

Who Can Tolerate a Marginal Donor Allograft

David P. Foley, MD
Professor of Surgery

University of Wisconsin School of Medicine and
Public Health



CUTTING EDGE of **TRANSPLANTATION**

TRANSPLANT SUMMIT 2019

NO SIZE FITS ALL: *Uncovering the
Potential of Personalized Transplantation*

I have no disclosures.

Learning Objectives

1. To identify the benefits of donor and recipient matching in liver transplantation.
2. To describe those patients who may not be ideally suited to receive a high risk deceased donor liver
3. To identify the liver transplant candidates who are best suited to receive a high-risk deceased donor liver

Liver Allocation Based on MELD

- Urgency based system
- Assign organs based on those with high wait list mortality
- Expense of utility:
High MELD may mean high post transplant mortality

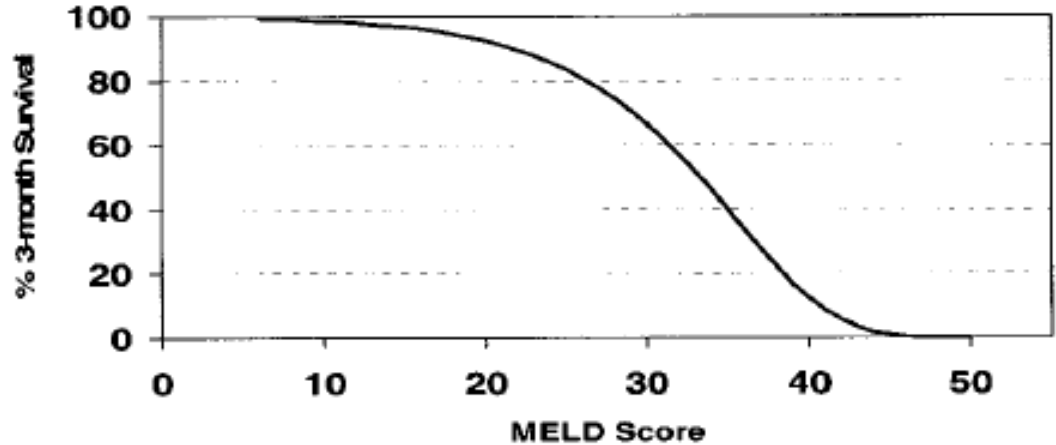
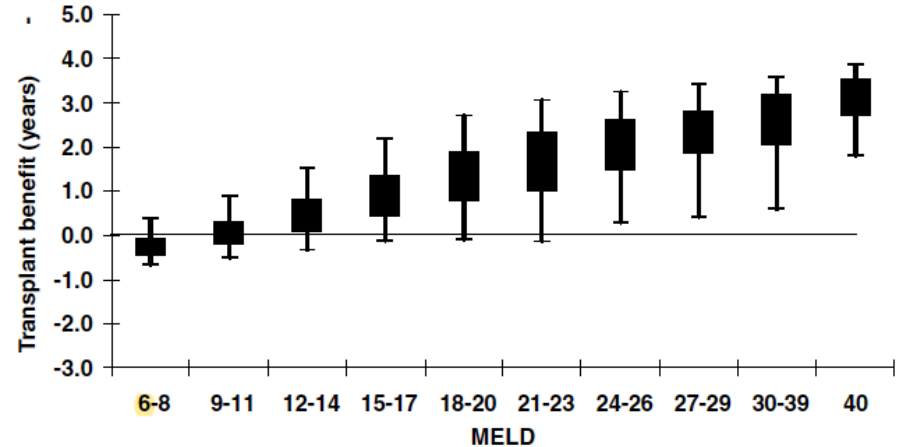
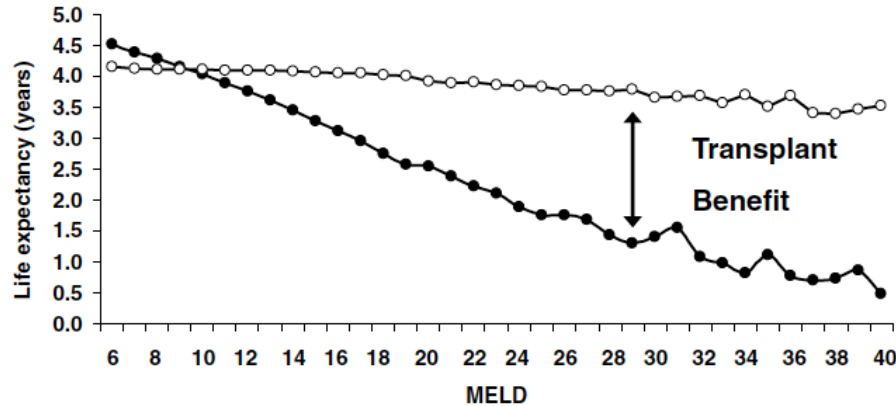


Figure 2. Estimated 3-month survival as a function of the MELD score.

Wiesner R et al. Gastroenterology, 2003

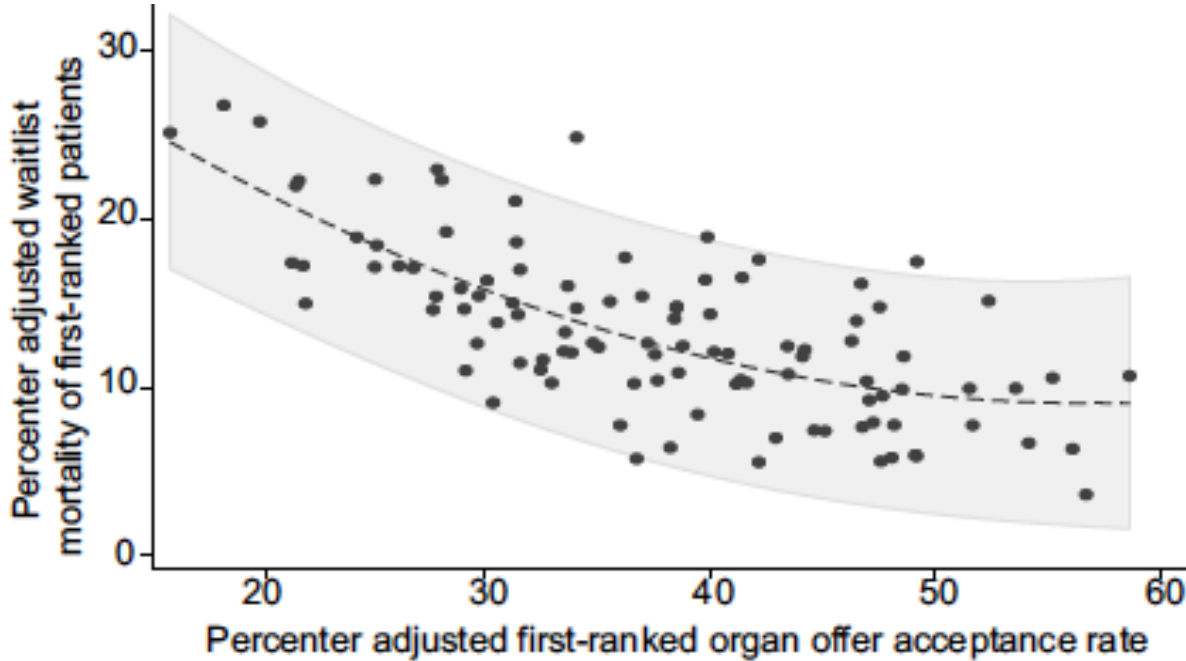
Transplant Benefit

- Transplants between 2001-2007
- Post transplant survival modeled by Cox regression
- Donor and recipient factors
- Survival benefit based on “typical liver donor” (reference level for donor factors)



Schaubel et al. AJT, 2009

Mortality Risk with Declining Liver Offer



Goldberg et al. J of Hepatology, 2015

Mortality Risk with Declining Liver Offer

Table 2. Unadjusted and adjusted waitlist outcomes among all non-Status 1 patients ranked first on at least one match run based on center acceptance patterns for first-ranked organ offers from 5/1/07-6/17/13, n = 11,533.*

Adjusted percentage of first-ranked offers accepted at center	Centers	Patients	Waitlist mortality, No. (%)†	Transplanted, No. (%)*	Estimated adjusted waitlist mortality rates (95% CI)‡
≥50%	9	1002	61 (6.1)	926 (92.4)	5.4% (3.5-7.3%)
40-49.9%	31	4392	338 (7.7)	3937 (89.6)	8.4% (7.2-9.6%)
30-39.9%	37	3889	451 (11.6)	3316 (85.3)	12.0% (10.5-13.4%)
<30%	27	2250	471 (20.9)	1689 (75.1)	17.9% (15.6-20.2%)

Goldberg et al. J of Hepatology, 2015

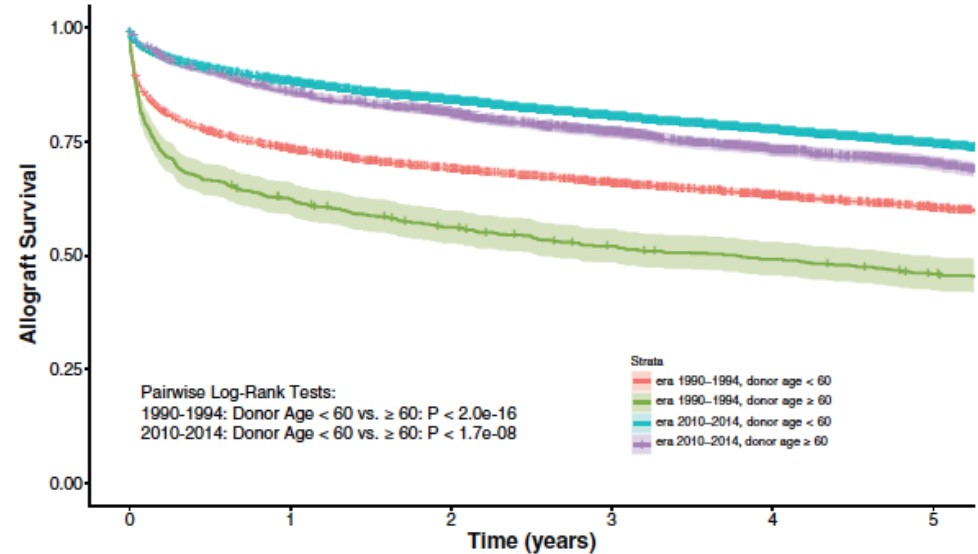
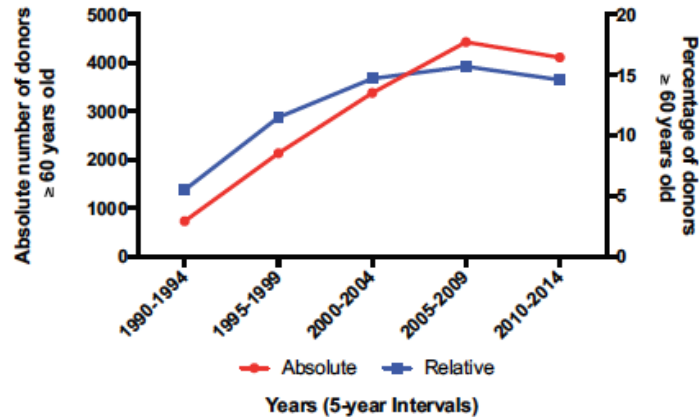
“Marginal” or High-Risk Donor Livers

- Older (Donor age > 60 y)
- Steatotic
- Donation after Circulatory Death (DCD)
- Combinations of the above
- Excluding HCV+ donor livers

Use of Older Donor Livers

- UNOS database analysis
- 14,796 LTx with Donor Age ≥ 60 years
- 1990 - 2014

Absolute and relative utilization of donors ≥ 60 years old



Gao, Q et al. Ann Surg, 2018

Use of Older Donor Livers

TABLE 1. Characteristics of Older Donors (≥ 60), From 1990 to 2014

Variables	Year of Transplantation					<i>P</i>
	1990–1994 (n = 730)	1995–1999 (n = 2137)	1999–2004 (n = 3382)	2005–2009 (n = 4431)	2010–2014 (n = 4116)	
Demographics						
Median donor age, years (IQR)	64 (61–67)	65 (62–70)	66 (62–71)	66 (62–71)	65 (62–69)	<0.001
Median cold ischemia time, hours (IQR)	10.0 (7.8–12.7)	8.4 (6.5–10.6)	7.6 (6.0–10.0)	7.0 (5.4–8.8)	6.0 (4.7–7.6)	<0.001
Laboratory tests, median (IQR)						
Sodium	N/A	N/A	137 (134–139)	137 (133–139)	137 (133–139)	0.69
Creatinine	1.1 (0.8–1.5)	1.0 (0.8–1.4)	1.1 (0.8–1.5)	1.2 (0.9–1.6)	1.1 (0.8–1.7)	<0.001
Total bilirubin	0.6 (0.4–1.0)	0.7 (0.5–1.0)	0.7 (0.4–1.0)	0.7 (0.5–1.1)	0.7 (0.4–1.0)	<0.001
Histology						
Median microvesicular steatosis (IQR)	N/A	N/A	5 (0–10)	5 (0–10)	5 (0–10)	0.77
Median macrovesicular steatosis (IQR)	N/A	N/A	5 (0–10)	5 (0–10)	5 (0–10)	0.055

Gao, Q et al. Ann Surg, 2018

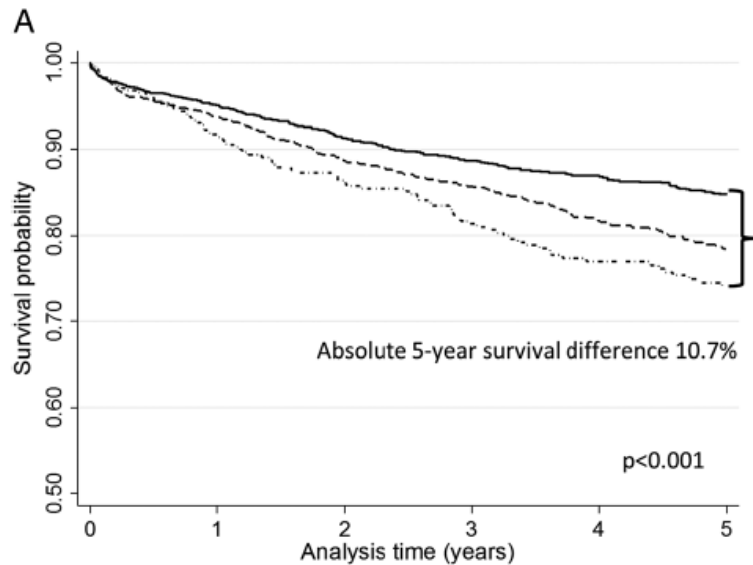
Use of Older Donor Livers

TABLE 2. Characteristics of Recipients of Older Grafts (≥ 60), From 1990 to 2014

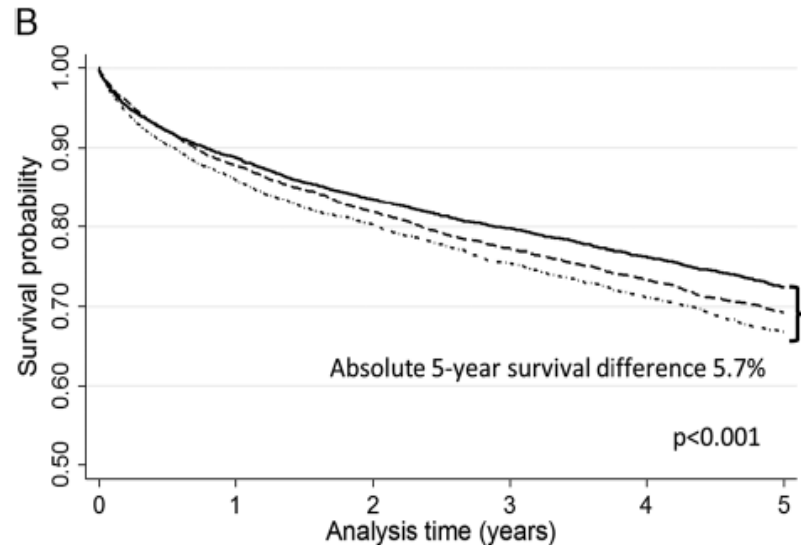
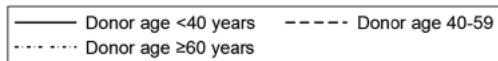
Variables	Year of Transplantation					P
	1990–1994	1995–1999	2000–2004	2005–2009	2010–2014	
Number of transplants (% of total)	730 (5.5%)	2137 (11.5%)	3382 (14.7%)	4431 (15.7%)	4116 (14.6%)	<0.001
Median age, years (IQR)	51 (42–60)	52 (44–60)	54 (48–60)	56 (50–62)	59 (53–64)	<0.001
Median time on waiting list, days (IQR)	53 (12–151)	125 (26–299)	103 (23–348)	76 (18–242)	121 (32–321)	<0.001
Ethnicity						<0.001
White	589 (80.7%)	1644 (76.9%)	2511 (74.2%)	3244 (73.2%)	2995 (72.8%)	
Black	43 (5.9%)	152 (7.1%)	254 (7.5%)	346 (7.8%)	316 (7.7%)	
Hispanic	71 (9.7%)	246 (11.5%)	440 (13.0%)	569 (12.8%)	531 (12.9%)	
Asian	22 (3.0%)	67 (3.1%)	134 (4.0%)	233 (5.3%)	227 (5.5%)	
Others/unknown	5 (0.6%)	28 (1.4%)	43 (1.2%)	39 (0.9%)	47 (1.1%)	
Patient acuity						<0.001
ICU	198 (27.2%)	509 (23.9%)	553 (16.4%)	468 (10.6%)	415 (10.1%)	
Hospitalized, not in ICU	176 (24.1%)	512 (24.0%)	487 (14.4%)	635 (14.3%)	648 (15.7%)	
Not hospitalized	355 (48.7%)	1113 (52.2%)	2342 (69.2%)	3328 (75.1%)	3053 (74.2%)	
Laboratory tests, median (IQR)						
Albumin	2.9 (2.5–3.3)	2.8 (2.4–3.2)	2.8 (2.4–3.3)	2.9 (2.5–3.5)	3.1 (2.6–3.6)	<0.001
INR	N/A	1.5 (1.2–1.9)	1.5 (1.3–1.9)	1.6 (1.3–2.0)	1.6 (1.3–2.1)	<0.001
Creatinine	1.1 (0.8–1.7)	1.0 (0.8–1.4)	1.0 (0.8–1.5)	1.1 (0.8–1.5)	1.0 (0.8–1.6)	<0.001
Bilirubin	N/A	N/A	3.2 (1.7–6.7)	3.4 (1.7–7.4)	3.3 (1.6–8.0)	0.181
Lab MELD	N/A	N/A	18 (13–24)	18 (13–25)	19 (13–27)	0.035

Gao, Q et al. Ann Surg, 2018

Impact of Donor and Recipient Age



Recipients < 40 years



Recipients > 60 years

Bitterman and Goldberg, Transplantation, 2018

Impact of Donor and Recipient Age

TABLE 1.

Results of multivariable model evaluating the interaction of donor and recipient age on the risk of graft failure and posttransplant mortality

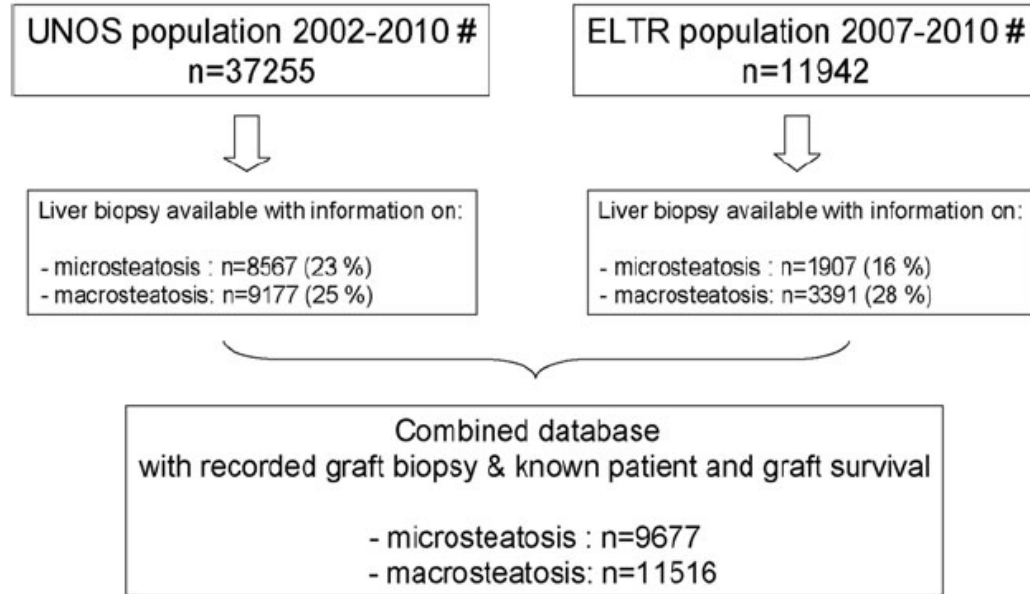
		Hazard ratio for the risk of graft failure (95% CI)		
		Recipient age category		
		<40 y	40-59 y	≥60 y
Donor age category, y	<40	Reference	Reference	Reference
	40-59	1.43 (1.25-1.65)	0.90 (0.81-0.99)	1.07 (0.96-1.19)
	≥60	1.89 (1.56-2.28)	0.91 (0.77-1.08)	0.95 (0.80-1.13)
		Hazard ratio for the risk of posttransplant mortality (95% CI)		
		Recipient age category		
		<40 y	40-59 y	≥60 y
Donor age category, y	<40	Reference	Reference	Reference
	40-59	1.37 (1.15-1.62)	1.10 (0.97-1.25)	1.49 (1.30-1.69)
	≥60	1.74 (1.37-2.20)	1.15 (0.93-1.42)	1.37 (1.11-1.70)

Bitterman and Goldberg, Transplantation, 2018

Steatosis in DBD LTx

- Microsteatosis not a significant problem.
- Macrosteatosis
 - Mild: 0-30%: Good outcomes
 - Moderate: 30-60%: Similar outcomes. Increased risk of EAD or PGF
 - Severe: Decreased patient and graft survival, higher rates of PNF

Adult liver transplants *



* partial grafts, DCD grafts, and combined transplants excluded
since documentation of MELD

Dutkowski et al. Ann Surg, 2012

TABLE 1. Development of the Adjusted BAR Score Based on a Logistic Regression Model

Predictor	Category	Odds Ratio, β	Regression Coefficient, β	Shrunk Regression Coefficient, β_s	P	Reference Value W_i (midpoint)	$\beta_s \times (W_{ij} - W_{ireference})$	Risk score ($\beta_s \times [W_i - W_{ireference}] / B^\dagger$)	Adjusted BAR	Original BAR*
Recipient age	≤40	1.018	0.018	0.018	<0.001	35.5 ($W_{1reference}$)	0	0	0	0
	>40–60					50.5	0.270	2	1	1
	>60					70.5	0.630	5	3	3
Laboratory model for end-stage liver disease score at transplantation	6–15	1.154	0.143	0.143	<0.001	10.5 ($W_{2reference}$)	0	0	0	0
	>15–25					20.5	1.430	10	6	5
	>25–35					30.5	2.860	19	11	10
	>35					40.5	4.290	29	16	14
Re-transplantation	No	3.193	1.161	1.161	<0.001	0 ($W_{3reference}$)	0	0	0	0
	Yes					1	1.161	8	5	4
Cold ischemia	0–6	1.019	0.019	0.019	0.007	3.0 ($W_{4reference}$)	0	0	0	0
	>6–12					9.5	0.124	1	1	1
	>12					15	0.228	2	1	2
Donor age	≤40	1.010	0.010	0.010	<0.001	35.5 ($W_{5reference}$)	0	0	0	0
	>40–60					50.5	0.150	1	1	1
	>60					70.5	0.350	3	2	1

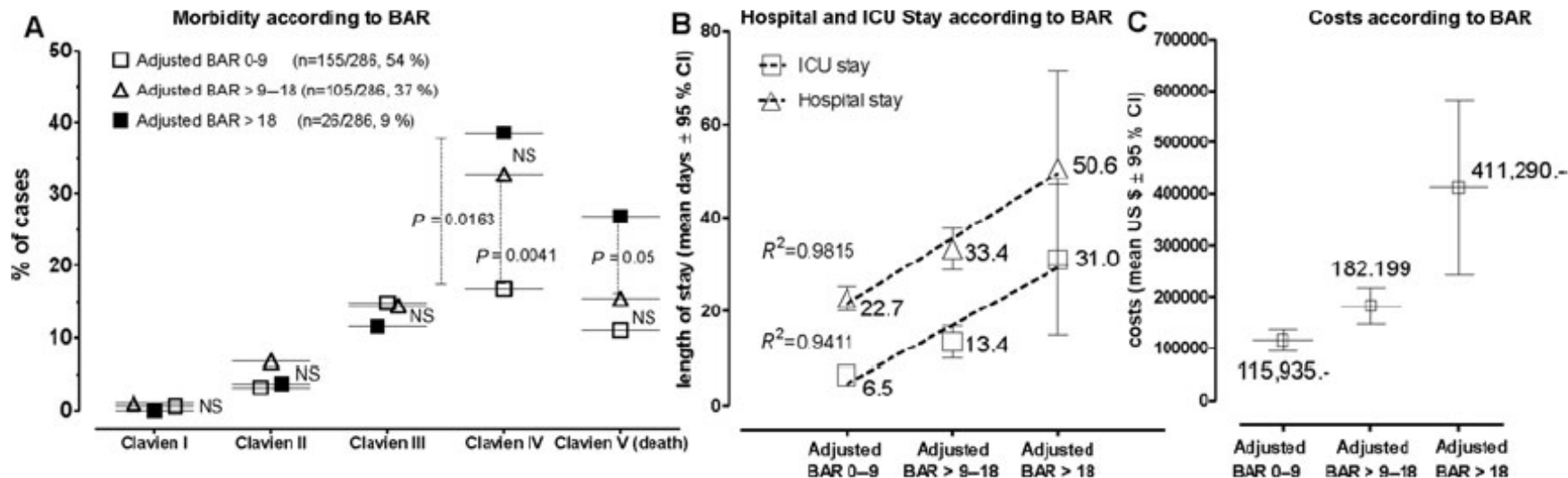
Points rounded to the next integer.

Shrinkage coefficient: 0.999

*Considering additional life support at the time of transplant (3 points).

†Constant B corresponds to an important change of 8 hours in cold ischemia, which is equivalent to a coefficient $8 \times 0.019 = 0.152$.

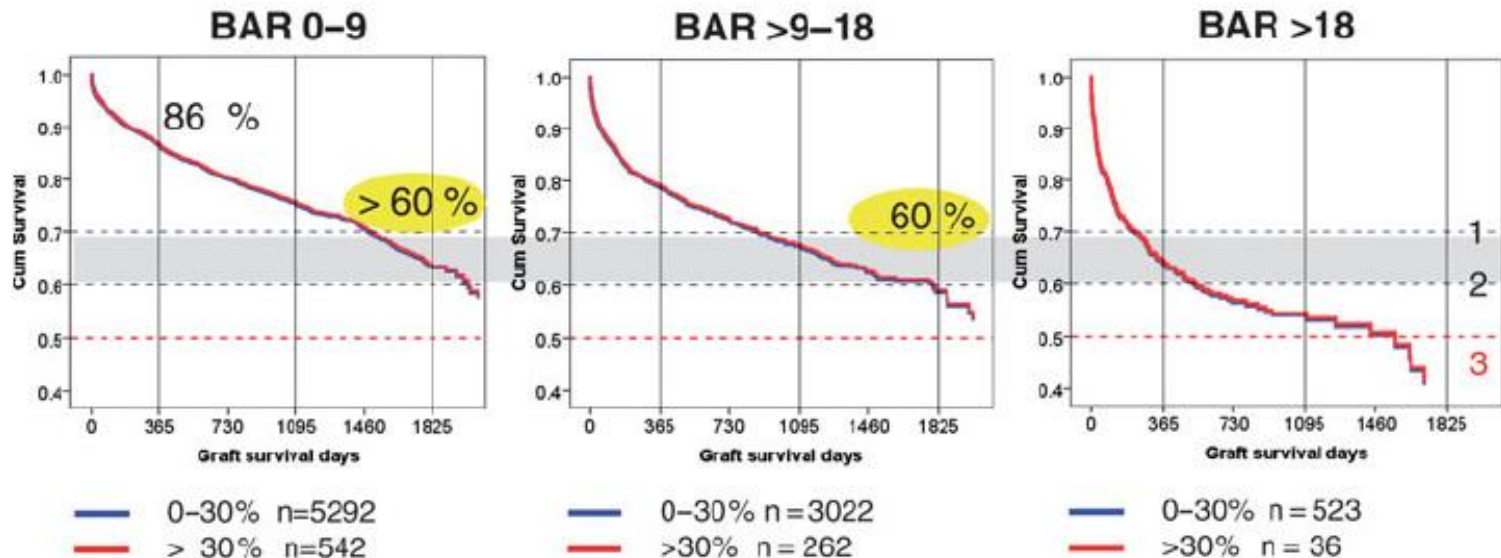
Dutkowski et al. Ann Surg, 2012



Dutkowski et al. Ann Surg, 2012

BAR + Microsteatosis

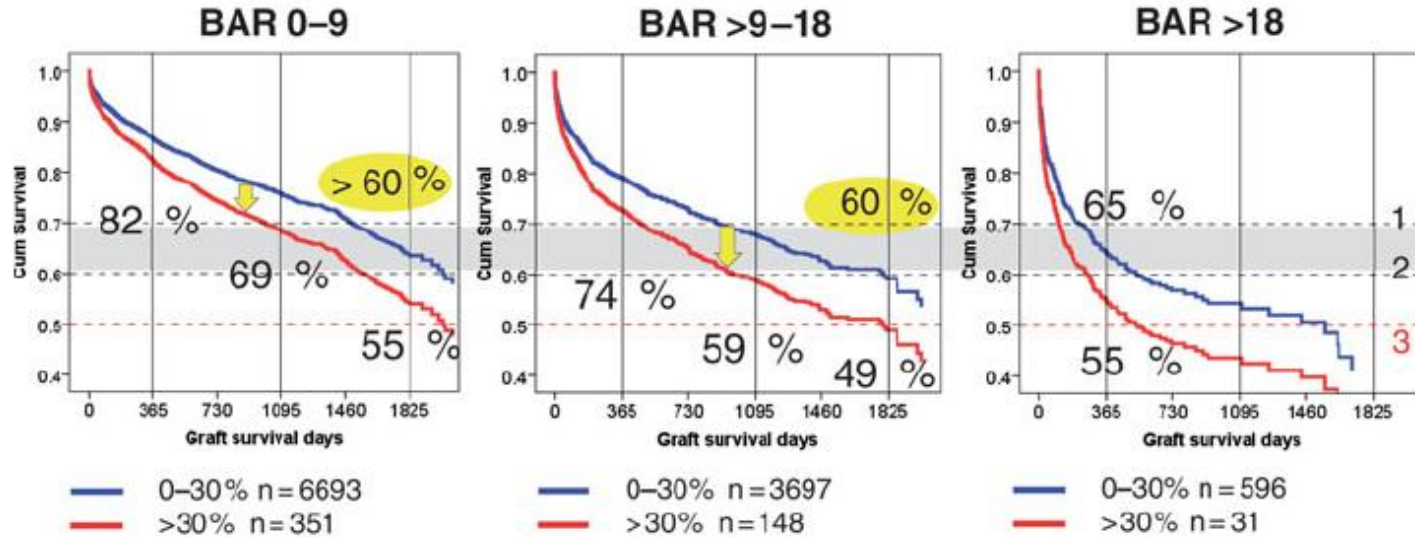
Pooled data (UNOS+ELTR, n=9677 biopsies of 49197 liver grafts, 20%)



Dutkowski et al. Ann Surg, 2012

BAR + Macrosteatosis

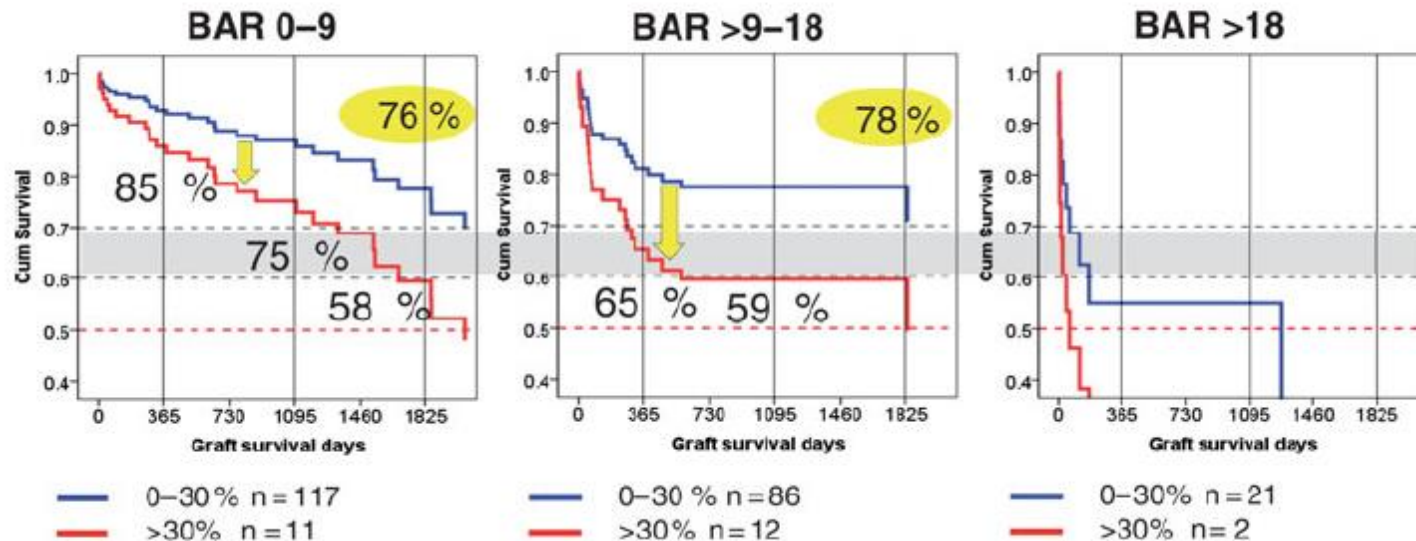
Pooled data (UNOS+ELTR, n=11516 biopsies of 49197 liver grafts, 23%)



Dutkowski et al. Ann Surg, 2012

BAR + Macrosteatosis

Own data (n=249 biopsies of 286 liver grafts, 87 %)



Dutkowski et al. Ann Surg, 2012

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	>15–25					20.5	1.430	10	6	5
	>25–35					30.5	2.860	19	11	10
	>35					40.5	4.290	29	16	14
Re-transplantation	No	3.193	1.161	1.161	<0.001	0 ($W_{3reference}$)	0	0	0	0
	Yes					1	1.161	8	5	4
Cold ischemia	0–6	1.019	0.019	0.019	0.007	3.0 ($W_{4reference}$)	0	0	0	0
	>6–12					9.5	0.124	1	1	1
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	>40–60					50.5	0.150	1	1	1
	>60					70.5	0.350	3	2	1

Points rounded to the next integer.

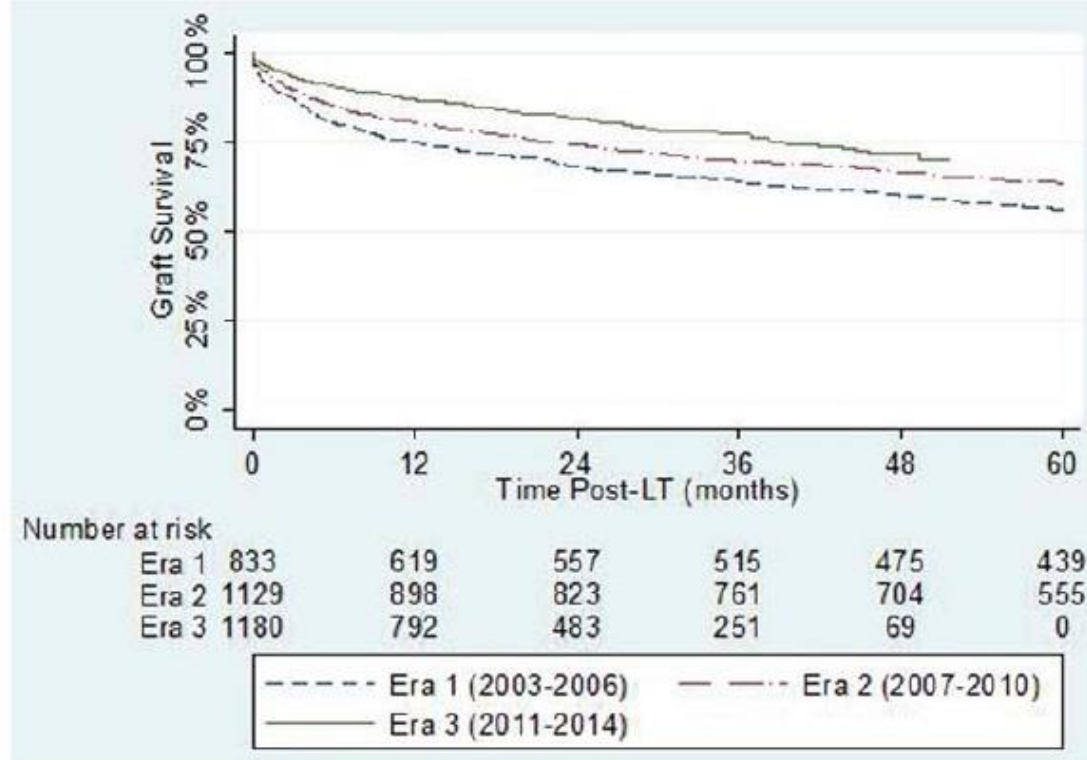
Shrinkage coefficient: 0.999

*Considering additional life support at the time of transplant (3 points).

†Constant B corresponds to an important change of 8 hours in cold ischemia, which is equivalent to a coefficient $8 \times 0.019 = 0.152$.

Dutkowski et al. Ann Surg, 2012

Improving US Results of DCD Liver Transplantation



Croome et al.
Transplantation, 2016

Improving US Results of DCD Liver Transplantation

TABLE 2.

Multivariate backwards stepwise regression predicting graft survival

Variable	HR	CI	P
Recipient age (per 5 y increase)	1.04	1.01-1.07	0.035
Biologic MELD score (per 5 unit increase)	1.07	1.03-1.11	0.002
On ventilator at LT	1.65	1.22-2.24	0.001
Recipient HCV+ serology	1.24	1.08-1.42	0.002
Donor age (per 5 y increase)	1.06	1.03-1.08	<0.001
Cold ischemic time (per 1 h increase)	1.03	1.02-1.05	<0.001
Era 2 (era 1 reference)	0.81	0.69-0.94	0.007
Era 3 (era 1 reference)	0.61	0.50-0.73	<0.001

Croome et al. Transplantation, 2016

Predictors of DCD Liver Graft Failure

- SRTR Analysis
- DCD LTx (2001-2009)
- 1567 DCD Liver Txp
- Risk Factors for graft loss
 - CIT > 6h, DWIT > 35 min, Donor age > 50 y, MELD > 35.

Table 2: Predictors of graft failure following DCD liver transplantation¹

	Variable	Hazard ratio	95% CI		p-Value
Recipient characteristics					
Age at transplant	<18 years (reference 18–55 years)	0.33	0.11	0.95	0.040
	≥55 years (reference 18–55 years)	1.26	1.05	1.52	0.014
Sex	Female (reference male)	0.73	0.59	0.91	0.004
Race	African American (reference white)	1.38	1.02	1.87	0.038
Diagnosis	Metabolic disorders (reference noncholestatic cirrhosis)	2.13	1.31	3.47	0.003
MELD Score	≥35 (reference 15–25)	1.47	1.00	2.16	0.048
Hospitalization status	ICU or non-ICU hospitalization at transplant (reference ambulatory)	1.39	1.09	1.78	0.008
Medical condition at transplant	On life support (reference no life support)	1.46	1.01	2.13	0.045
Hepatitis C virus serology	Positive (reference no, unknown, missing)	1.23	1.01	1.51	0.041
Donor characteristics					
Donor age	<18 years (reference 18–50 years)	0.71	0.50	1.00	0.0498
	50–60 years (reference 18–50 years)	1.39	1.11	1.75	0.0047
	≥60 years (reference 18–50 years)	1.88	1.29	2.74	0.0011
Donor weight	> 100 kg	1.56	1.20	2.04	0.0010
Transplant characteristics					
Donor warm ischemia time ²	≥35 mins (reference <35 mins)	1.84	1.23	2.74	0.0028
Cold ischemia time	6–10 h (reference <6 h)	1.64	1.29	2.08	<0.0001
	10–13 h (reference <6 h)	2.04	1.50	2.78	<0.0001
	≥13 h (reference <6 h)	3.84	2.57	5.74	<0.0001
	Missing (reference <6 h) ³	2.42	1.77	3.30	<0.0001

¹Also adjusted for: donor cause of death, race, sex and height, recipient BMI, diabetes, diagnosis, status 1/1A/1B, on dialysis, previous liver transplant, previous malignancy, previous abdominal surgery, history of portal vein thrombosis at transplant, HBV serology and ABO compatibility.

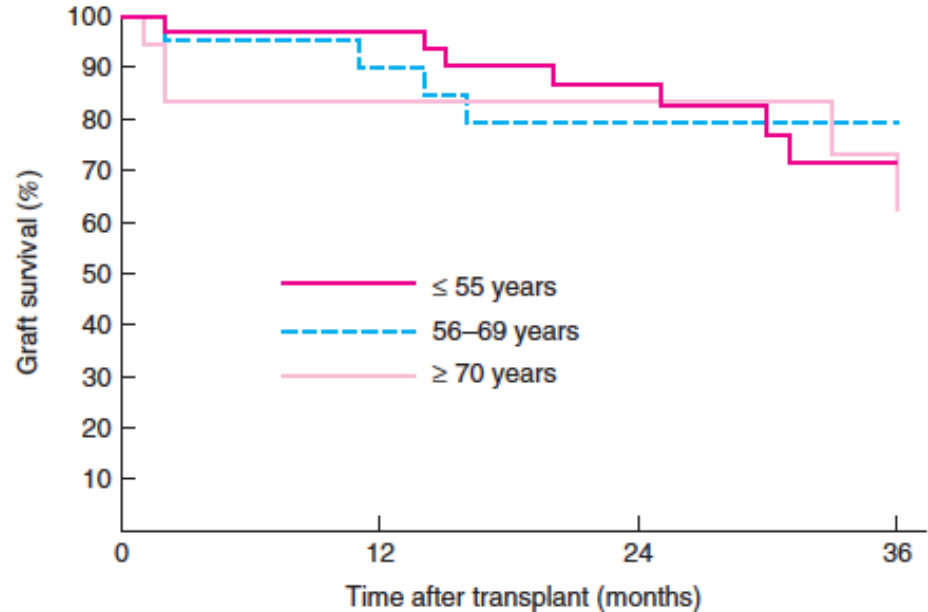
²Warm ischemia time was missing in 8.6% of DCD liver recipients.

³Cold ischemia time was missing in 10.3% of DCD liver recipients.

Mathur AK et al. AJT, 2010; 10: 2512.

Donor Age and DCD LTx

- 70 DCD LTx
- Age < 55, 56-69, ≥ 70 years
- 18 donor livers ≥ 70 years
- No difference in graft survival
- No PNF
- No difference in biliary comps.



Detry, 2014. Br. Journal of Surg.

Recipient and Procurement Characteristics

	Donor group			P§
	≤ 55 years (n = 32)†	56–69 years (n = 20)	≥ 70 years (n = 18)	
Age (years)*	58 (51–63)	60 (51–64)	59 (52–64)	0.929
Sex ratio (M : F)	29 : 3	16 : 4	15 : 3	0.536¶
Laboratory MELD score*	14.5 (11.2–17.7)	12.5 (9.2–17.7)	17.0 (14.0–25.2)‡	0.032
Liver disease				
HCC in cirrhotic liver	11	11	3	
Other cancer	2	1	1	
Cirrhosis without cancer	17	8	14	
Retransplant for HAT	2	0	0	

	Donor group			P†
	≤ 55 years (n = 32)	56–69 years (n = 20)	≥ 70 years (n = 18)	
HTK solution	30	15	17	0.078‡
Use of heparin	30	20	17	0.530‡
Donation warm ischaemia time (min)*	20 (15–22)	21 (17–28)	19 (16–27)	0.382
Withdrawal phase	10 (7–12)	13 (8–19)	9 (6–17)	0.300
Acirculatory phase	9 (8–10)	8 (7–11)	9 (7–10)	0.603
Hepatectomy time (min)*	23.0 (20.7–27.5)	24.5 (17.2–30.7)	22.5 (18.2–23.5)	0.206
Cold ischaemia time (min)*	236 (212–287)	245 (204–323)	210 (187–270)	0.395
Suture time (min)*	41 (36–47)	42 (38–46)	39 (33–44)	0.339
Total ischaemia time (min)*	299 (274–348)	306 (280–382)	277 (246–332)	0.277

Detry, 2014. Br. Journal of Surg.

UK DCD Risk Score

Table 1. Donor, graft, and recipient characteristics in the three DCD cohorts in the UK, UNOS, and in our centre in Birmingham.

Parameters of DCD liver transplantation	UK n = 1,153	UNOS n = 1,861	Birmingham n = 315
Donor and graft variables:			
Age (years)	49 (35–59)	34 (21–47)	51 (36–62)
Body-Mass-Index (kg/m ²)	25 (23–28)	25.1 (22.0–29.1)	25 (22.7–27.7)
Total warm ischaemia time (min)	27 (22–31)	-	27 (22–32)
Functional warm ischaemia time (fDWIT) (min)	17 (14–20)	14 (9–21)	17 (14–21)
No. of donors with fDWIT >20 min	254 (22%)	364 (19.6)	82 (26)
No. of donors with fDWIT >30 min	40 (3.5%)	124 (6.7)	13 (4.1)
Asystolic warm ischaemia time (min)	13 (11–15)	-	12 (10–14)
Cold ischaemia time (h)	7.1 (6–8.2)	7 (5.3–9)	7 (5.7–8.1)
No. of grafts with CIT >6 h	853 (74%)	1,145 (61.5%)	222 (70.5%)
Recipient variables:			
Age (years)	55 (48–61)	54 (49–60)	58 (51–64)
Body-Mass-Index (kg/m ²)	27 (24–30)	27.4 (23.8–31.2)	27 (24–30)
lab-MELD score at transplantation (points)	15 (11–19)	16.4 (10.8–23.5)	13 (9–17)
UKELD score at transplantation (points)	53 (50–57)	-	53 (49–56)
BAR-Score at transplantation (points)	5 (3–8)	7 (3–10)	5 (3–7)
Follow-up (days)	865 (364–1,704)	600 (160–1,355)	936 (426–1,602)

Data presented as median and IQR for continuous variables or as number and percent for categorical variables. BAR, Balance of Risk Score; BMI, Body-Mass-Index; CIT, cold ischaemia time; DCD, donation after circulatory death; fDWIT, functional donor warm ischaemia time; IQR, interquartile range; MELD, model of end-stage liver disease; UKELD, United Kingdom model of end-stage liver disease; UNOS, United Network for Organ Sharing.

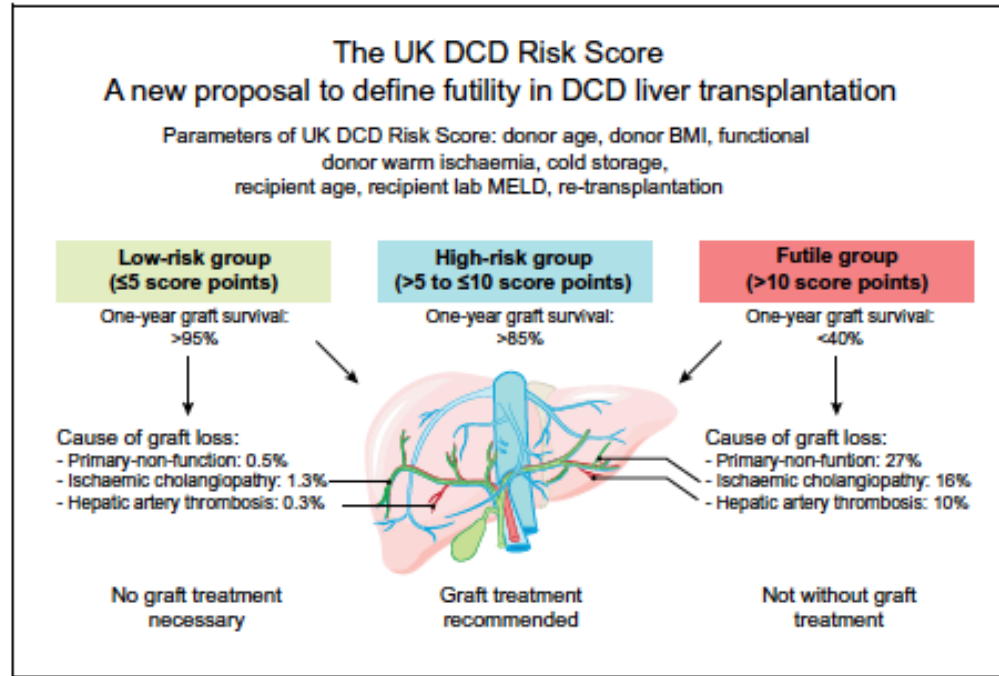
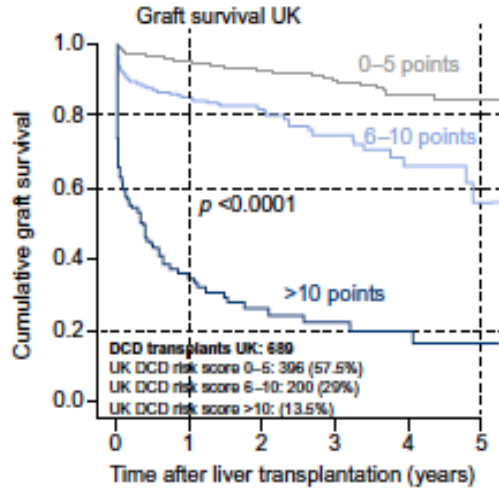
Schlegel A et al. J Hepatology, 2018

UK DCD Risk Score

Parameter	Category	Regression coefficient β	p value	Reference value W_i (Midpoint)	$\beta \times (W_{ij}-W_{i\text{reference}})$	Risk score
Donor age	≤ 60 yr	0.084	0.001	46 (W_1 reference)	0	0
	> 60 yr			66	1.688	2
Donor BMI	≤ 25 kg/m ²	0.519	0.0001	23 (W_2 reference)	0	0
	> 25 kg/m ²			28	2.598	3
Functional donor warm ischaemia	≤ 20 min	0.341	< 0.0001	15 (W_3 reference)	0	0
	> 20 to ≤ 30 min			24	3.069	3
	> 30 min			32	5.797	6
Cold ischaemia time	≤ 6 h	0.791	0.001	5.5 (W_4 reference)	0	0
	> 6 h			7.7	1.740	2
Recipient age	≤ 60 yr	0.241	0.0001	52 (W_5 reference)	0	0
	> 60 yr			64	2.892	3
Recipient lab MELD	≤ 25 points	0.109	0.0001	14 (W_6 reference)	0	0
	> 25 points			30	1.744	2
Retransplantation	No	8.571	< 0.0001	0 (W_7 reference)	0	0
	Yes			1	8.571	9
Total score points						0–27

Schlegel A et al. J Hepatology, 2018

UK DCD Risk Score



Schlegel A et al. J Hepatology, 2018

Selecting the Optimal Recipient

- No significant cardiac disease
 - Avoid complications with post-reperfusion syndrome
 - **Steatotic and DCD livers**
- Re transplants (PNF or HAT first 1-2 weeks): OK
- Re transplants (chronic)
 - **Avoid with old, steatotic and DCD livers**
 - Prolonged CIT
- Prior major upper abdominal surgery: avoid
- MELD > 35: Acceptable outcomes with highly selected DCD livers
 - Other variables: low risk
- MELD < 25 ideal

Conclusions

- Donor-recipient matching is an important component of personalized transplantation to optimize outcomes
- Critical for successful transplants of high risk donor livers
- Scoring systems used as guidance
- Risk of accepting high risk liver > risk of waiting for better offer?
- Good clinical judgment is necessary

Always Do What is Best for the Patient!