, but 2 result of continuing complications
- Deaths reported in literature (n=11)
  - 8 in first 60 days
  - 3 >60 days
- 2 Additional Deaths known but not reported to either

“Near Miss” Events Occur in Addition to Reported Complications and Deaths

- **61% of programs included in the survey reported a “near miss event”**
- **127 Events in 126 Patients (43 Programs)**
- **1% Overall incidence of a “Near Miss” Event** (127/11553=1.1%)

Cheah YL et al., Liver Transpl. 2013;19:499–506.

So How Do We Perform Live Donor Adult Liver Transplantation with Acceptable Risk?



Ethical considerations

Even in countries with adequate access to DDLT, **live liver donation is appropriate due to organ shortages**

Donor safety is of paramount importance in living donor liver transplantation and **yet living donor complications and deaths occur even in the most experienced hands** **(0.1–0.5% mortality, 10–38% morbidity)**

"Vancouver Forum" (2006) established practice principles for LDLT:

- Live liver donation should only be performed if the **risk to the donor is justified by the expectation of an acceptable outcome in the recipient**

Barr ML et al., Transplantation 2006; 81:1373–85.

Preventable complications in living liver donors

Abecassis, et al. AJT 2012

Table 3: Type and severity of complications (intraoperative/postoperative) of donors with nonaborted procedure according Clavien grade (n = 740)[1]

Complication	Number of complications	Number of donors	Highest Clavien g 1	2
Intraoperative				
Intraoperative injury[2]	4	4		
Intraoperative other complications[2]	11	11		

Preventable Complications	Cause
Respiratory arrest	Over-sedation (Opioid)
Pulmonary embolism (PE), Deep vein thrombosis (DVT)	Immobility, No heparin/SCDs
Neuropraxia	Nerve compression during surgery (positioning)

- Cardiopulmonary
  - Pneumothorax
  - Pleural effusion
  - Pulmonary edema
  - Respiratory arrest
  - Aspiration
  - Pulmonary embolism
- Hepatic
  - Encephalopathy/hepatic coma
  - Ascites
  - Liver failure
  - Hepatic artery thrombosis
  - Portal vein thrombosis
  - Inferior vena cava thrombosis
- Other
  - Deep vein thrombosis
  - Neuropraxia
  - Infections[2]

Preventable complications and catastrophes are the tip of the iceberg

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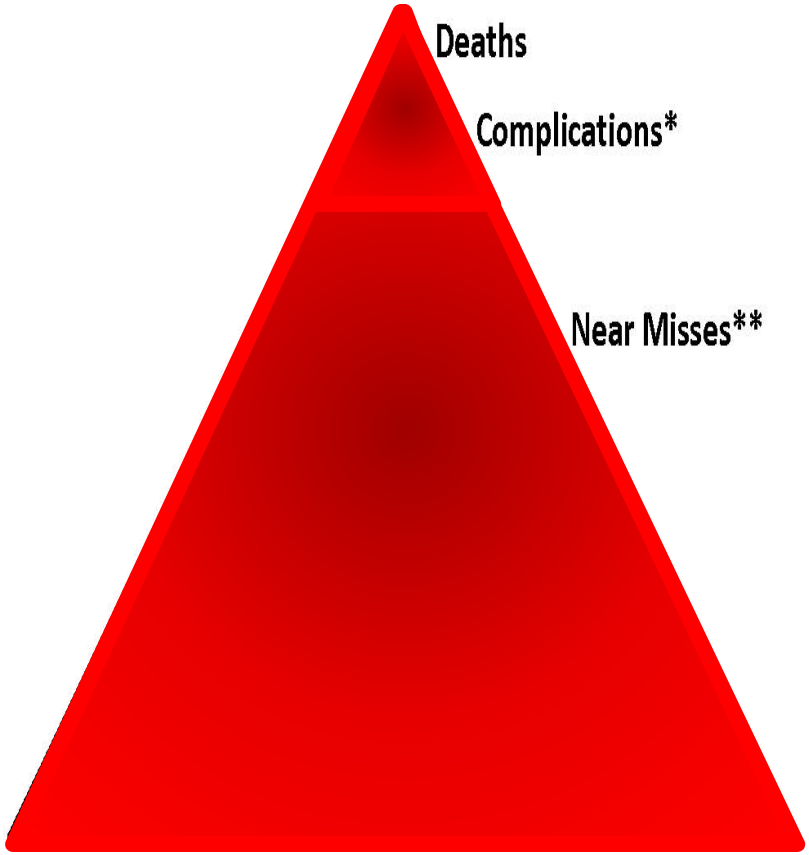

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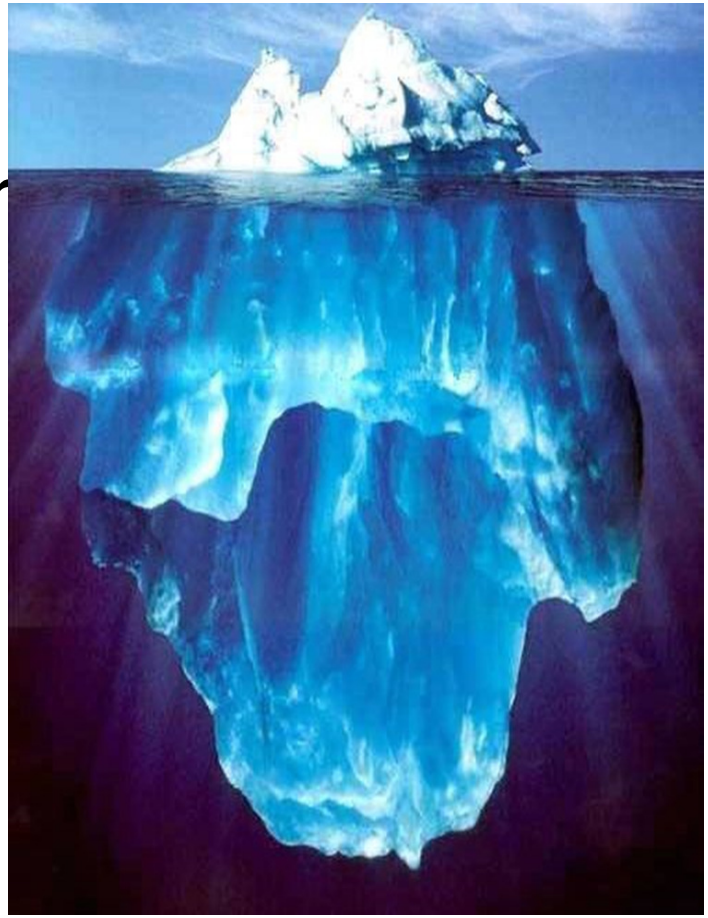
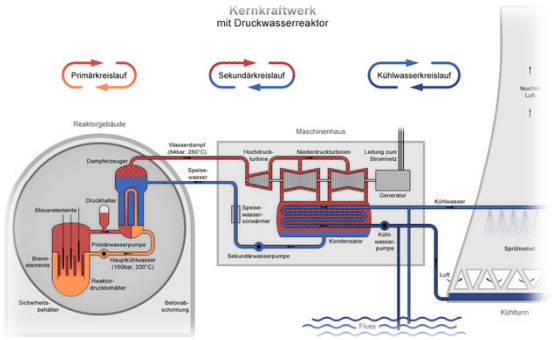


Ladner, et al; Liver Transplant, 2013

Prospective Multimodal Approach to Living Liver Donor Safety

- Learning from the production industry, airline and nuclear power industry we designed a multimodal approach to find vulnerabilities in the delivery of care that occur frequently and are at high risk to lead to preventable complications



A2ALL SAFETY STUDY

- **NIH/NIDDK R01DK090129**
- **Study Period:** 09/01/11 – 05/31/15
- **Four Participating A2ALL Transplant Centers (TC):**
  - **Northwestern University (NU) – Lead TC**
    Daniela Ladner, MD and Donna Woods, PhD
  - **Columbia University Medical Center**
    James Guarrera, MD
  - **Lahey Clinical Medical Center**
    Elizabeth Pomfret, MD and Mary Ann Simpson, PhD
  - **Virginia Commonwealth University**
    Robert Fisher, MD

Living Liver Donor Pain Management

- Donors experience pain during hospitalization
  - Experienced pain by donors is significant
    - ✓73% of patients experience pain scores above 4
    - ✓49% of patients experience pain scores over 6
    - ✓Pain is worst after day 3
- Pain management associated complications
  - **20%** suffer from <u>sequelae of opioid overdose</u>
    - ✓Somnolence (requiring treatment), respiratory events requiring treatment (e.g. reintubation, Narcan)
    - ✓Events primarily within first 24 hours

Evidence-based Donor Pain Management Solution Elements (Opioid sparing)

- Preoperative Assessment and Management:
  - ✓ Risk factor assessments (e.g. OSA Assessment)
  - ✓ Bowel preparation
  - ✓ Educational handout on postoperative pain
- At the end of the case in OR:
  - ✓ Local Anesthetic (TAP block, intrathecal)
  - ✓ I.V. Ketorolac (when adequate hemostasis is determined by surgeon and urine output is > 500cc)
  - ✓ I.V. Steroids (Dexamethasone or Solumedrol)
- Postoperative Assessment and Management:
  - ✓ NSAIDS x 72 hours followed by PO cox-inhibitor until discharge
  - ✓ Opioids (PCA followed by oral opioids)
  - ✓ CO2 monitoring in PACU/ICU for early monitoring of respiratory depression

Complications* Related to Donor Pain Management (PRE vs POST-Implementation of Opioid Sparing Protocol

* Verified by Medical Monitor

	CAUSE	PRE (N=90)	POST (N=23)	Change PRE/POST	P-Value
Hypotension	Opioid	41 (46%)	2 (9%)	-37%	0.00
Hypoxia	Opioid	50 (56%)	7 (30%)	-25%	0.03
Tachycardia	Pain	25 (28%)	2 (9%)	-19%	0.05
Vomiting	Opioid	13 (14%)	0 (0%)	-14%	0.05
Tachypnea	Pain	31 (34%)	4 (17%)	-17%	0.11
Constipation	Opioid	43 (48%)	7 (30%)	-17%	0.14
Dizziness	Opioid	13 (14%)	1 (4%)	-10%	0.19
Hyperglycemia	Steroid	13 (14%)	4 (17%)	3%	0.72
Bradypnea	Opioid	34 (38%)	6 (26%)	-12%	0.30
Nausea	Opioid	55 (61%)	12 (52%)	-9%	0.44
Pruritis	Opioid	19 (21%)	3 (13%)	-8%	0.38
Urinary Retention	Opioid	14 (16%)	3 (13%)	-3%	0.76
Bradycardia	Opioid	8 (9%)	2 (9%)	-0.19%	0.98
Hypertension	Pain	23 (26%)	7 (30%)	5%	0.64

Living Donor Pain; Likert Scale (0-10): PRE (N=90) and POST (N=23) Comparison

		POSTOPERATIVE DAY								
	PAIN	0	1	2	3	4	5	6	7	8
PRE	> 6	41%	56%	41%	45%	60%	57%	55%	50%	55%
POST	> 6	35%	30%	30%	38%	38%	29%	50%	33%	50%

Conclusion

- The most effective way to improve living donor safety is to prevent preventable complications
- ~50% of complications are preventable
- Near miss events are 100 x more frequent than preventable complications
- We can learn from other industries, even if they are less complex than medicine (proactive and prospective)

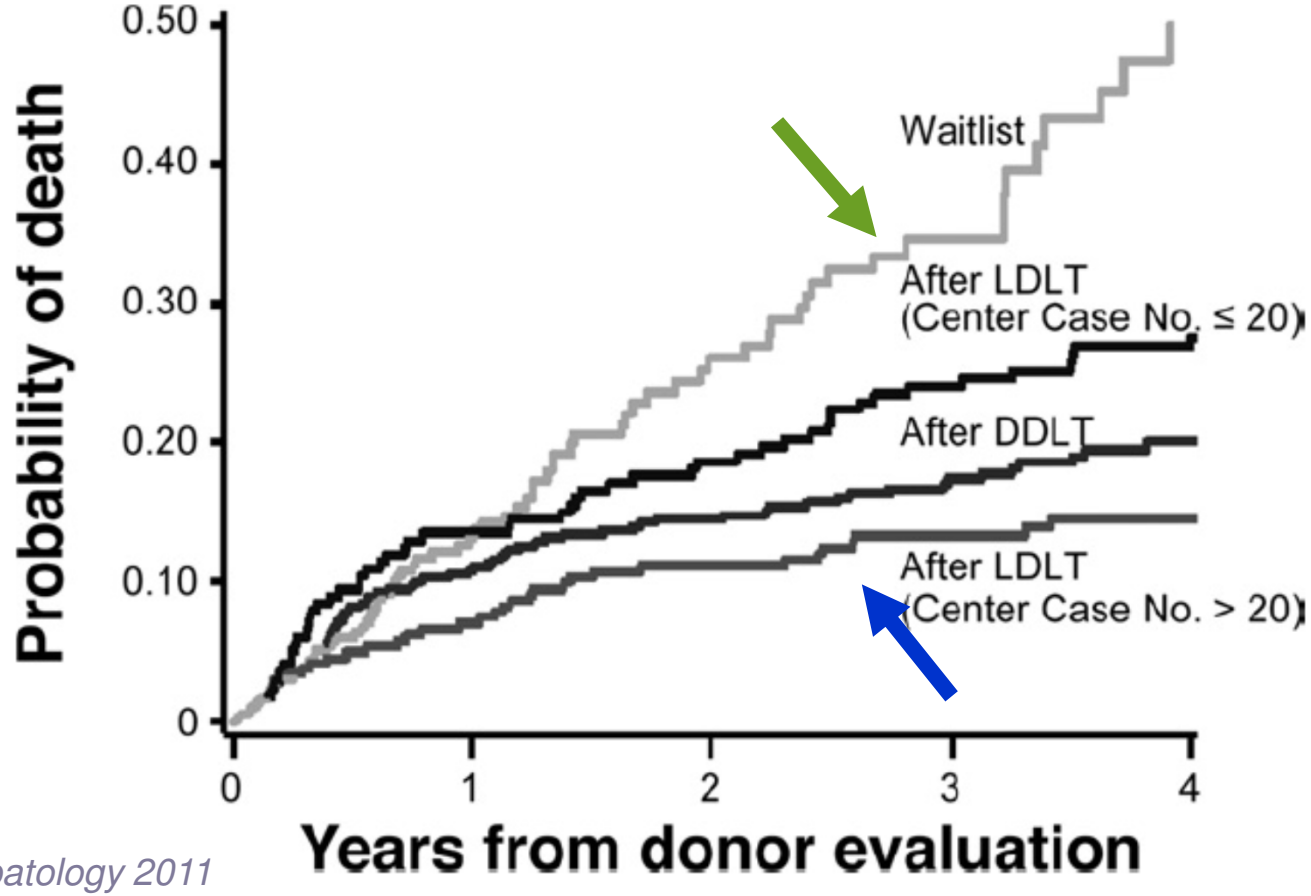
Recipient Outcomes

Background

- Living donor liver transplantation (LDLT) provides an important surgical option for end-stage liver disease
- Initial outcomes demonstrated inferior post-transplant results compared to deceased donor liver transplantation (DDLT)
  - Centers with < 20 associated with 83% higher risk of graft failure ($p<0.0045$)
    - *Olthoff et al Ann Surg 2005*
- Advantage of LDLT over DDLT related to decreased death on the waitlist due to more timely transplantation, regardless of MELD score
    - *Berg et al, Gastroenterology 2007*
    - *Berg et al, Hepatology 2011*

Cumulative Risk of Death After Initial LD Evaluation for Patients Undergoing LDLT vs. DDLT Stratified by Center Experience

Adjusted for age, MELD score and HCC



Berg et al, Hepatology 2011

Defining Long-term Outcomes With Living Donor Liver Transplantation in North America

KM Olthoff, AR Smith, M Abecassis, T Baker, J Emond, C Berg, CA Beil, J Burton, R Fisher, C Freise, BW Gillespie, D Grant, A Humar, I Kam, RM Merion, E Pomfret, B Samstein, A Shaked

Ann Surg

Olthoff K, et al Ann Surg 2015; 262(3):465-75

National Institute of Diabetes and Digestive and Kidney Diseases

Department of Health and Human Services HRSA Health Resources and Services Administration

The FOUNDATION of the ASTS American Society of Transplant Surgeons

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Study Population

- 1600 completed transplants enrolled in A2ALL between 1/1/1998 – 1/31/2014
  - All patients had a living donor evaluated, but some ultimately received a DDLT
  - 173 LDLT "learning curve" cases excluded
    - First 20 at each A2ALL-1 institution*
    - A2ALL-2 centers contributed transplants occurring after 8/31/2009, by which time each had completed > 20 LDLT cases
- 1427 completed transplants analyzed
  - 963 living donor recipients
  - 464 deceased donor recipients

Olthoff K, et al Ann Surg 2015; 262(3):465-75

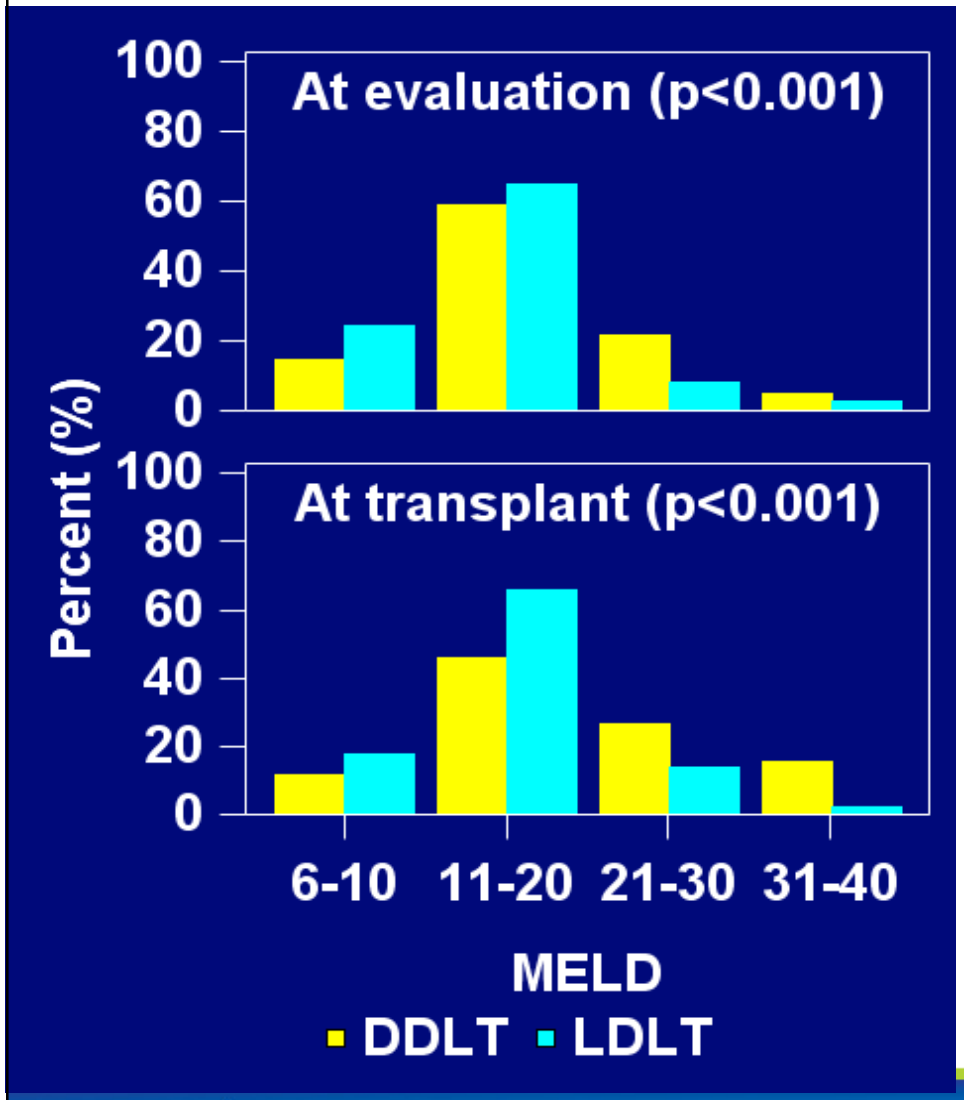
Recipient Characteristics:
Demographics

	DDLT (n=464)		LDLT (n=963)		P-value
	N	%	N	%	
Hispanic	87	19%	126	13%	0.005
Race					<0.001
White	390	84%	877	91%	
Black	33	7%	29	3%	
Asian	17	4%	31	3%	
Other race	24	5%	26	3%	
Diagnosis (multiple diagnoses possible)					
HCC	98	21%	154	16%	0.02
HCV	210	45%	339	35%	<0.001
PBC	12	3%	81	8%	<.001
Other diagnosis	21	5%	90	9%	0.001

*Age, Female, BMI, Additional Diagnoses (Acute Liver Failure, Alcohol-related Cirrhosis, Autoimmune Hepatitis, Cryptogenic Cirrhosis, Hemochromatosis, Other Metabolic Liver Disease, Malignancy other than HCC, and PSC) were not significantly different between DDLT and LDLT. *Olthoff K, et al Ann Surg 2015; 262(3):465-75*

Recipient Characteristics:

Disease Severity



Medical Condition	DDLT	LDLT
ICU	11%	2%
Hospital	15%	6%
Ventilator	6%	1%
HD	5%	1%
Ascites	62%	46%

P< 0.001

Olthoff K, et al Ann Surg 2015; 262(3):465-75

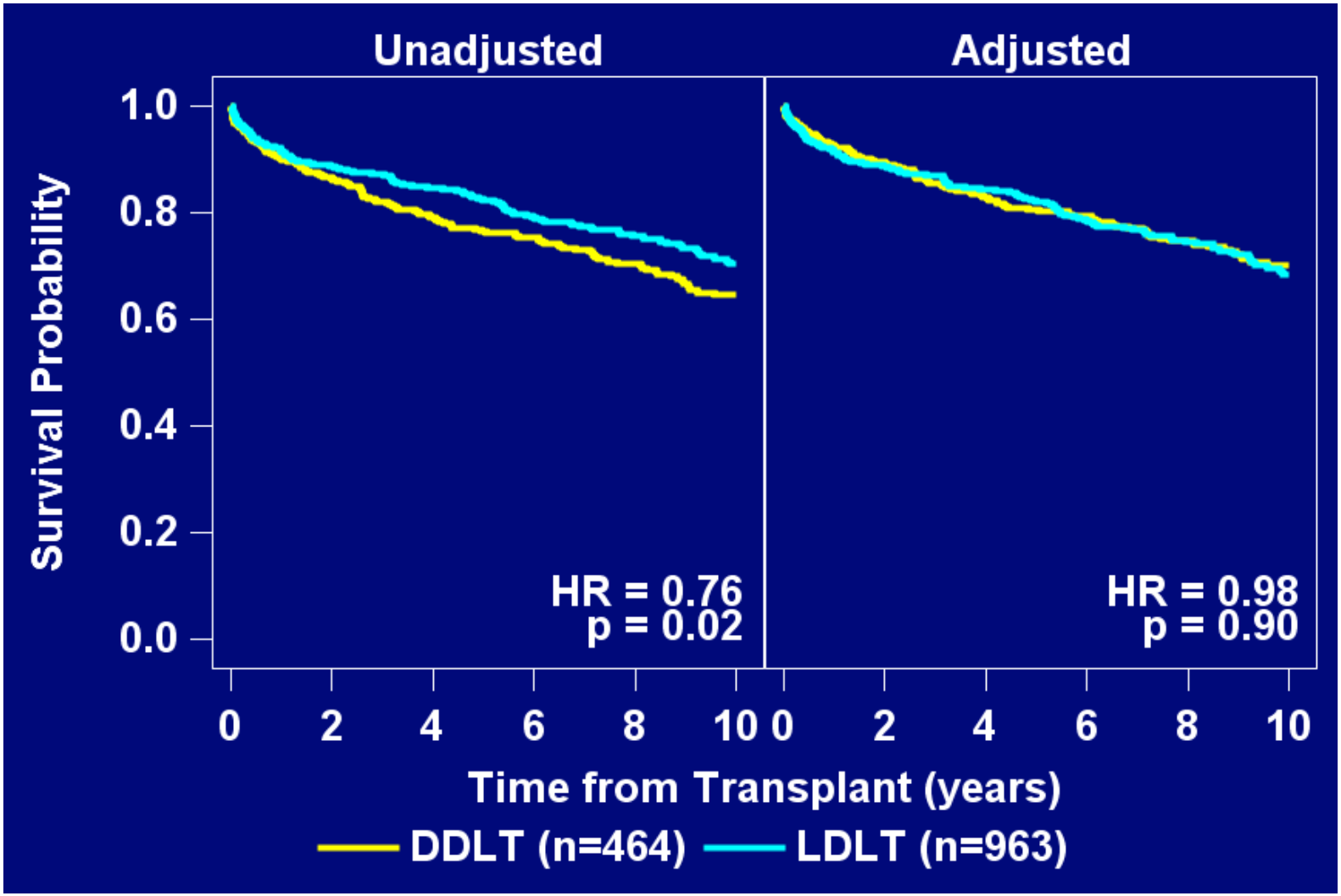
Perioperative Characteristics

	DDLT		LDLT		
	Median	IQ range	Median	IQ range	P-Value
Duration of surgery (hrs)	**5.78**	5-7	**7.57**	7-9	<0.001
Total ischemia time (mins)	**486.50**	364-600	**98.00**	71-140	<0.001
PRBCs (units)*	**6.00**	3-11	**4.00**	2-8	<0.001
Recipient ICU LOS (days)	2.00	1-5	2.00	1-3	0.05
Recipient total LOS (days)	10.00	7-17	10.00	7-15	0.65

Olthoff K, et al Ann Surg 2015; 262(3):465-75

*Collected in A2ALL-1 only
PRBC = packed red blood cells; ICU = intensive care unit; LOS = length of stay

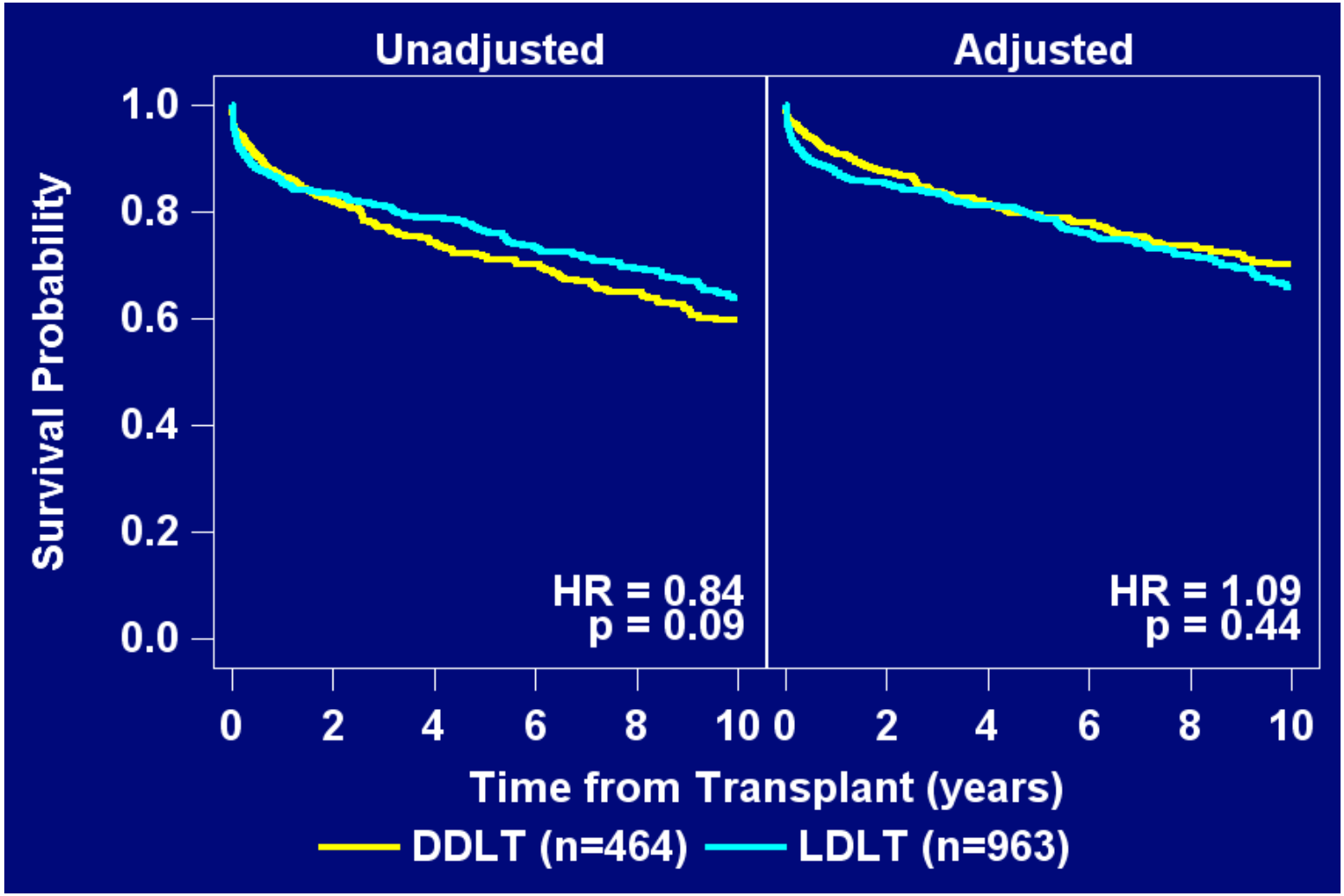
Patient Survival



*Adjusted model shows survival curves for 53 year old male patient without non-HCC malignancy or PSC, not dialysis at transplant, MELD of 16, and received a liver from a donor under 50 years old.

Olthoff K, et al Ann Surg 2015; 262(3):465-75

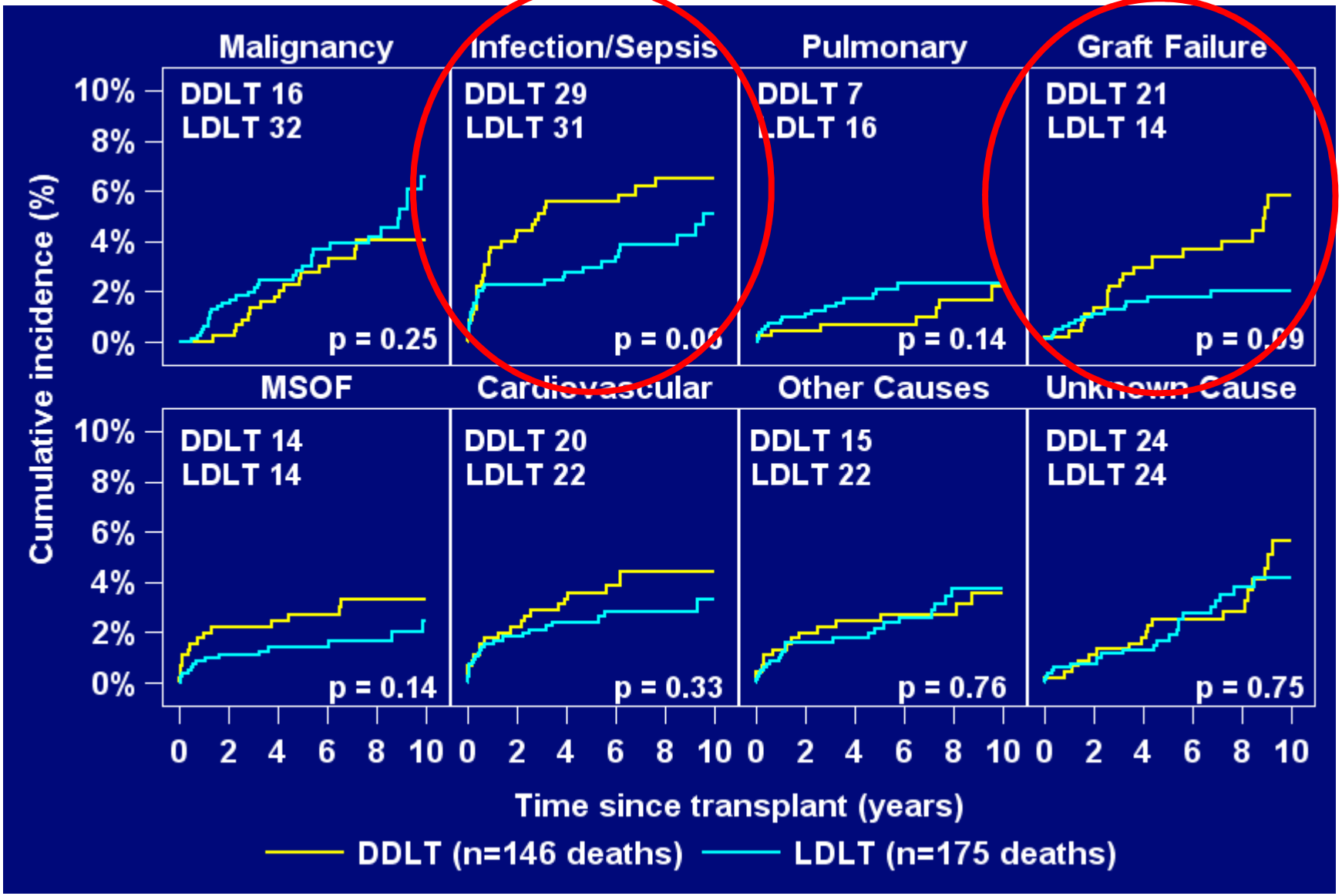
Graft Survival



*Adjusted model shows survival curves for a 53 year old patient without autoimmune hepatitis, HCC, or PSC, a MELD of 16 at transplant, not on dialysis at transplant, and received a liver from a donor under 50 years old.

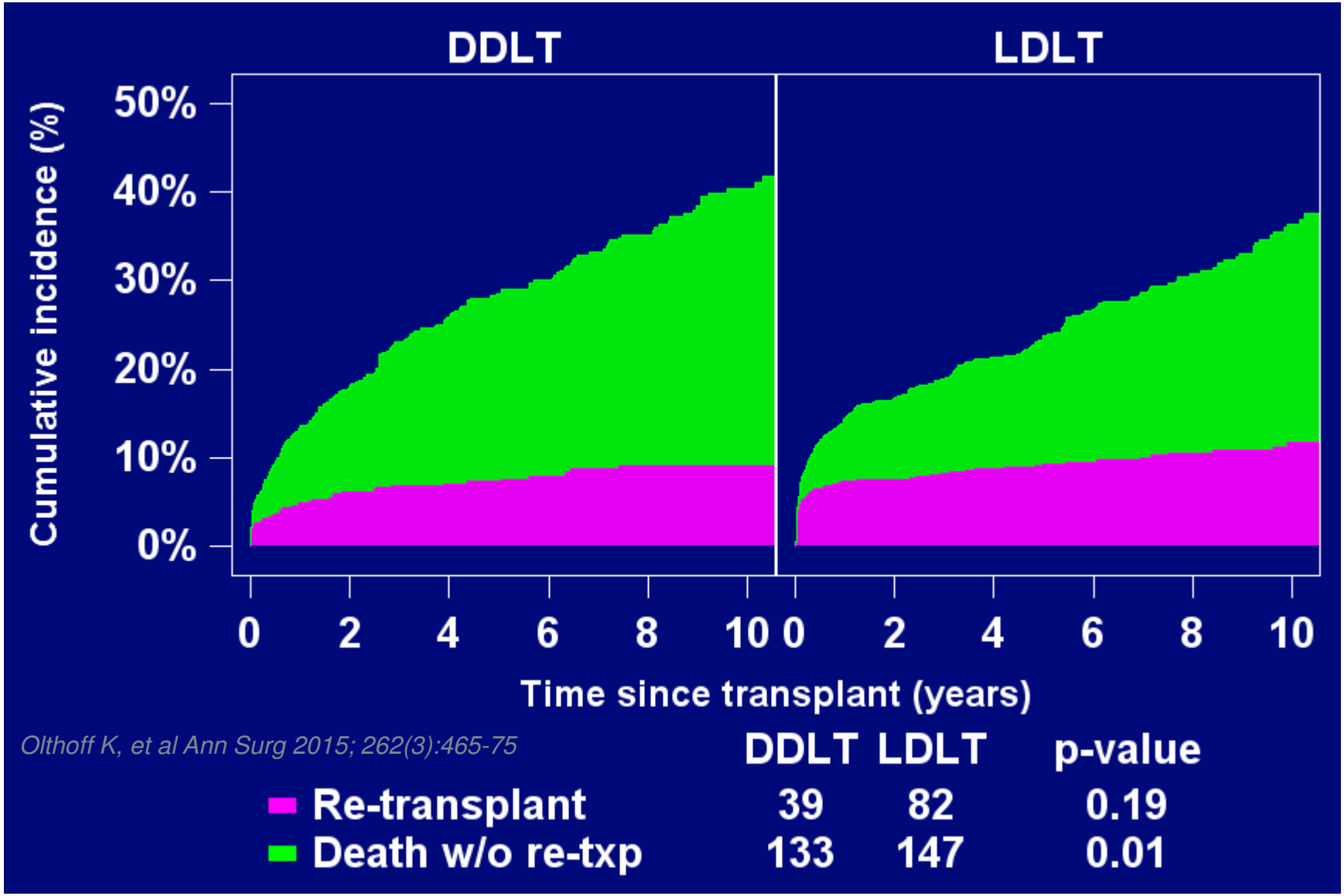
Olthoff K, et al Ann Surg 2015; 262(3):465-75

Primary Causes of Death



Olthoff K, et al Ann Surg 2015; 262(3):465-75

Graft Failure: Death or Re-transplant



Predictors of Mortality
Combined Model

Parameter	Hazard Ratio (HR)	95% Lower CI for HR	95% Upper CI for HR	p-value
LDLT vs. DDLT	**0.98**	**0.77**	**1.27**	**0.90**
Female vs. male	0.74	0.58	0.94	0.01
Recipient diagnosis: malignancy other than HCC	2.16	1.13	4.11	0.02
Recipient diagnosis: PSC	0.45	0.30	0.69	<.001
On dialysis at transplant	3.59	2.05	6.28	<.001
Recipient age at transplant (per 10 years), < 55	1.20	1.00	1.44	0.05
Recipient age at transplant (per 10 years), > 55	1.65	1.27	2.15	<.001
Donor age > 50 vs. < 50	1.49	1.14	1.94	0.003
MELD at transplant (per 5 points)	1.06	0.98	1.16	0.15

*Variables tested for inclusion: Recipient age, gender, race, ethnicity, BMI, diagnosis, medical severity at transplant (on ventilator or on dialysis), MELD at transplant, cold ischemia time, donor age, and donor type.

Olthoff K, et al Ann Surg 2015; 262(3):465-75

Predictors of Graft Failure

Combined Model

Parameter	Hazard Ratio (HR)	95% Lower CI for HR	95% Upper CI for HR	p-value
LDLT vs. DDLT	1.09	0.87	1.37	0.44
Recipient diagnosis: autoimmune hepatitis	0.44	0.24	0.82	0.009
Recipient diagnosis: HCC	1.32	1.01	1.73	0.05
Recipient diagnosis: PSC	0.66	0.47	0.93	0.02
On dialysis at transplant	2.54	1.50	4.31	<.001
Recipient age at transplant (per 10 years), < 55	1.03	0.89	1.19	0.71
Recipient age at transplant (per 10 years), > 55	1.39	1.08	1.78	0.009
Donor age > 50 vs. < 50	1.52	1.20	1.93	<.001
MELD at transplant	1.09	1.00	1.17	0.04

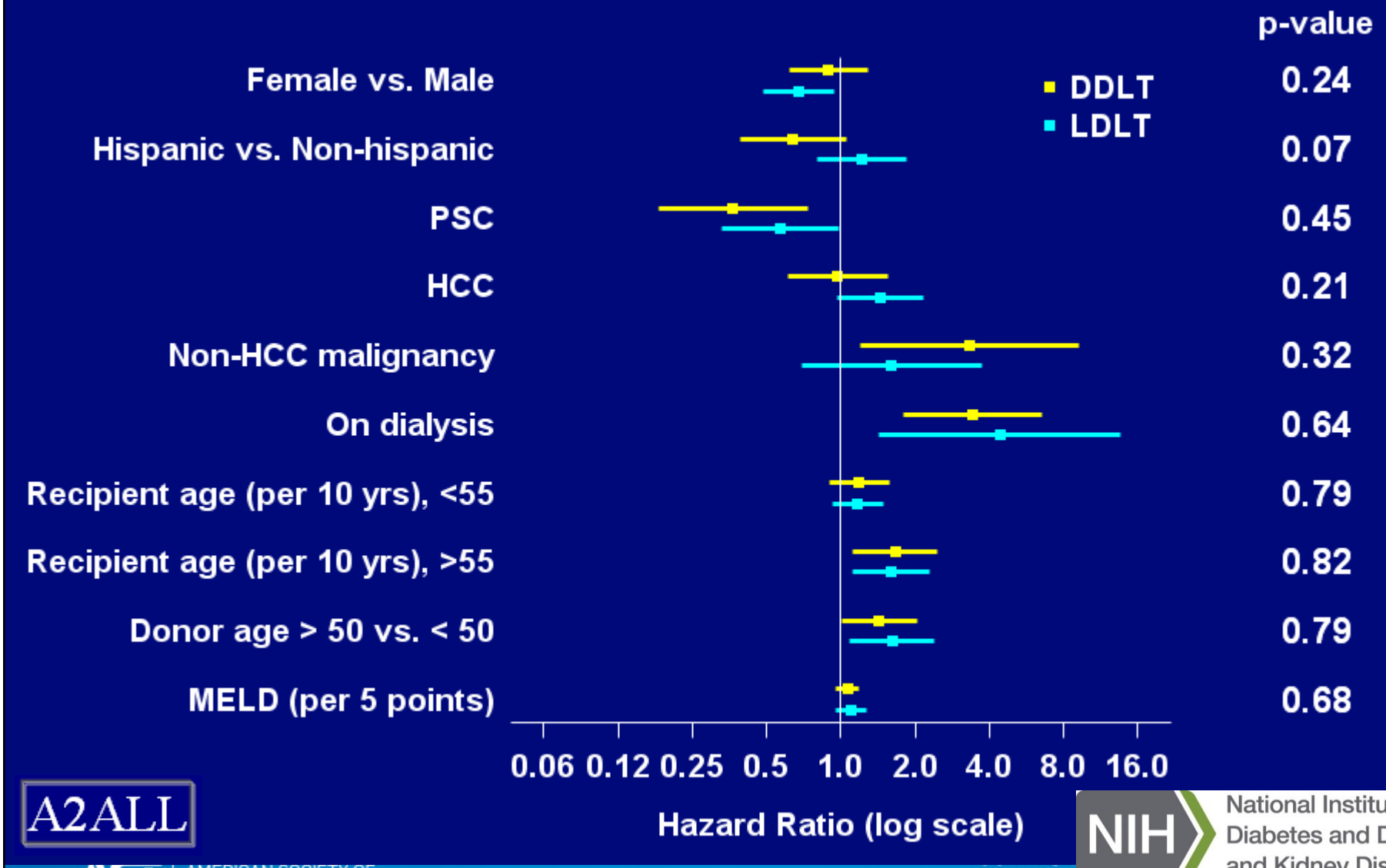
*Variables tested for inclusion: Recipient age, gender, race, ethnicity, BMI, diagnosis, medical severity at transplant (on ventilator or on dialysis), MELD at transplant, cold ischemia time, donor age, and donor type.

Olthoff K, et al Ann Surg 2015; 262(3):465-75

Variables Impacting Mortality

Olthoff K, et al Ann Surg 2015; 262(3):465-75

Separate Model



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Variables Impacting Graft Failure

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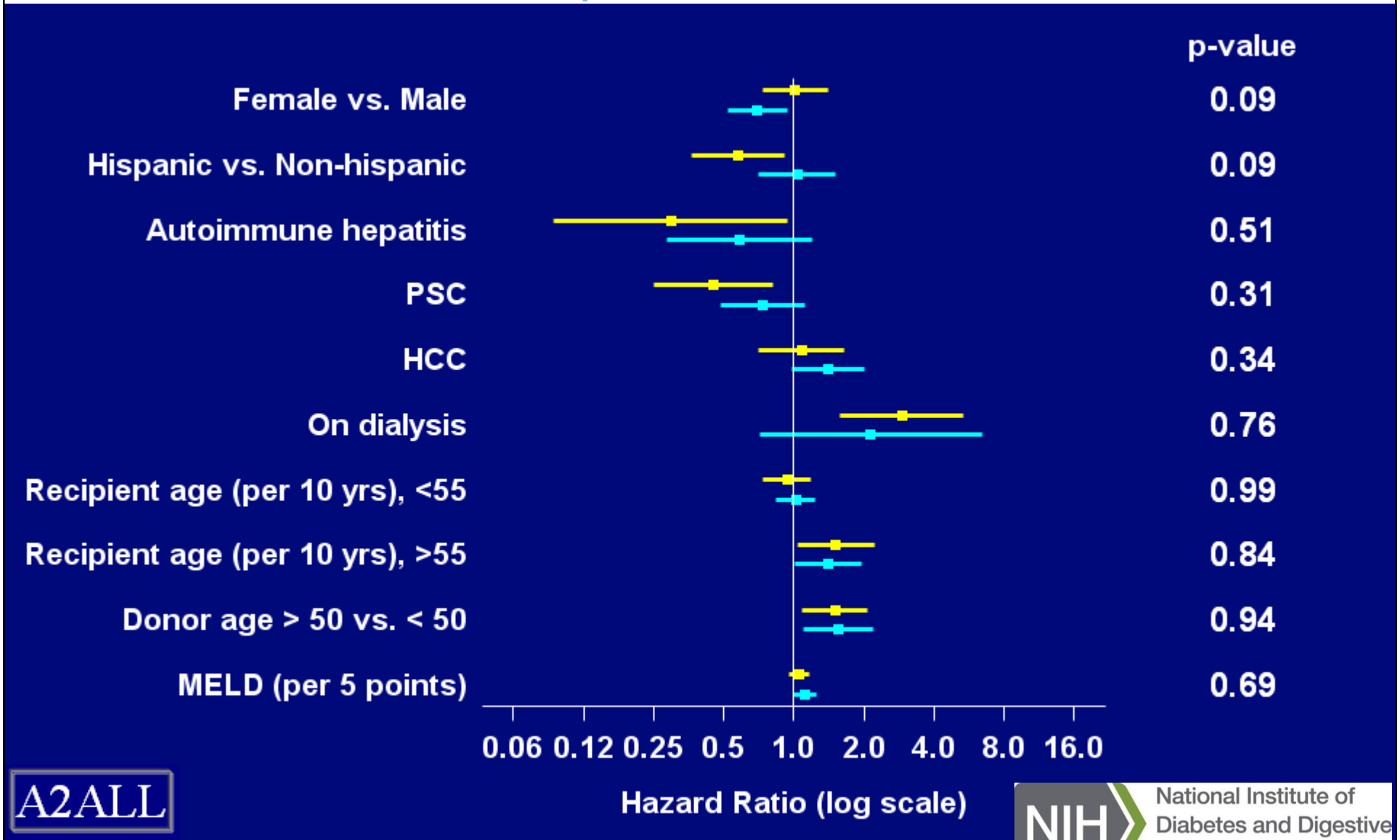
Separate Model



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RESOLVE

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Variables Not Impacting Mortality

- Era of transplant
- Year of transplant
- Right vs left lobe
- Time on waitlist

Olthoff K, et al Ann Surg 2015; 262(3):465-75

Summary

- Patients receiving LDLT have lower disease severity than those receiving DDLT resulting in better overall unadjusted survival
- Long-term adjusted post-transplant outcomes for recipients of DDLT and LDLT are comparable
- LDLT and DDLT have similar causes of death, but more graft loss due to death with DDLT

Implications

- LDLT provides significant benefit, allowing transplantation at lower MELD score, decreased death on the waitlist, and equivalent post-transplant survival to DDLT
- Accumulated data from 12 centers over 15 years demonstrates compelling reasons to consider LDLT for appropriate recipients
- Decreasing donor risk must remain central to any efforts to increase LDLT