Modelos de Gestion de la lista de espera En Europa

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ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

EL CONTEXTO

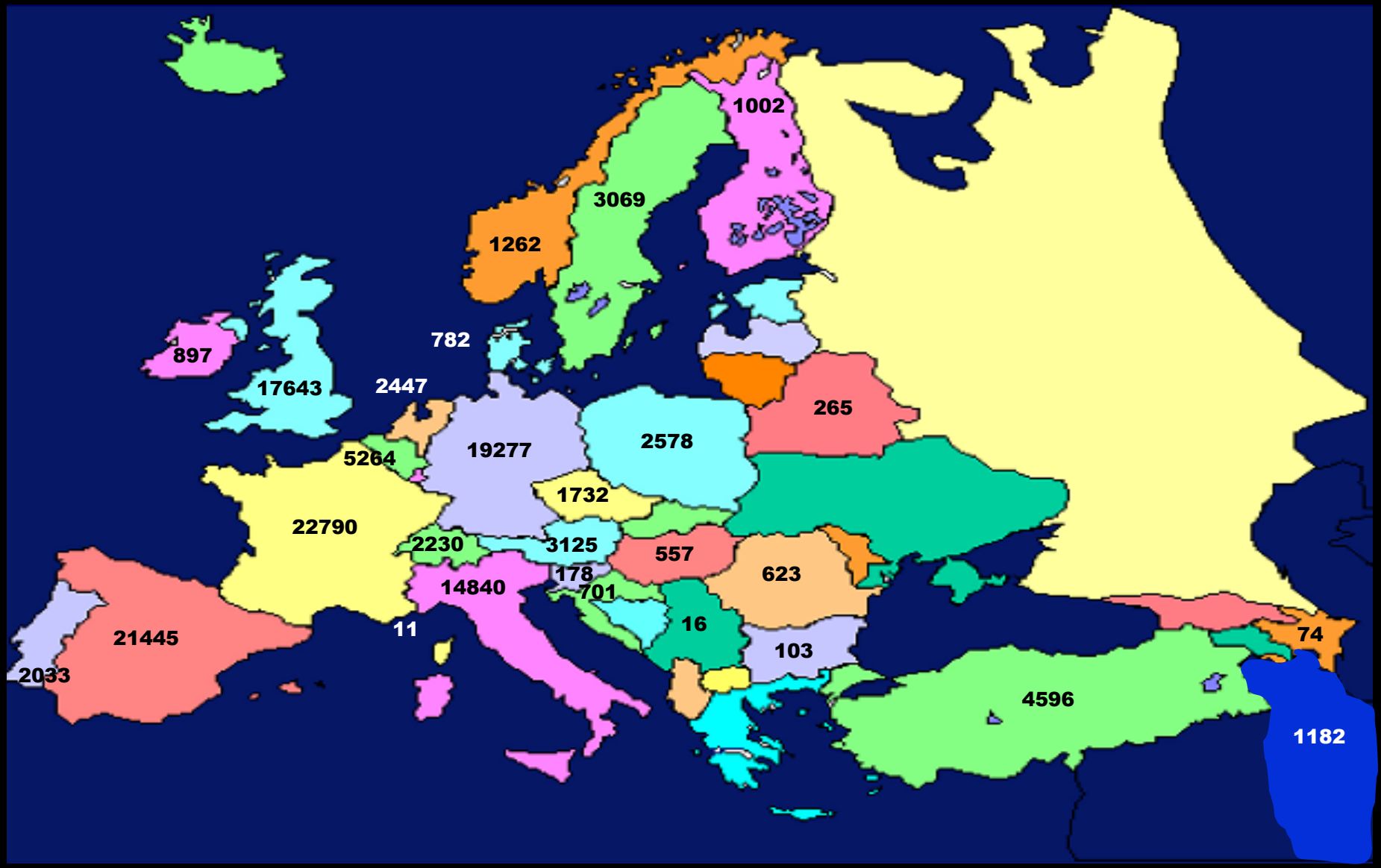
EUROPEAN LIVER TRANSPLANT REGISTRY

29 countries - 158 institutions

130,772 transplantations - From May 1968 to September 2015

ELITA

ELTR

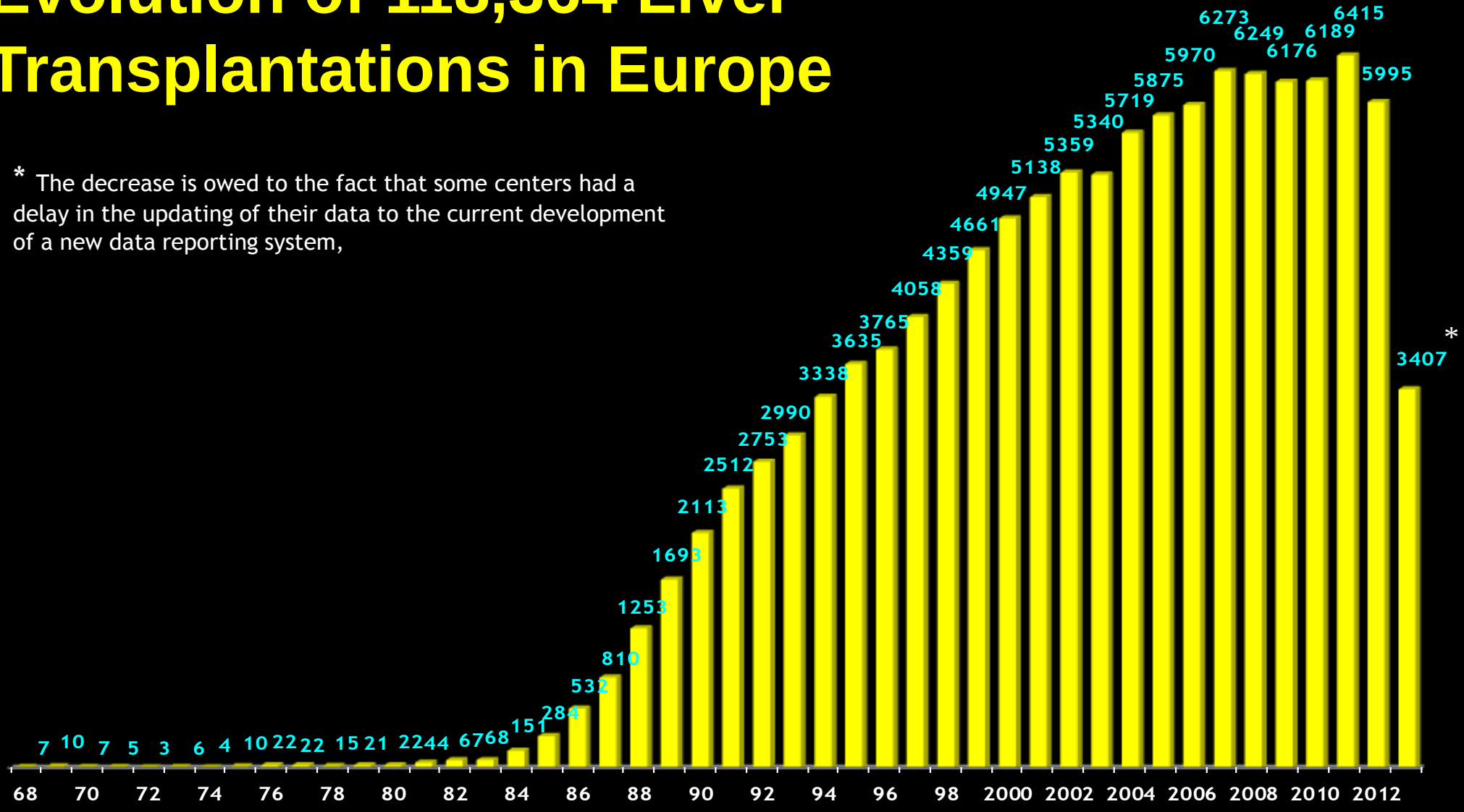


ELITA

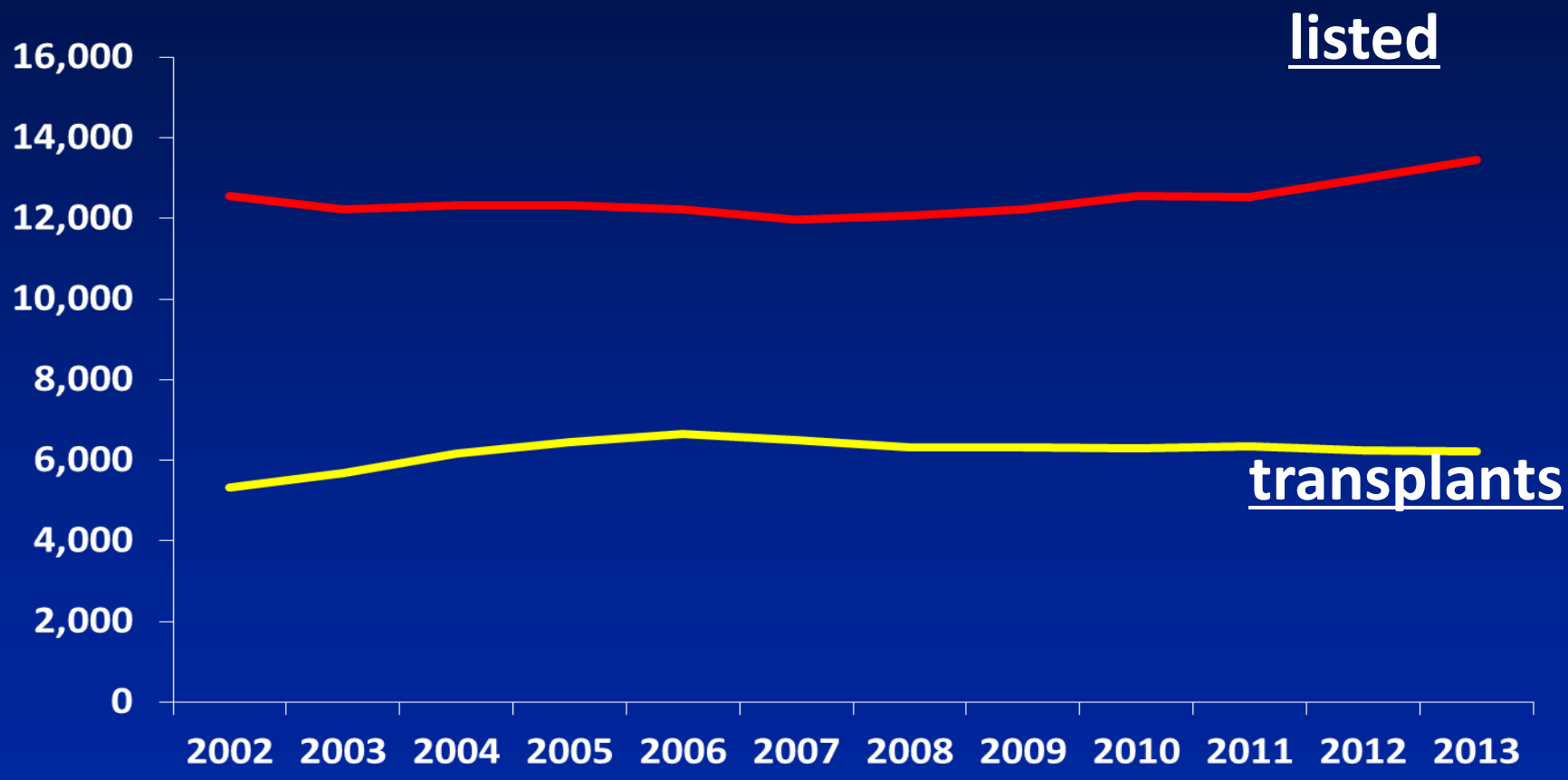
ELTR

Evolution of 118,364 Liver Transplantations in Europe

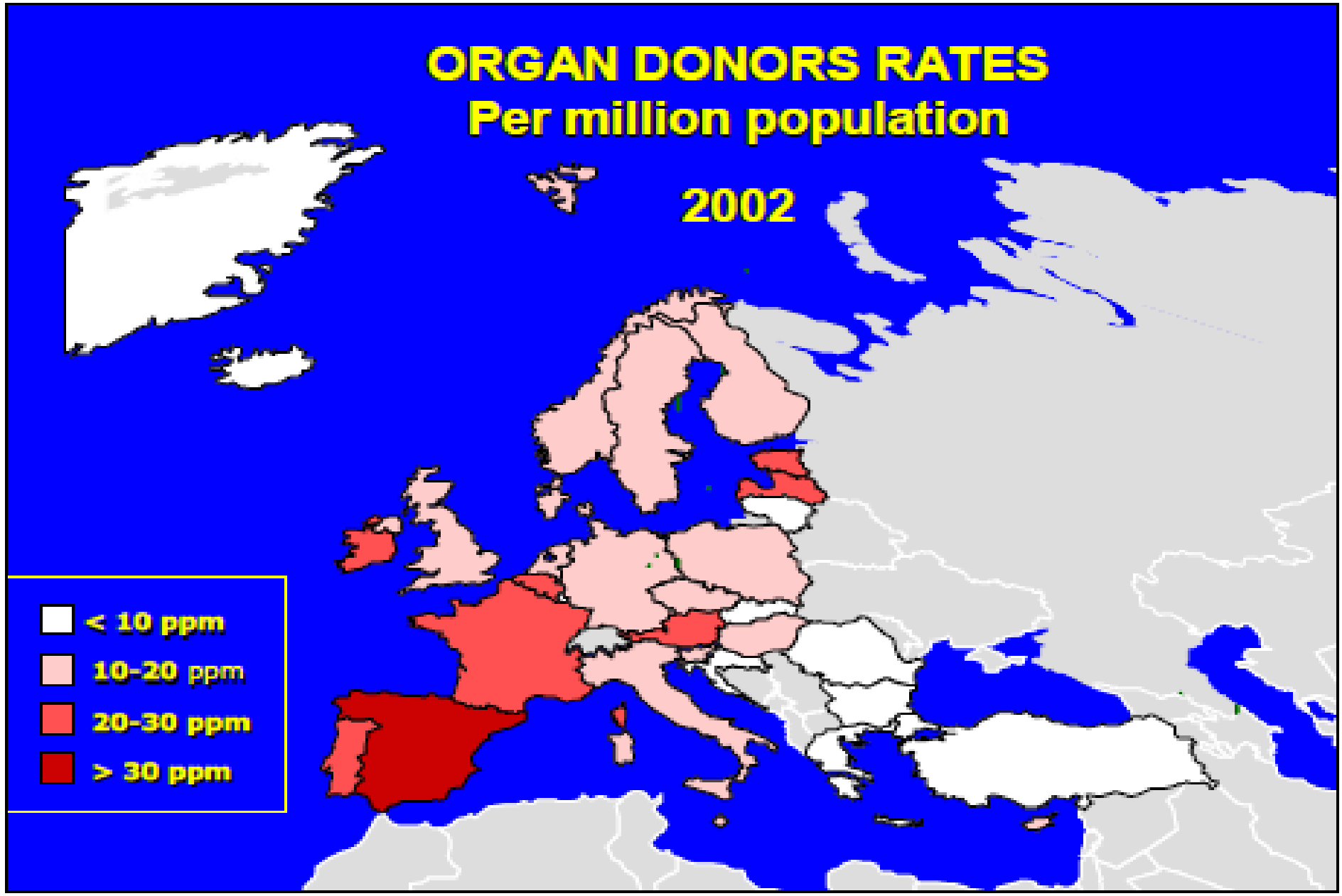
* The decrease is owed to the fact that some centers had a delay in the updating of their data to the current development of a new data reporting system,



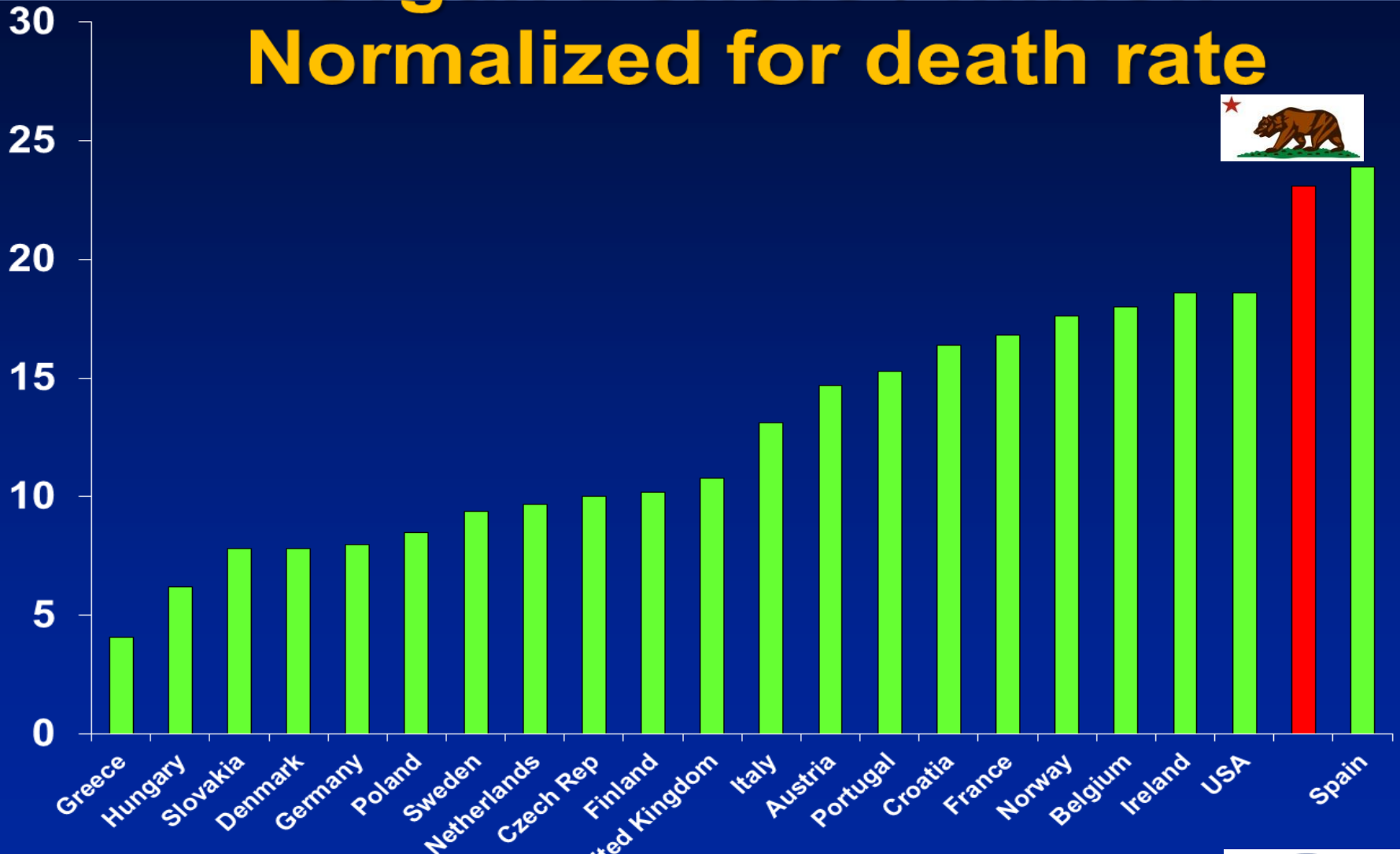
Liver transplants by year



The Center for Liver Disease & Transplantation
NewYork-Presbyterian Hospital


ORGAN DONORS RATES
Per million population
2002
< 10 ppm
10-20 ppm
20-30 ppm
> 30 ppm

Organ Donors / million
Normalized for death rate



Source: donatelifecalifornia.org

The Center for Liver Disease & Transplantation
NewYork-Presbyterian Hospital

Donor pool will never be sufficient for the demand.

To expand the criteria that define what grafts are acceptable.

Which patient with liver failure should receive the transplant.

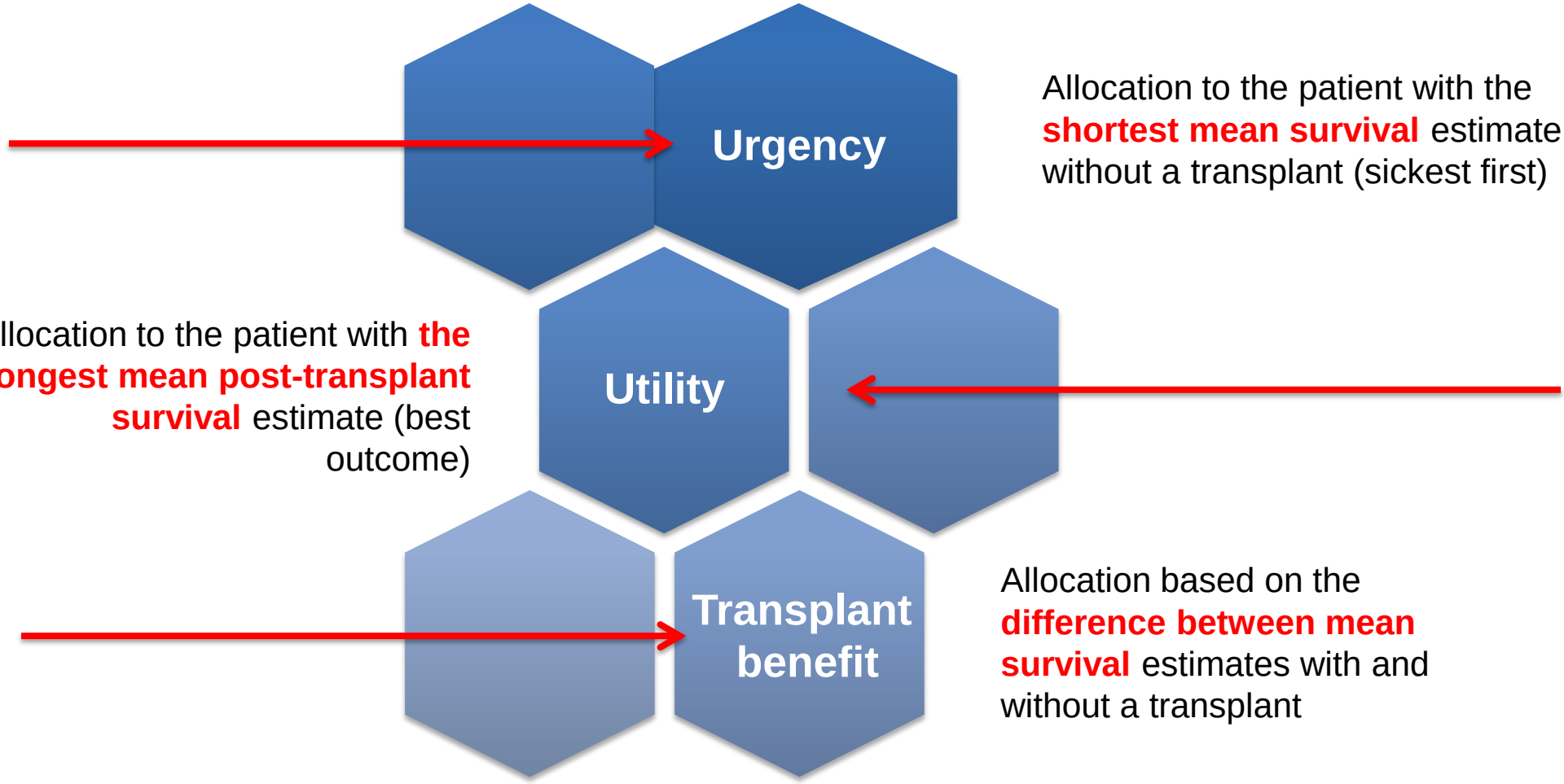
Freeman J Hepatol 2009

J Hepatol 2009;50:664-673

Who should get a liver graft?

Freeman RB, Jamieson N, Schaubel DE,
Porte RJ, Villamil FG

Different Allocation Schemes

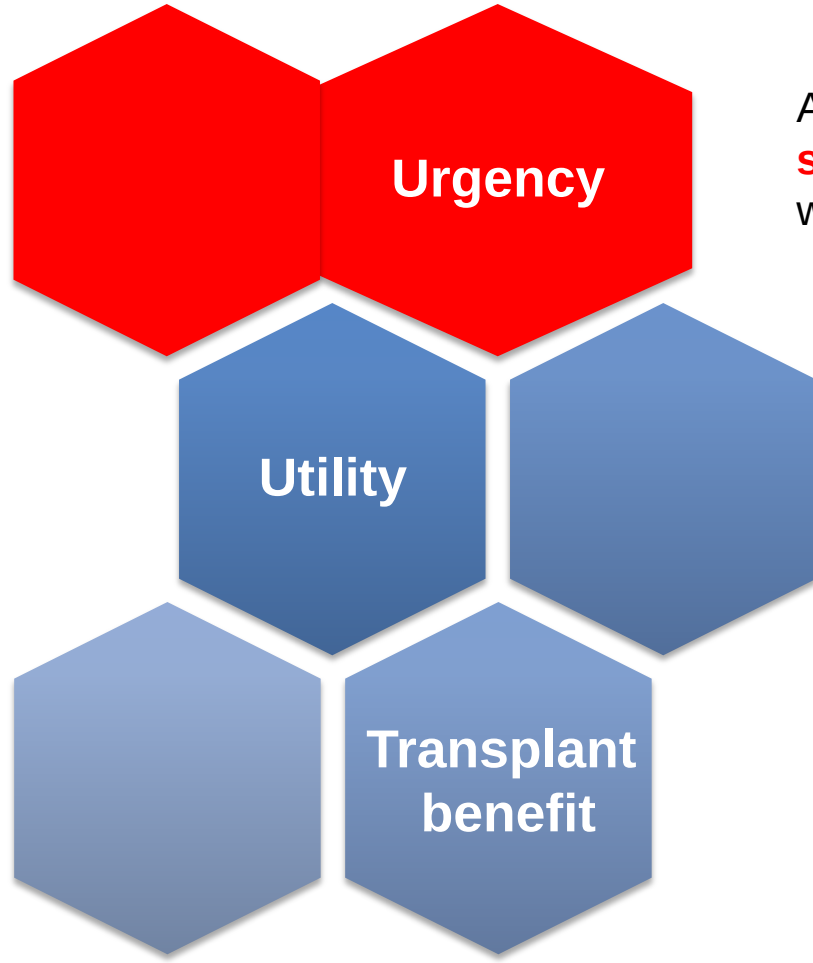


Allocation to the patient with the **shortest mean survival** estimate without a transplant (sickest first)

Allocation to the patient with **the longest mean post-transplant survival** estimate (best outcome)

Allocation based on the **difference between mean survival** estimates with and without a transplant

Urgency-based allocation systems



Allocation to the patient with the **shortest mean survival** estimate without a transplant (sickest first)

Potential problems with Child-Pugh

- Subjective assessment of ascites, PSE
- Influence of medical therapy (albumin, diuretics, …)
- Cut off values for continuous variables
  - Ceiling effect – bilirubin >3mg/dL has only one score
  - Floor effect – albumin <28 g/L has only one score
- Lack of important factors : renal function
- Arbitrary categorisation
- No validation

Model for End Stage Liver Disease (MELD)

- Prediction of 3 month mortality after TIPS
  (Malichoc 2000)
- Aetiology, bilirubin, INR, creatinine (logs)

- Applied to those awaiting liver transplantation
  (Kamath 2001)
- Validated in separate cohorts

A Model to Predict Survival in Patients With End-Stage Liver Disease

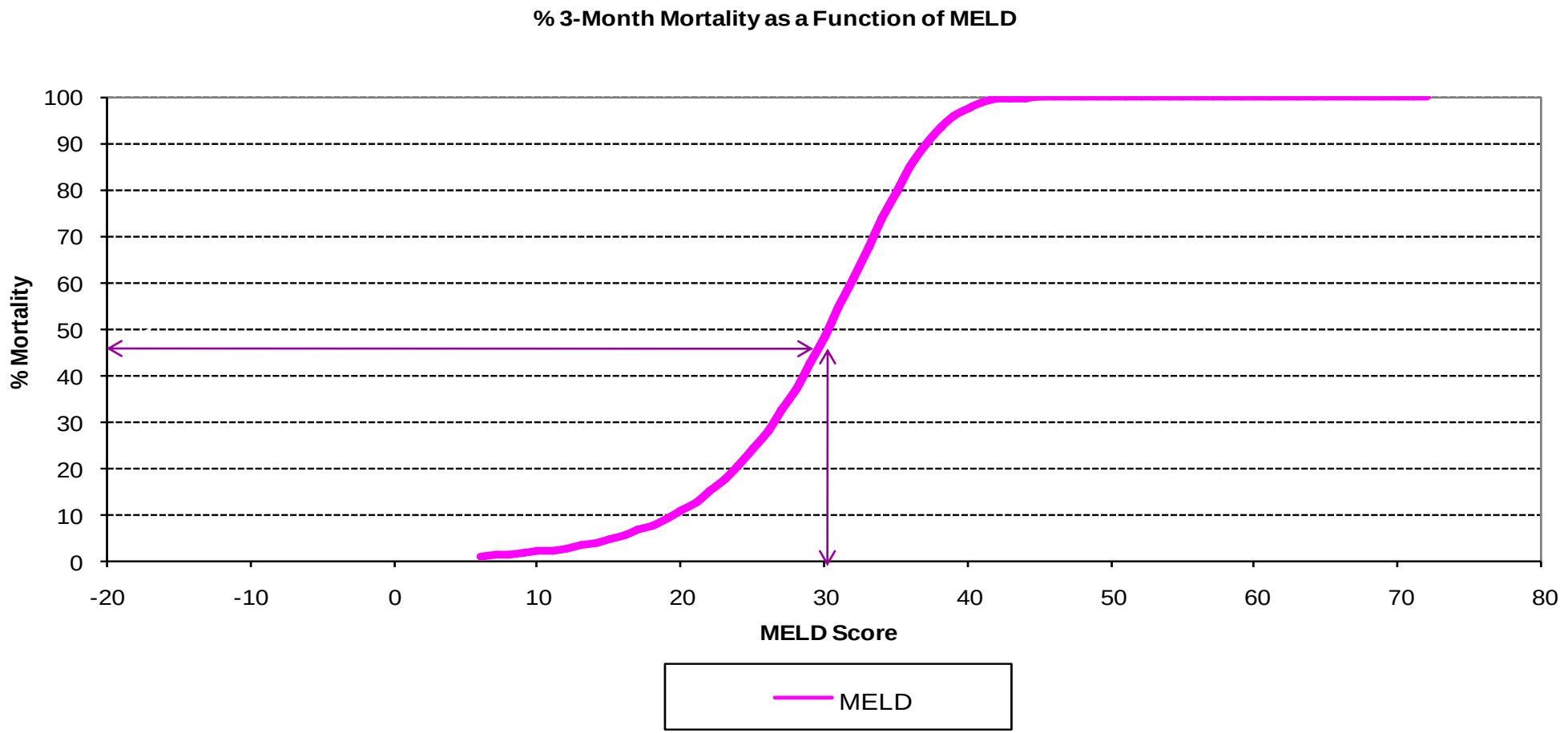
3-month Death rates

MELD	≤9	10-19	20-29	30-39	≥40
Hospitalized	4%	27%	76%	85%	100%
Ambulatory non-Chol.	2%	5.6%	50%	-	-
Ambulatory PBC	1%	13%	0%	-	-
Historical group	8%	26%	56%	66%	100%

Concordance statistic: 0.78 – 0.87 **Dropped aetiology of liver disease**

Kamath PS, Hepatology 2001;33:464-470

Model for End-stage Liver Disease (MELD)



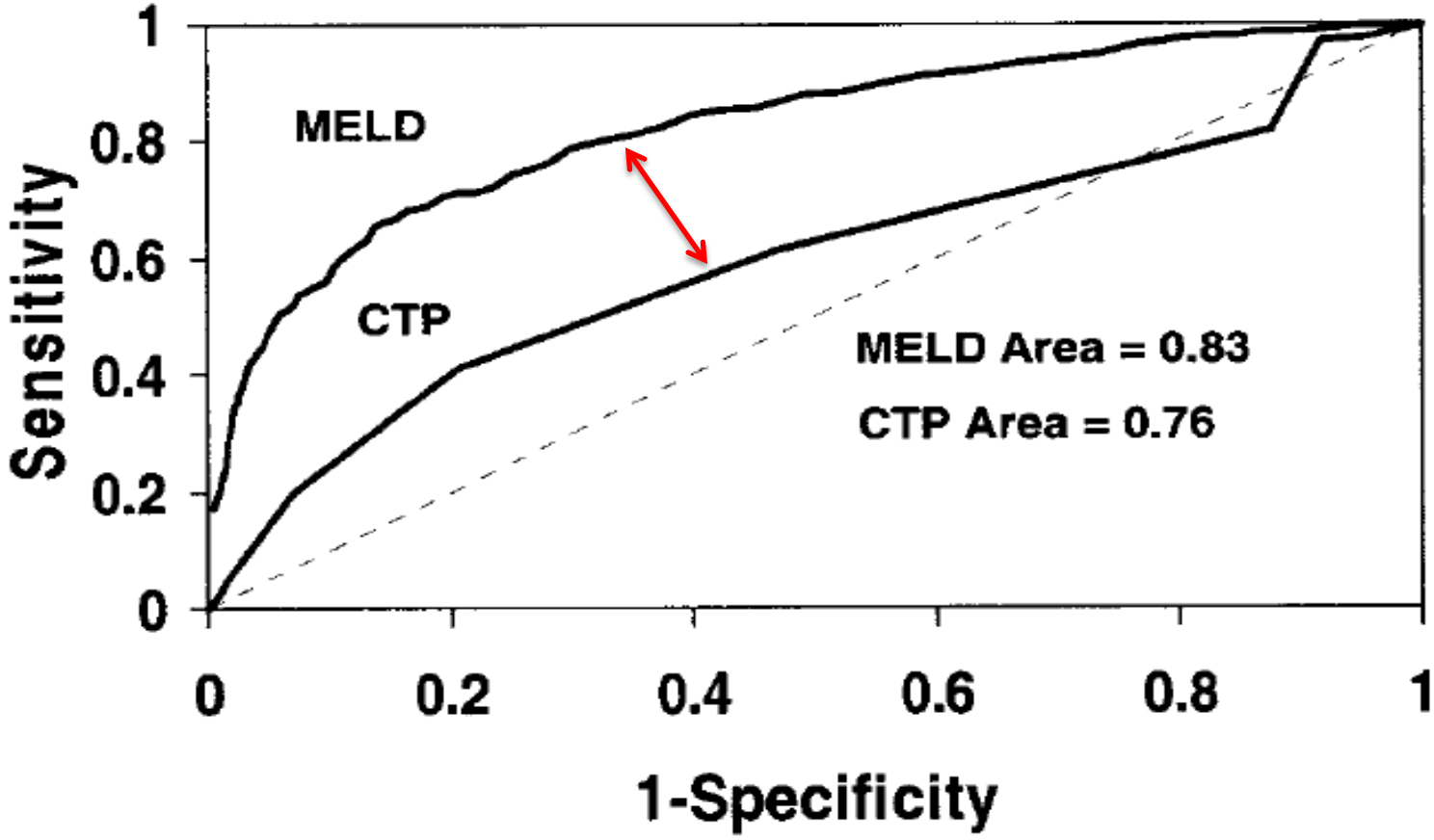
Model for End-stage Liver Disease (MELD)

MELD equivalents

MELD score	%MELD mortality equivalent
20	10
22	15
24	20
25	25
26	30
28	35
29	40
29	45
30	50
31	55
32	60
33	65
33	70
34	75
35	80
36	85
37	90
39	95
40	100%

MELD and Allocation of Donor Livers

3437 adults Cirrhosis, UNOS data (2A, 2B)
November 1999 – December 2001

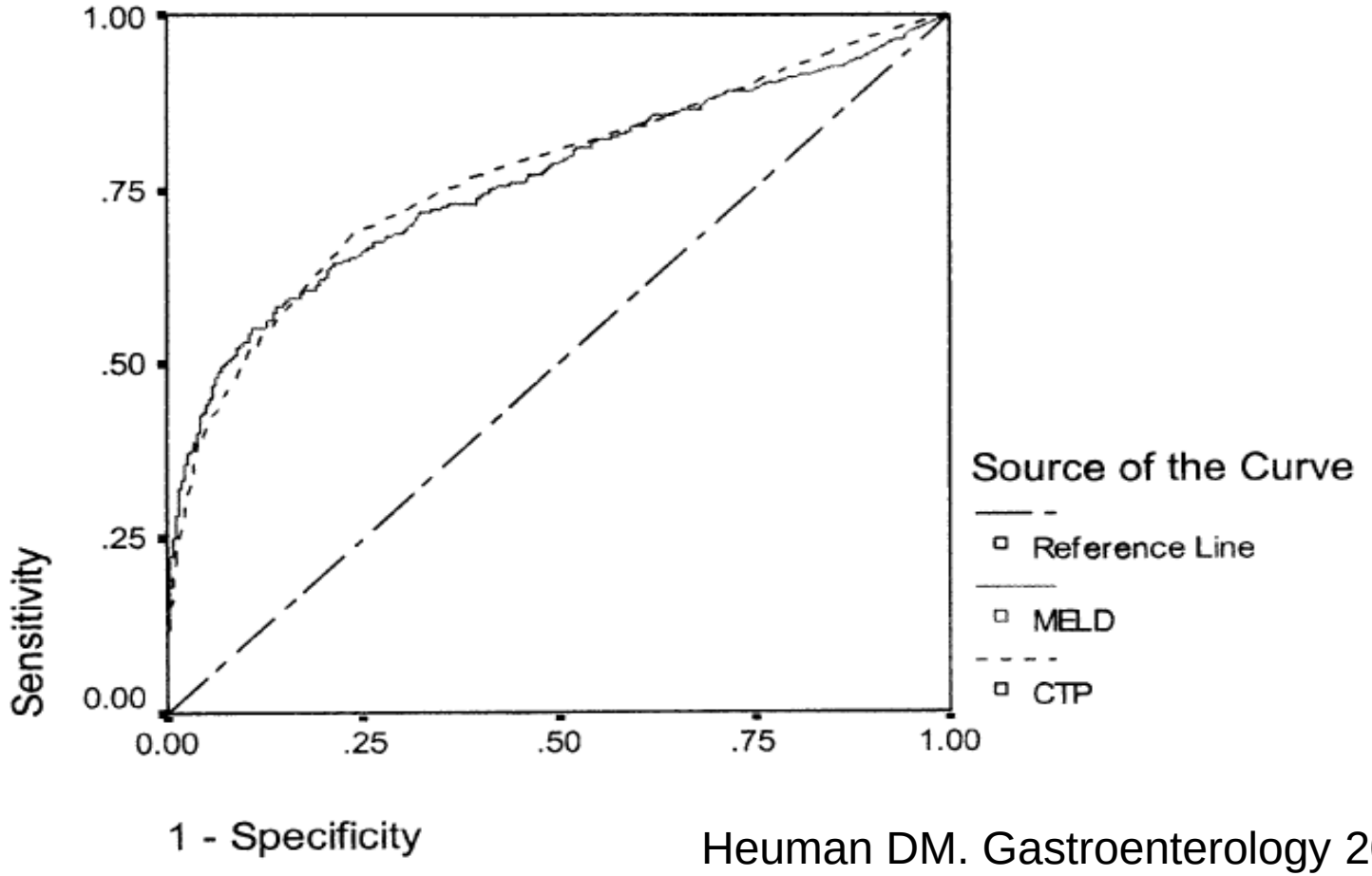


CTP : Child-Turcotte-Pugh

Wiesner R. Gastroenterology 2003

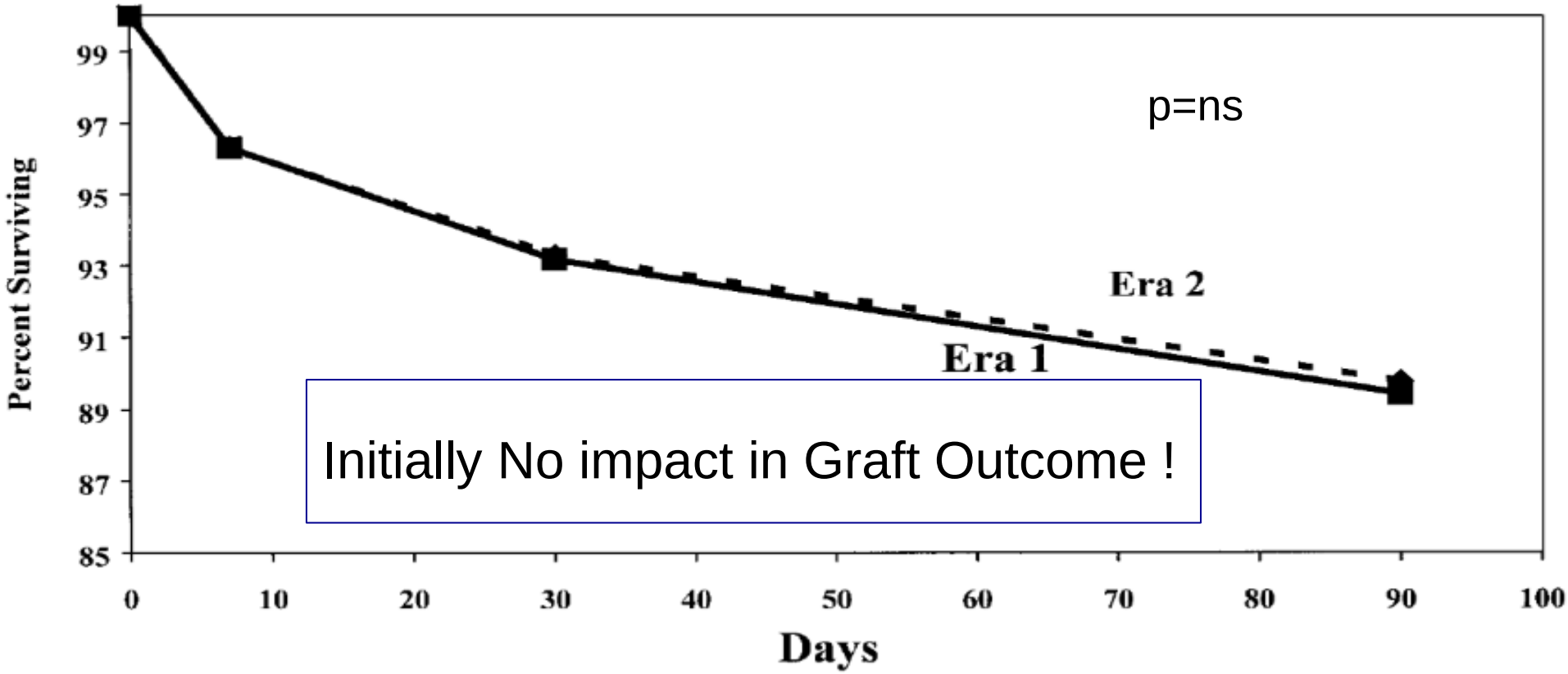
Utility of the MELD Score for Assessing 3-Month Survival in Patients With Liver Cirrhosis

17,743 adults cirrhosis (UNOS data 2A, 2B, 3)
May 2001 – November 2001



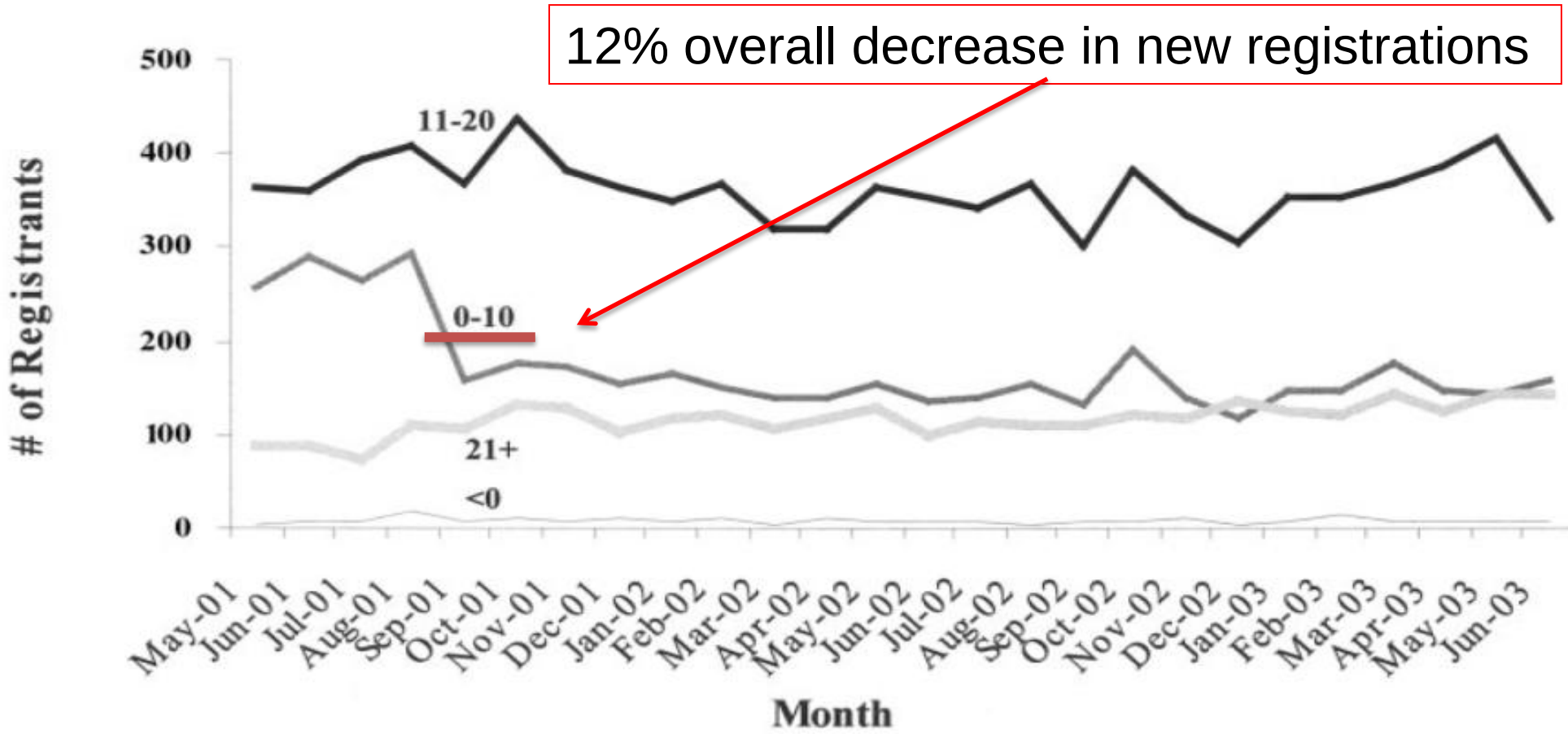
Heuman DM. Gastroenterology 2003

Post-transplant graft survival 1 year prior to and after MELD implementation



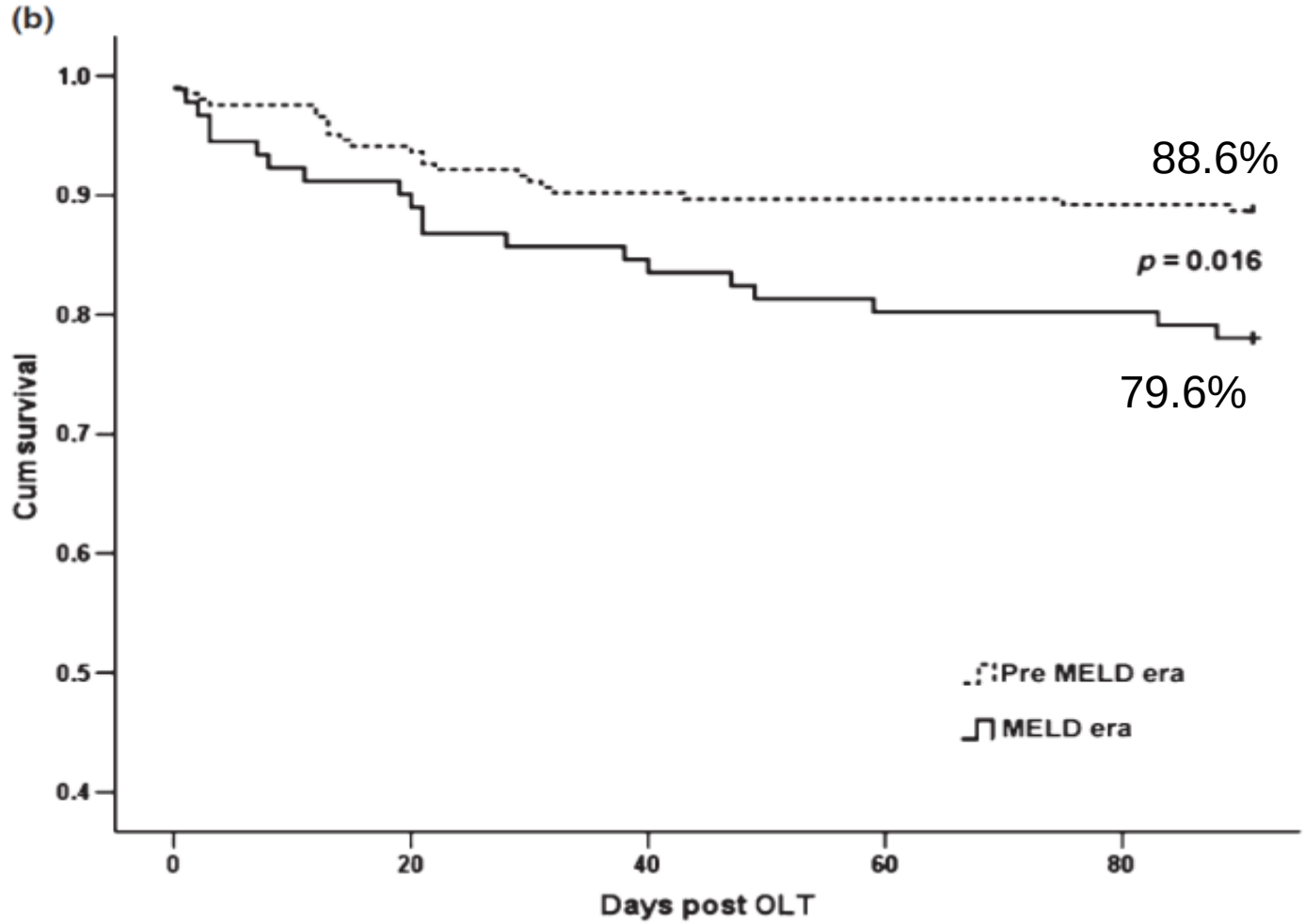
Freeman RB, Liver Transpl 2004

Time trends in MELD scores of New registrants



Freeman RB, Liver Transpl 2004

Pre- and Post-introduction of MELD: 3-month Survival for 1st liver transplantation



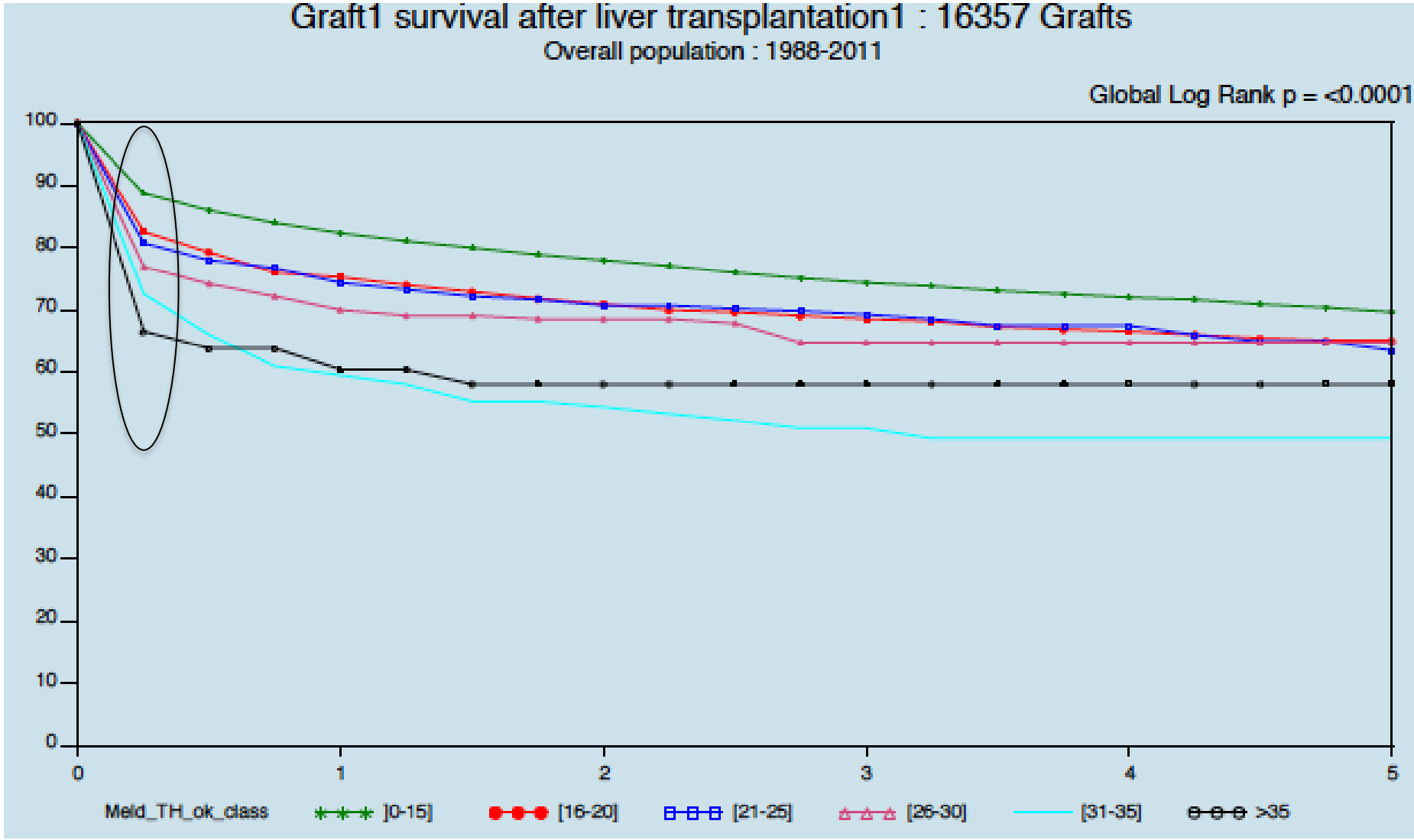
Weismuller TJ. Transpl Int 2009

Increased MELD at liver transplant results in Prolonged hospitalization and overall ICU Costs

Factor	MELD <11	MELD 11-18	MELD 19-24	MELD >24	p
Post-LT ICU stay (days)	2	2	3	8	0.0009
Post-LT hospital stay (days)	18	20	23.5	23.5	0.008
Renal replacement therapy	9.4%	10.5%	12.9%	37.5%	0.0002
Costs (£)	3600	3600	5400	12024	0.0001

Foxton MR Liver Transpl 2010

Graft Survival Vs MELD (ELTR)



INR and MELD (Trotter 2007)

- INR has the highest multiplicative value of the 3 MELD variables
- Lab to lab variation in INR in 14 laboratories USA – 5 samples

	INR range	MELD range
Sample 1	1.2-2.0	8-14
Sample 2	1.4-2.5	10-17
Sample 3	1.7-3.4	12-20
Sample 4	1.9-3.7	14-21
Sample 5	2.4-5.1	16-25

- INR variability increased as the mean INR increased (p=0.017)

MELD Exceptions in the Context of the French Model for End-Stage Liver Disease Score–Based Liver Allocation System

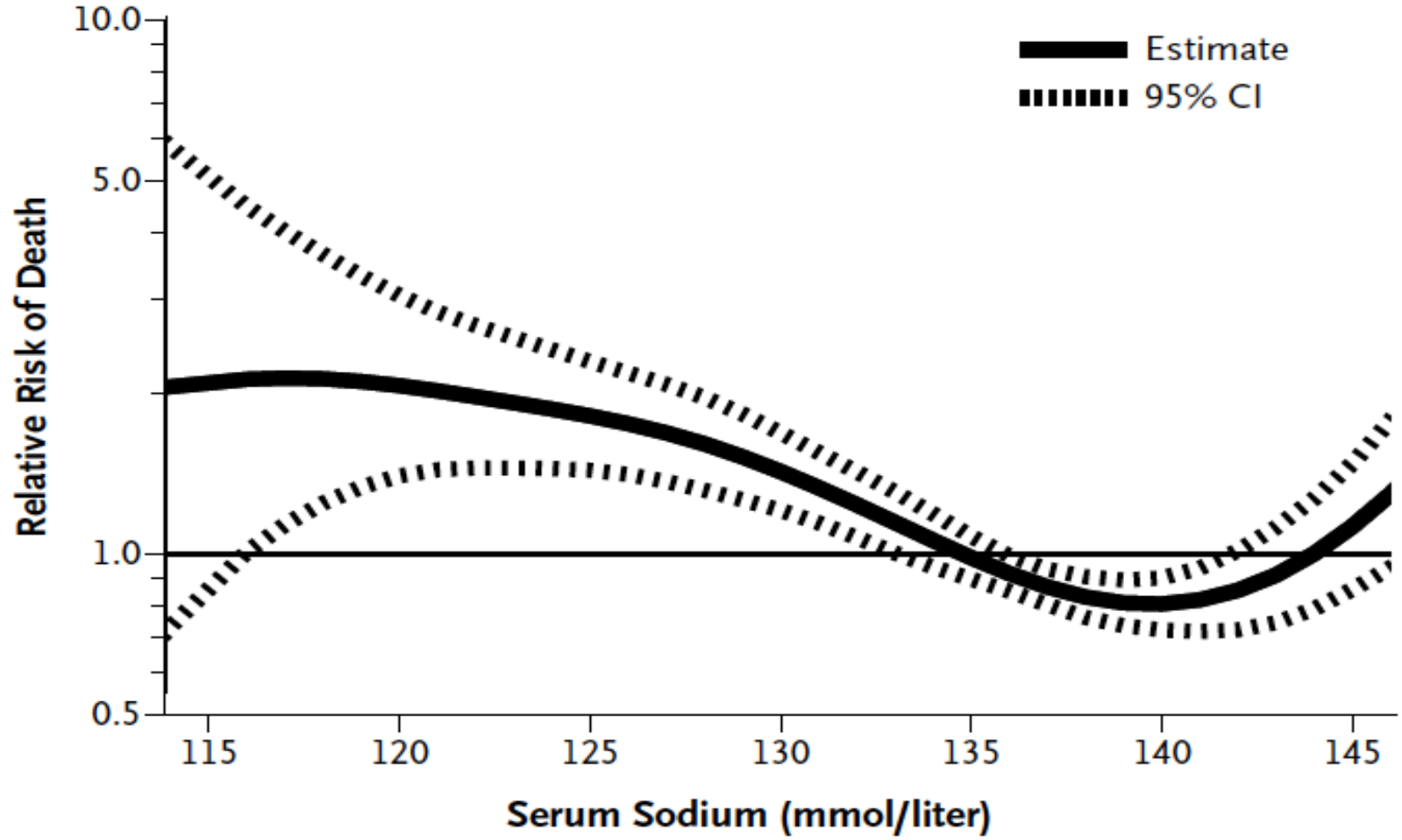
Francoz C. Liver Transpl 2011

The importance of other variables

“In patients with liver disease, serum Na levels below 130 mEq/L must be regarded as serious and if below 125 mEq/L ominous”

Prof. Dame Sheila Sherlock
Lancet 1956;271:1121-25

Serum sodium concentration and the relative risk of death after adjustment for MELD score



Kim WR. NEJM 2008

Discriminatory value of MELD-Na and standard MELD scores

Study	Patients (n)	MELD-Na c-statistic	MELD c-statistic	P-value
Heuman et al. (2004)	507	0.86	0.80	**<0.05**
Ruf et al. (2005)	262	0.91	0.89	**0.026**
Londono et al. (2007)	308	0.78	0.77	ns
Biggins et al. (2007)	753	0.88	0.86	ns
Luca et al. (2007)	310	0.69	0.78	ns
Barber et al. (2007)	1555	NA	NA	NA
Huo et al. (2007)	213	0.79	0.79	ns
Kim et al. (2008)	13940	0.88	0.86	**<0.001**
Somsouk et al. (2009)	1003	0.77	0.73	NA
Boursier et al. (2009)	308	0.87	0.89	ns
Biselli et al. (2009)	487	0.77	0.72	**<0.005**

Proposed modifications of MELD

- MELD-Na (MELD and serum sodium)
- iMELD (integrated MELD score)
- MELD-XI (without INR)
- MELD-gender
- Delta-MELD (changes in MELD over time)
- Re-weightned MELD

MELD

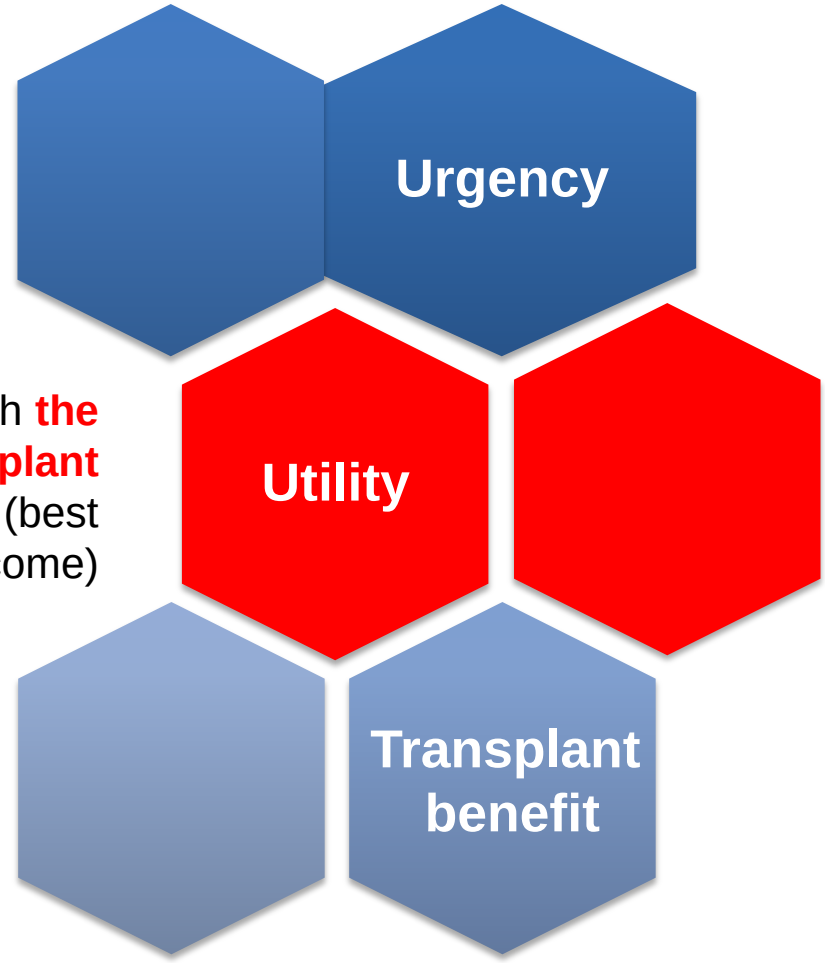
- Mejor que el clasico Child Pugh
- Bastante robusto para preveer la mortalidad de los pacientes en lista de espera
- Cierta variabilidad interlaboratorio (INR)
- Mejorable con el sodio pero menos practico…

→ Un sistema bien adaptado para el manejamiento de los pacientes en lista de espera

Utility-based allocation systems

Utility-based allocation systems

Allocation to the patient with **the longest mean post-transplant survival** estimate (best outcome)



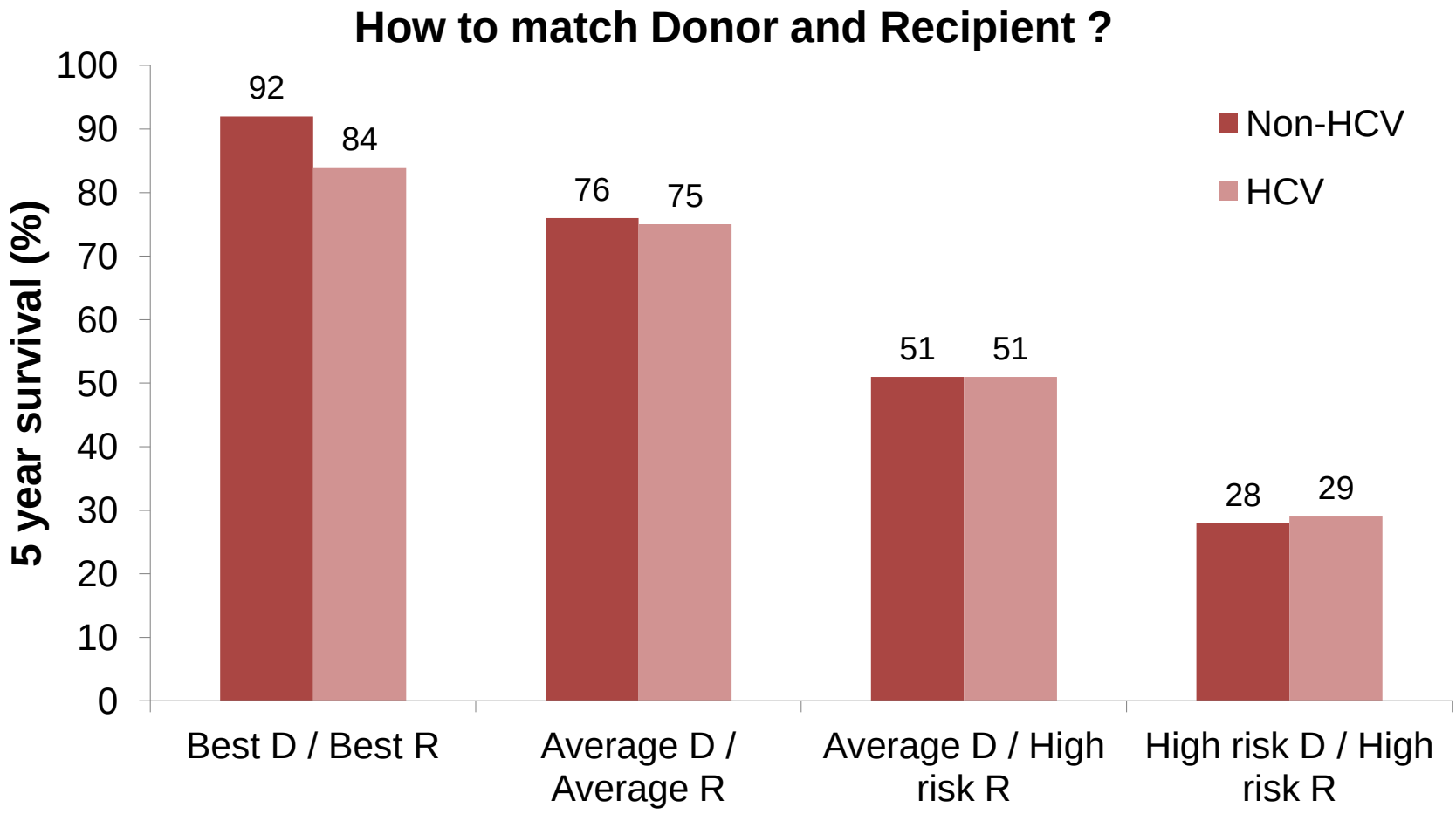
Utility-based allocation

- Expected post-transplant outcome

- MELD weak predictor of post-transplant mortality
- MELD not used in utility-based allocation systems

- Impact on recipient outcome is quality of donor
- Matching donor/recipient crucial
- Extended criteria donor

Survival for Graft and Patient: UNOS database for non-HCV/HCV patients



+non HCV recipient – MELD 24 , alb<21g/l, BMI>40, age≥63, male, white, no diabetes, alcoholism
non HCV donor – age 60, CIT≥14.3h, white, male

° HCV recipient – MELD 24, BMI 15-25, age ≥63, male, white, diabetes
HCV donor – age 60, CIT 11.3-14.3h, male, white

Ioannou Liver Transpl 2006

Characteristics associated with liver graft failure: the concept of donor risk index (DRI)

20.023 adult recipients (1998-2002) – 64% not hospitalized

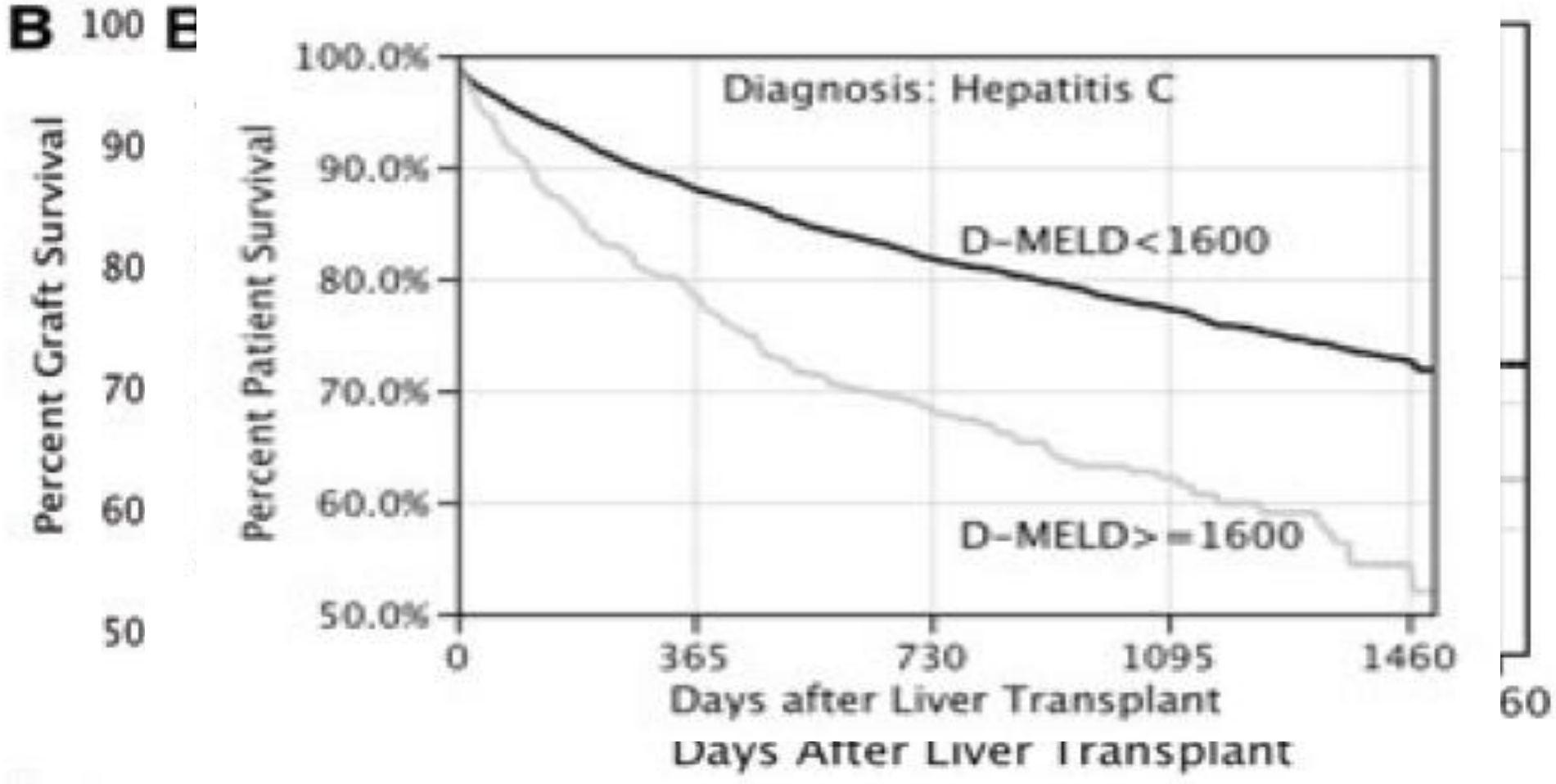
	RR (95%CI)	p-value
Donor age >60 years	1.53 (1.39-1.68)	<0.0001
DCD	1.51 (1.19-1.91)	0.0006
Partial/Split	1.52 (1.27-1.83)	<0.0001
African-American	1.19 (1.10-1.29)	<0.0001
Donor Height (per 10cm decrease)	1.07 (1.04-1.09)	<0.0001
COD = CVA	1.16 (1.08-1.24)	<0.0001
COD = Other	1.20 (1.03-1.40)	0.018
Cold ischemia time (per 1h increase)	1.01	0.008
Grafts outside the local area	1.11	0.002
Grafts beyond the region	1.28	<0.0001

Feng et al. Am J Transpl 2006

Models that could be used in utility-based allocation in liver transplantation

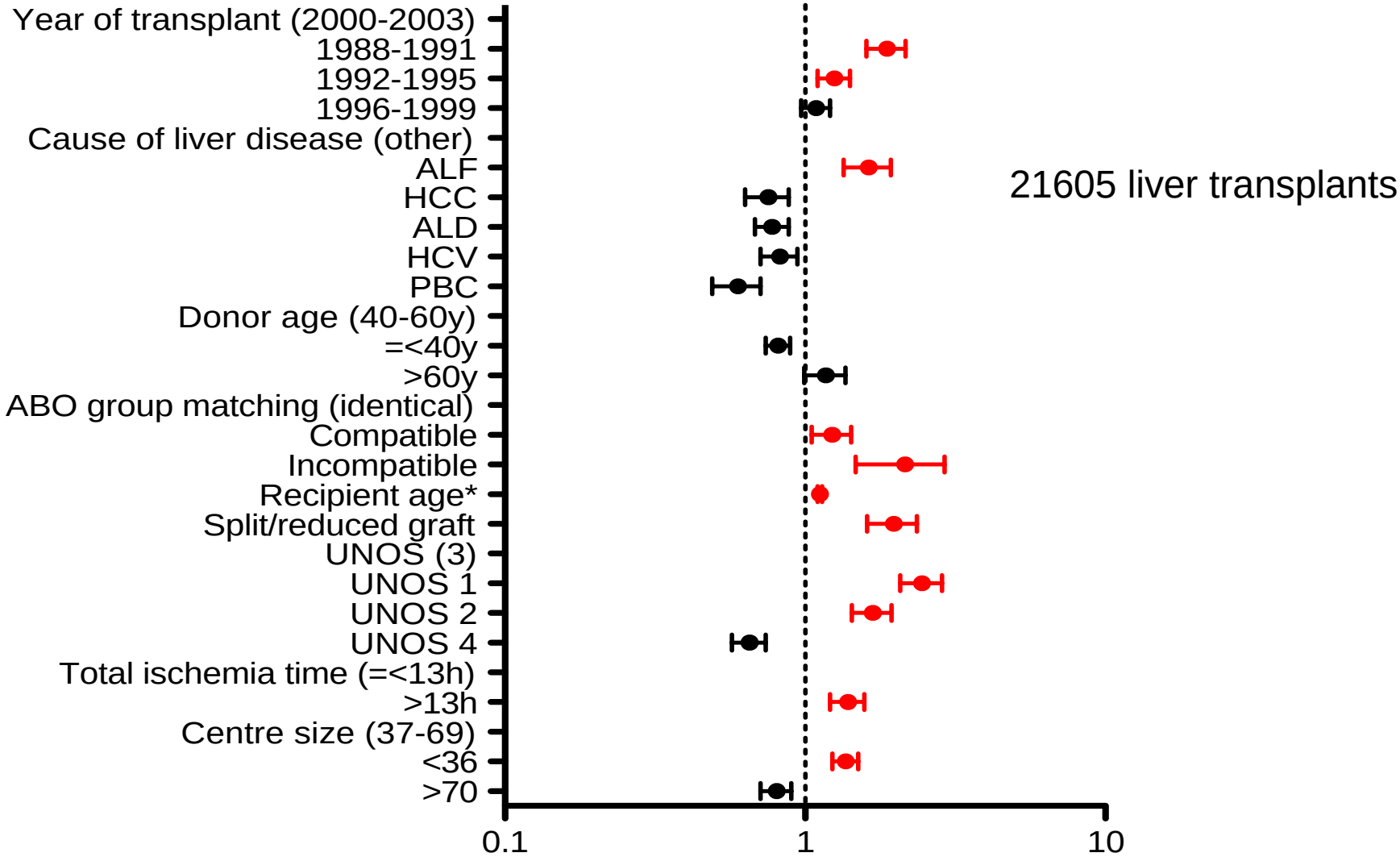
MELDD	Donor characteristics	(Burroughs 2007)
DMELD	Age donor x MELD	(Halldorson 2009)
DMELD	Age donor x MELD	(Avolio 2011)
ELTR	Age donor, total ischaemic time, aetiology liver disease, donor/recipient ABO matching, HBsAg positivity, age recipient, UNOS status, graft size, centre size	(Burroughs 2006)

D-MELD, a predictor of post-transplant mortality for optimization of donor/recipient matching



Halldorson JB Am J Transpl 2009

Factors associated with 3-month survival (ELTR)
Estimates from multivariable logistic regression



Burroughs AK. Lancet 2006

Are There Better Guidelines for Allocation in Liver Transplantation?

A Novel Score Targeting Justice and Utility in the Model for End-Stage Liver Disease Era

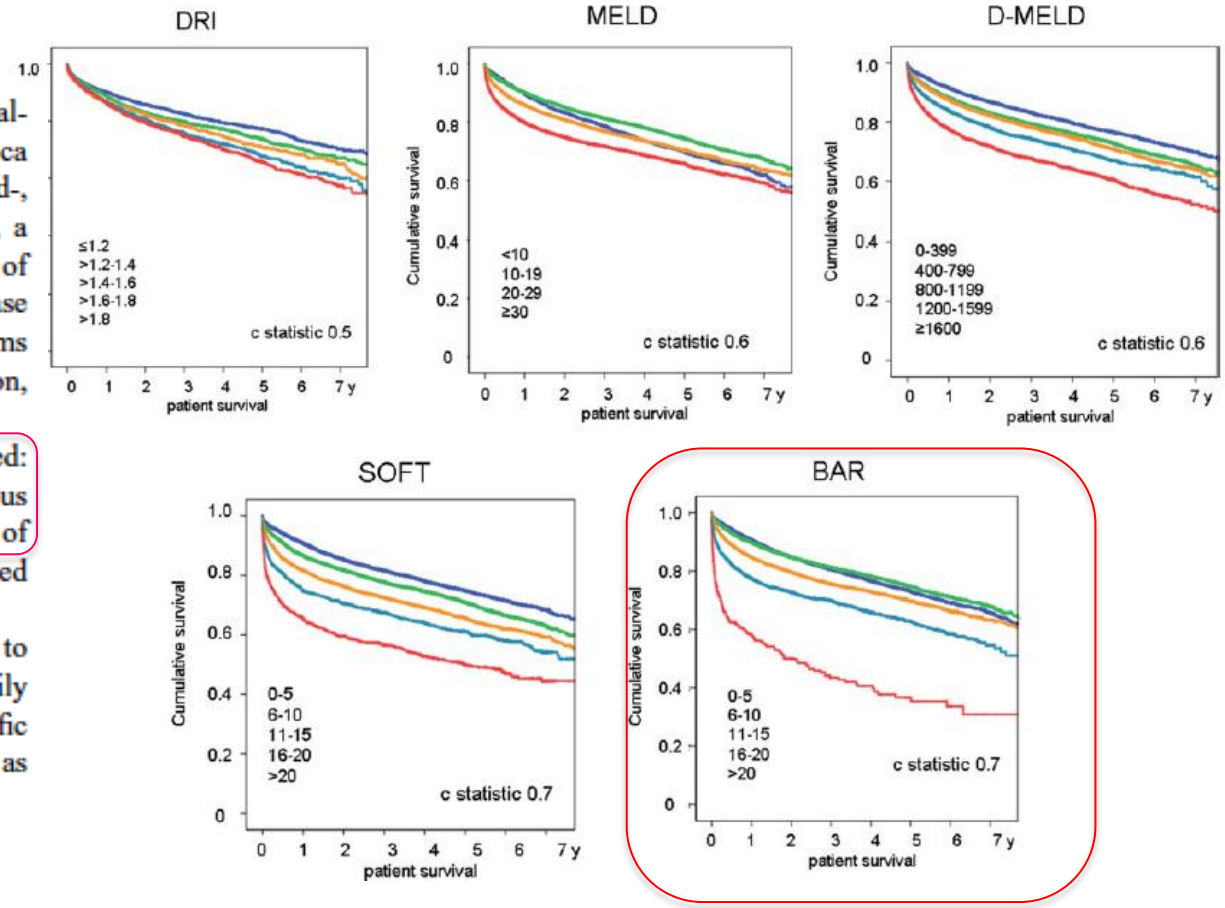
Philipp Dutkowski, And Coll

Annals of Surgery • Volume 254, Number 5, November 2011

Methods: Using the United Network for Organ Sharing database, a risk analysis was performed in adult recipients of OLT in the United States of America between 2002 and 2010 (n = 37,255). Living donor-, partial-, or combined-, and donation after cardiac death liver transplants were excluded. Next, a risk score was calculated (balance of risk score, BAR score) on the basis of logistic regression factors, and validated using our own OLT database (n = 233). Finally, the new score was compared with other prediction systems including donor risk index, survival outcome following liver transplantation, donor-age combined with MELD, and MELD score alone.

Results: Six strongest predictors of posttransplant survival were identified: recipient MELD score, cold ischemia time, recipient age, donor age, previous OLT, and life support dependence prior to transplant. The new balance of risk score stratified recipients best in terms of patient survival in the United Network for Organ Sharing data, as in our European population.

Conclusions: The BAR system provides a new, simple and reliable tool to detect unfavorable combinations of donor and recipient factors, and is readily available before decision making of accepting or not an organ for a specific recipient. This score may offer great potential for better justice and utility, as it revealed to be superior to recent developed other prediction scores.



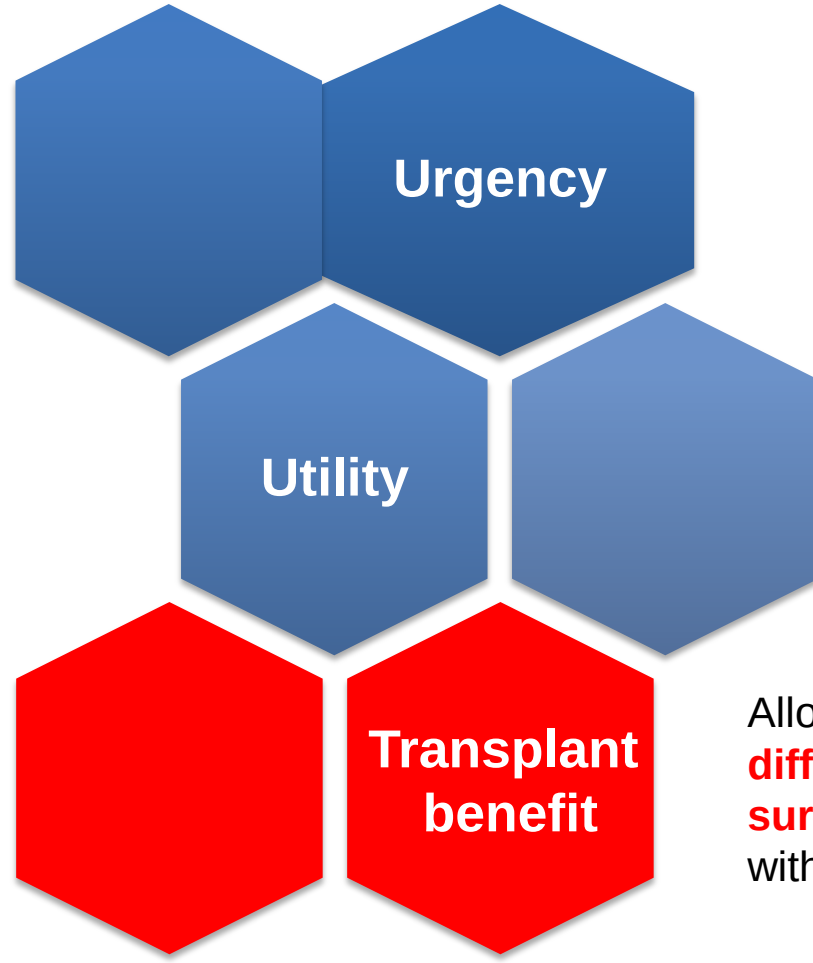
MELD para el post-trasplante

- No predictivo por si mismo
- No tiene en cuenta el donante…
- Predictivo con el D-Meld…

Basar la atribucion de higados en solo el MELD no permite una utilizacion optima de los injertos !

Transplant Benefit

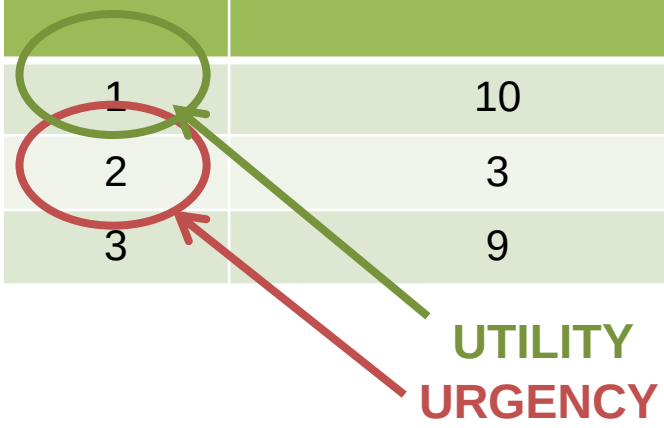
Different Allocation Schemes



Allocation based on the **difference between mean survival** estimates with and without a transplant

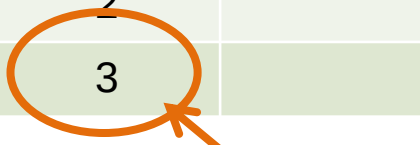
Organ allocation schemes

Patient	Predicted life time Post-transplant	Predicted life time Waiting-list
1	10	7
2	3	2
3	9	5



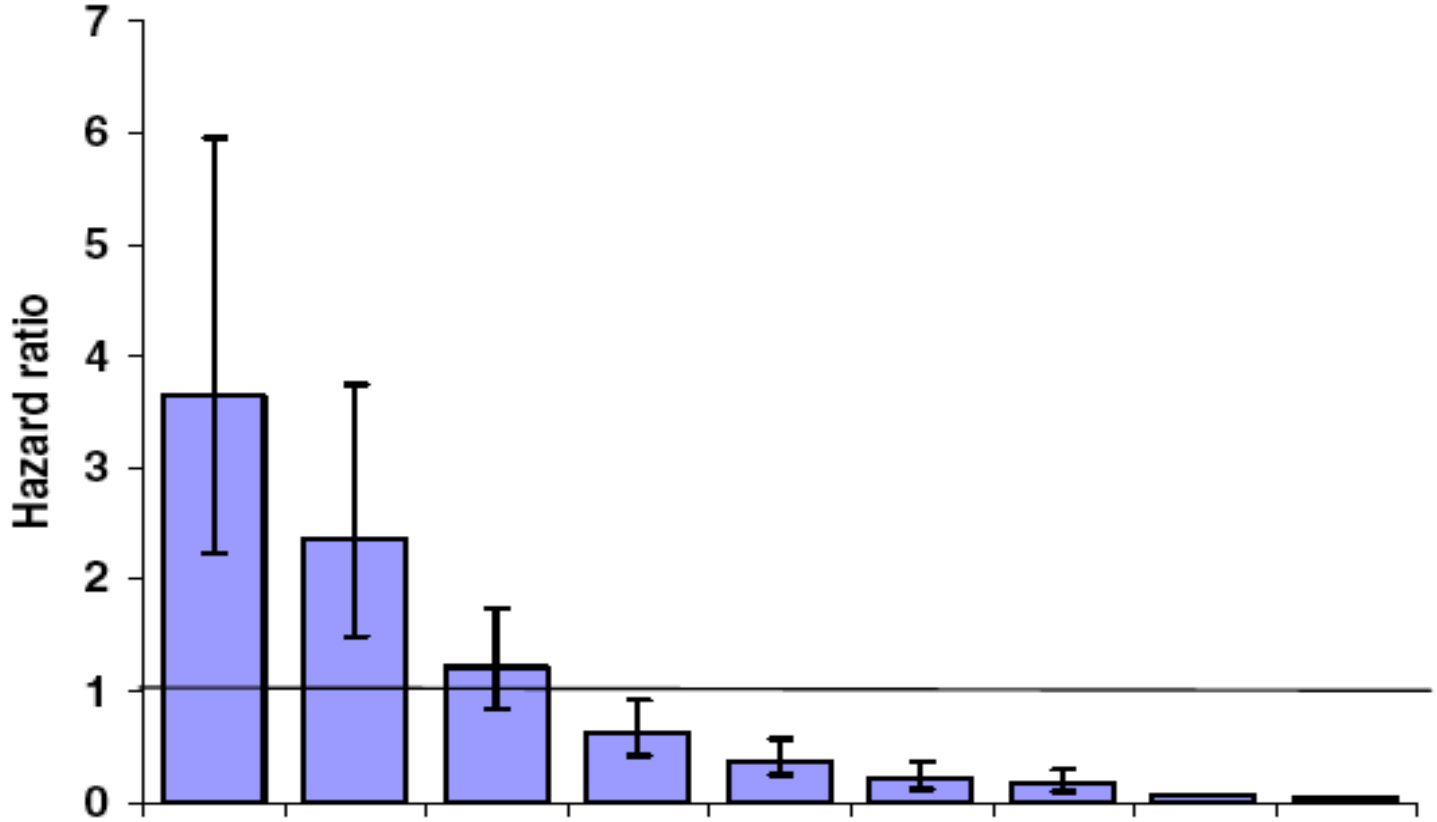
Organ allocation schemes

Patient	Predicted life time Post-transplant	Predicted life time Waiting-list	Predicted survival benefit
1	10	7	3
2	3	2	1
3	9	5	4



TRANSPLANT BENEFIT

Survival Benefit of OLT by MELD

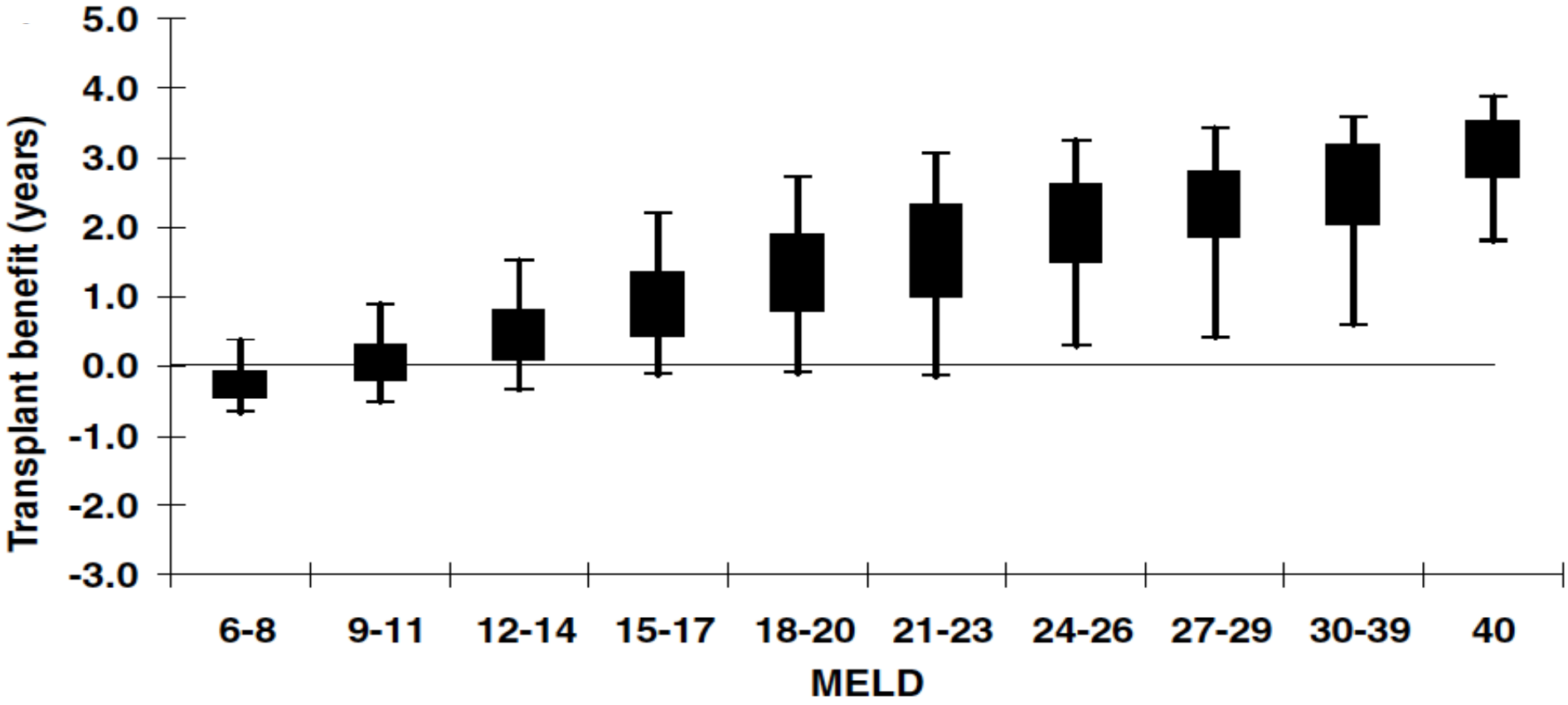


MELD	6-11	12-14	15-17	18-20	21-23	24-26	27-29	30-39	≥40
Hazard Ratio	3.64	2.35	1.21	0.62	0.38	0.22	0.18	0.07	0.04
P value	<0.001	<0.001	0.41	<0.01	<0.001	<0.001	<0.001	<0.001	<0.001

Merion et al. AJT 2005

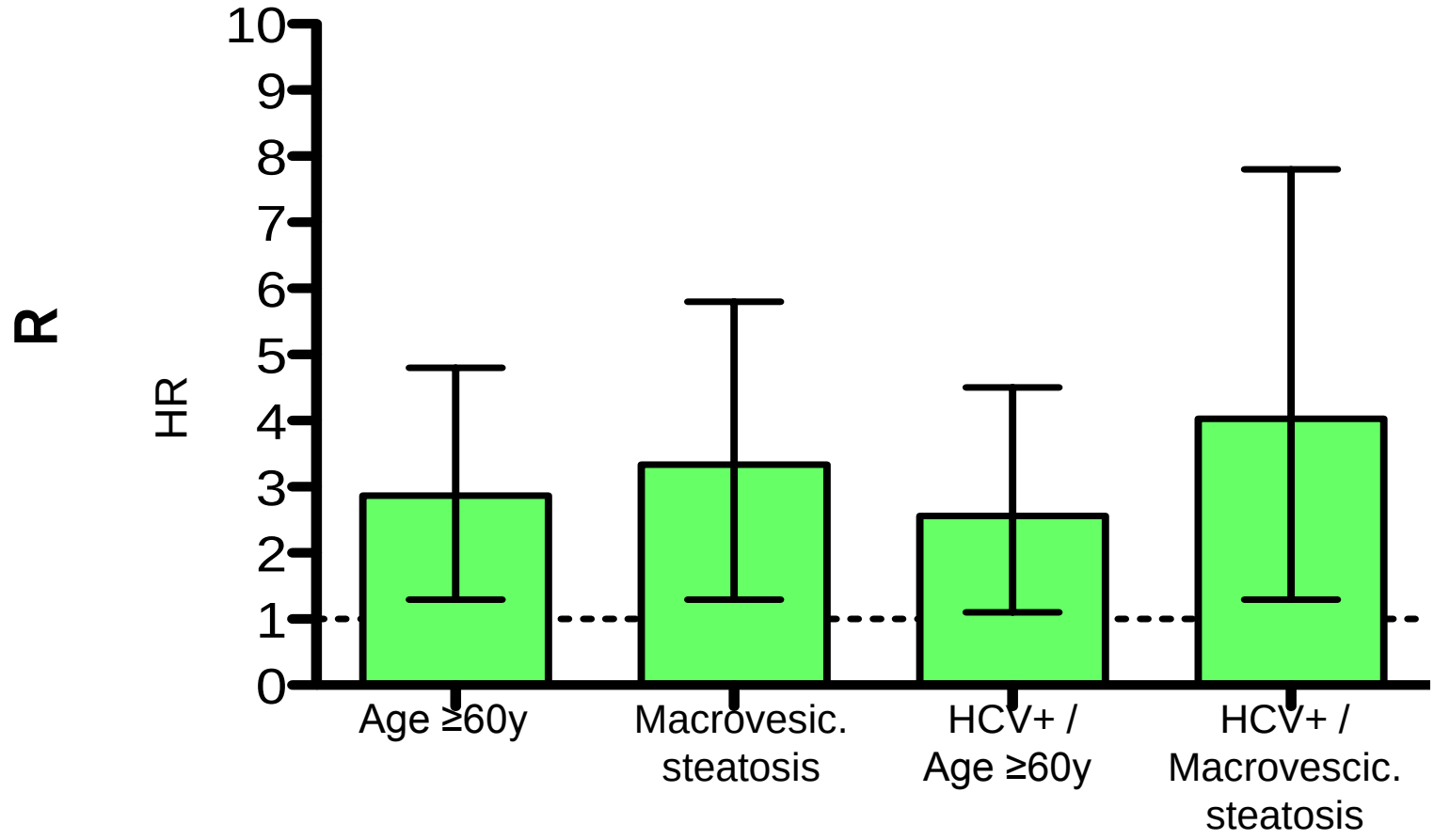
Transplant benefit by MELD box plots

Rank correlation between transplant benefit score and MELD = 0.67



Schaubel Am J Transpl 2009

Transplant Benefit in patients with MELD >20 according to Donor characteristics



LT should be reserved for cirrhotic patients with MELD score ≥ 20 independently of other recipient and donor matches

Ravaioli Transplantation 2009

Beneficio del trasplante…

- Un concepto qui quizas sea el mas adaptado a la falta de organos ya que optimiza el uso de cada higado…
- Pierde el caracter « humanitario » del trasplante sacrificando la gravedad de un paciente urgente al largo plazo de un paciente electivo….

When is a patient too sick for a liver transplant ?

When is a patient too sick for a liver transplant ?

Merion LT 2004

- It is difficult to identify patients who are too sick rendering a transplant futile:

(1) relative mortality risk of the transplant vs continued residence on the waiting list

(2) the MELD-based allocation policy caps the score at 40

(3) absolute post-transplant survival rate may be extremely low

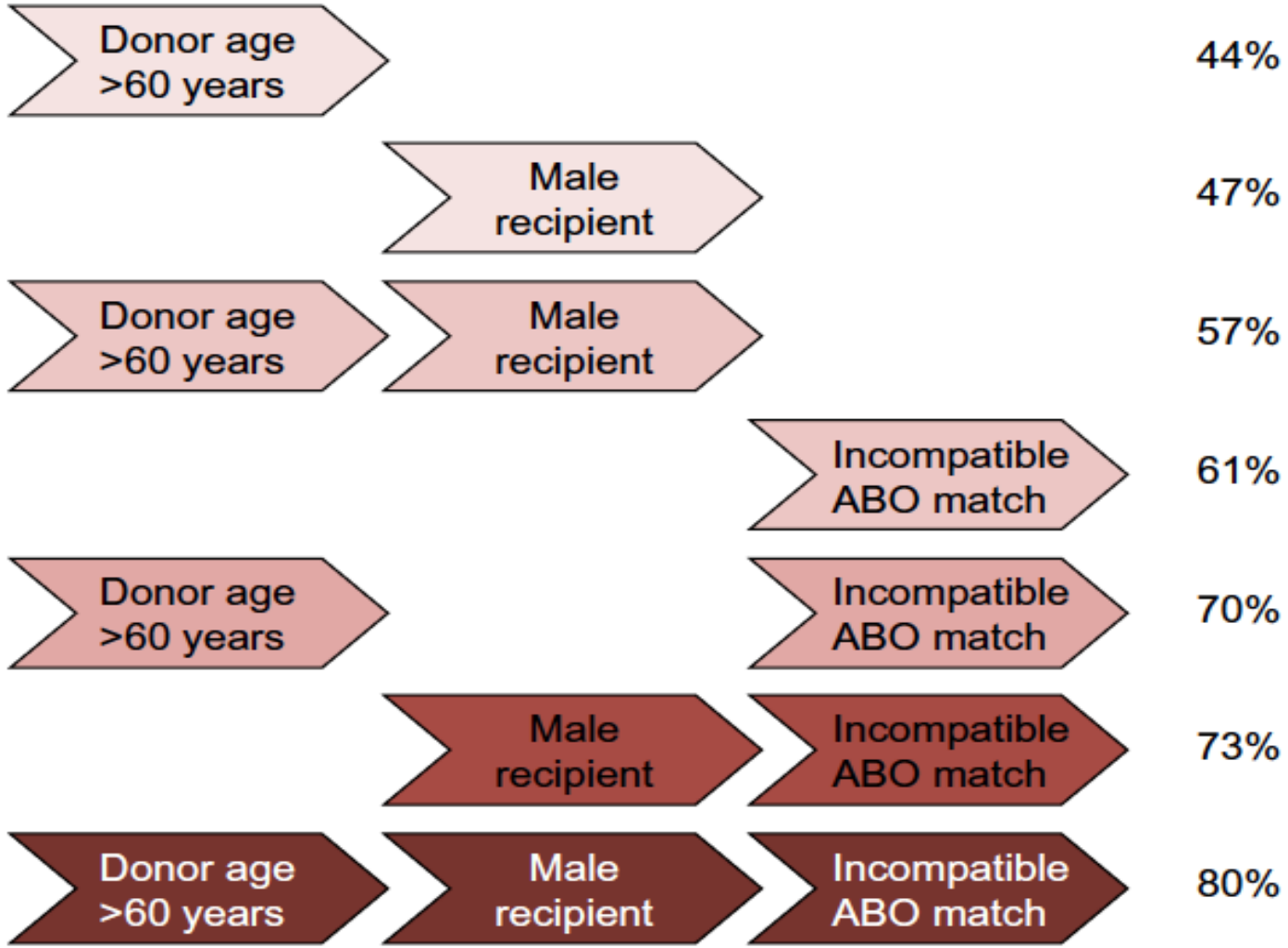
When is a liver transplant futile ?

Perkins, Liver Transplantation Worldwide LT 2008

- Different etiologies of liver failure (Acute liver failure vs ReTx) : separate definition of futile LT?

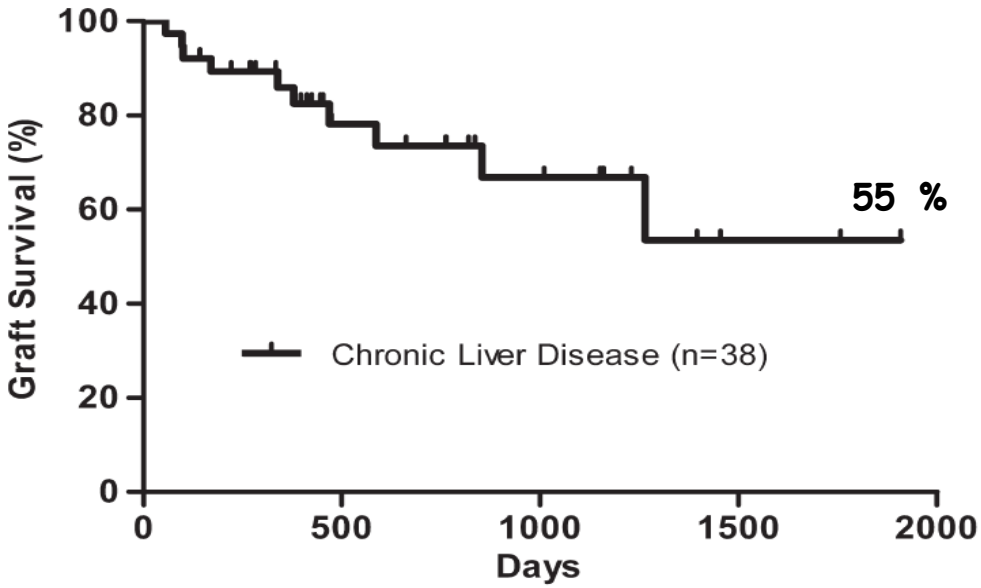
- Would predictive models for survival indicating a certain survival percentage – 60% 50% 40% at 5 years – provide a cutoff point for not proceeding with LT ?

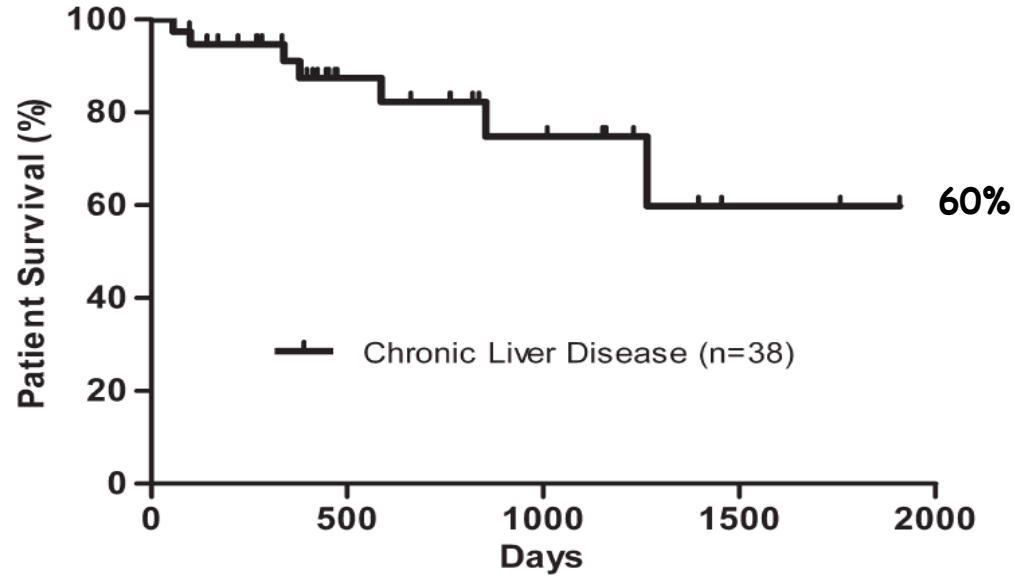
One-year Mortality or Graft loss in patients > 50 yrs transplanted for **acute liver failure**



Germani G, et al. J Hepatol 2012

Overall Graft and Patient survival after transplantation with a MELD score ≥ 40



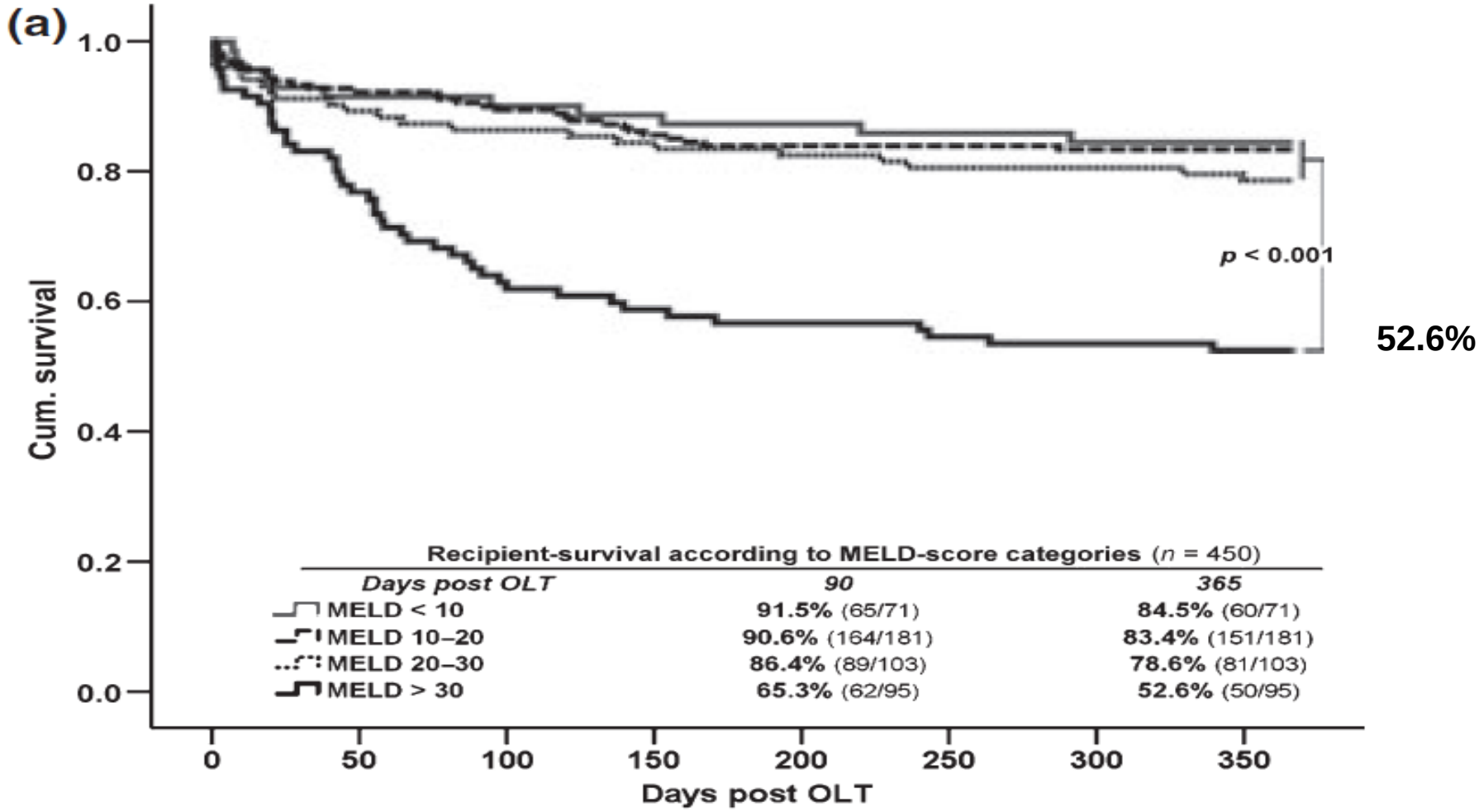


Alexopoulos S. Transplantation 2013

When is a patient too sick for a liver transplant ?

Weissmuller Transplant International 2010

- MELD >30 major risk factor for outcome

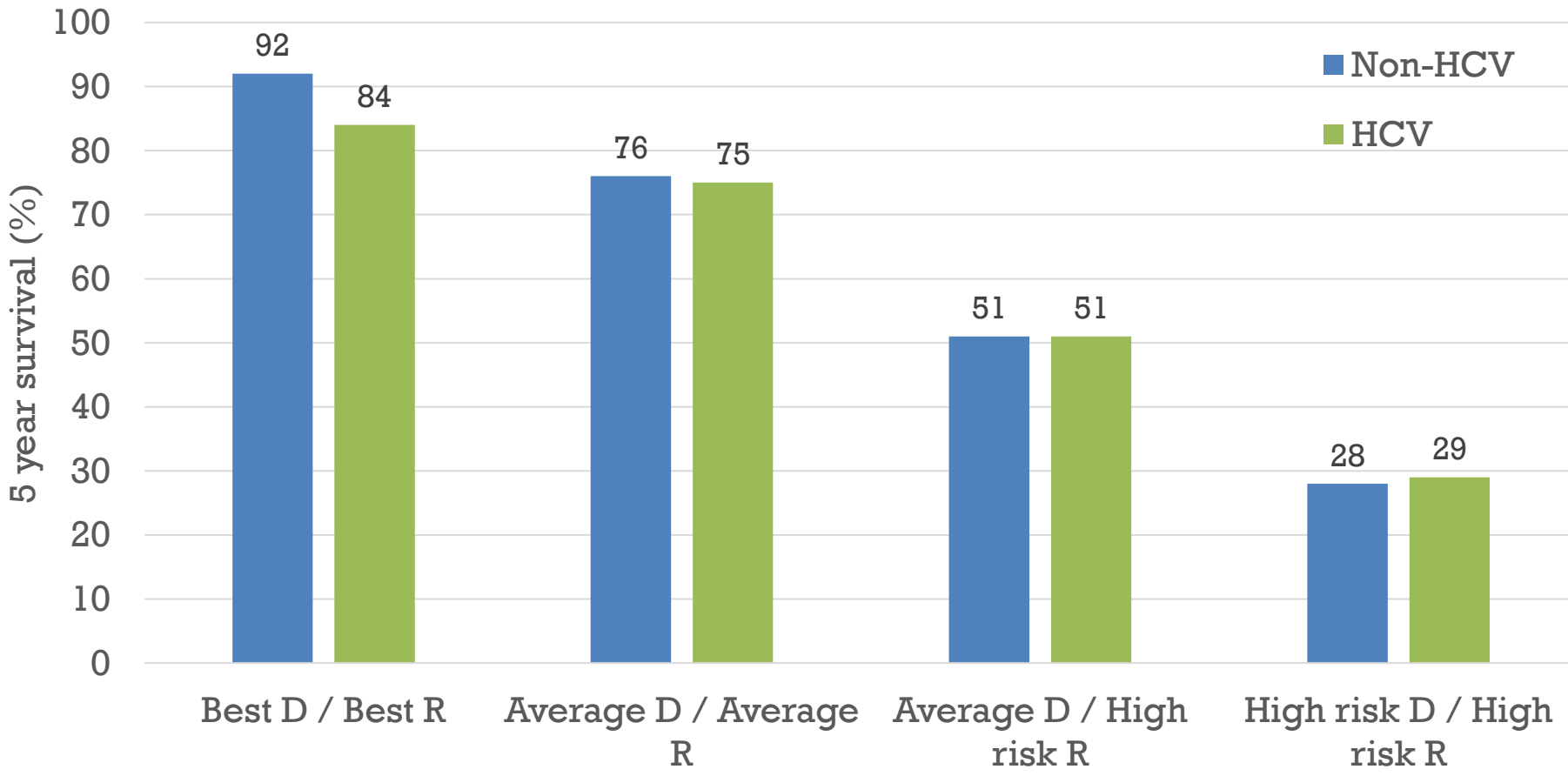


Lack of strategy regarding treatment withdrawal

«… the persistence of 3 or more organ failure after 3 days spent in the ICU my lead to consider a limitation in life-sustaining treatments as a fatal outcome is almost constant »

Gines J Hepatol 2012 EASL Guidelines

Survival for graft and/or patient: UNOS database for non-HCV/HCV patients



+non HCV recipient – MELD 24 , alb<21g/l, BMI>40, age≥63, male, white, no diabetes, alcoholism
non HCV donor – age 60, CIT≥14.3h, white, male
° HCV recipient – MELD 24, BMI 15-25, age ≥63, male, white, diabetes
HCV donor – age 60, CIT 11.3-14.3h, male, white

Ioannou Liver Transpl 2006

Conclusions (I)

- MELD is a short term survival model
  - Works for prioritization of candidates
  - Need to remove variability biases in measurement
  - Not calibrated for spectrum of severity of cirrhosis
  - Add new variables – ie. sodium addition
  - Categorization is clinically useful (bedside)

- Use of score for specific diseases (i.e. HCC)

Conclusions (II)

- Neither MELD nor CTP are useful to predict post-transplant survival

- Need new models
  - Include donor characteristics
  - ELTR models – MELDD (D for donor)

- Move towards donor/recipient matching

- Utility combined with justice (BENEFIT)

MELD y Hepatocarcinoma

- MELD : no disenado para predecir la progression de Hepatocarcinoma mas alla de los criterios de Milan o de cualquier estadio de HK

- Construir un modelo predictivo de progression con predictores especificos del patiente del riesgo de drop out …

- El MELD tiene que combinarse con las caracteristicas del tumor para estimar la progression tumoral y de drop out…

Referral to Liver Transplant Center for patients with HCC

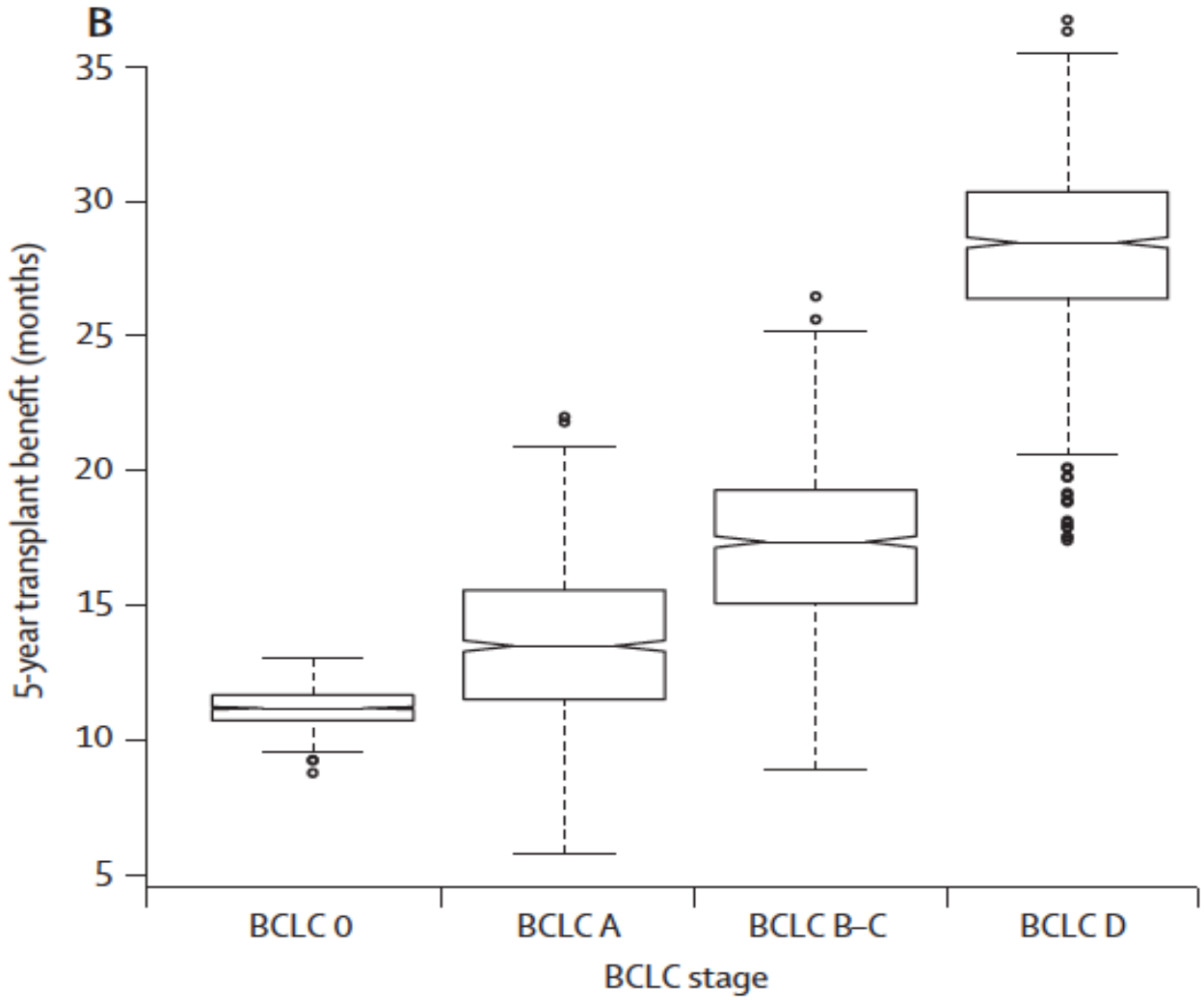
Milan Criteria : mainly a “utility-based” allocation

A **specific HCC score** without MELD extra points based on:

- response to down staging treatment of HCC
- tumor stage
- time from diagnosis of HCC

Vitale A, et al. Transplant Proc. 2009
Gambato M, et al. SITO 2009

5-year transplant benefit by BCLC stages derived from adjusted Monte Carlo simulations



Vitale A. Lancet Oncol 2011

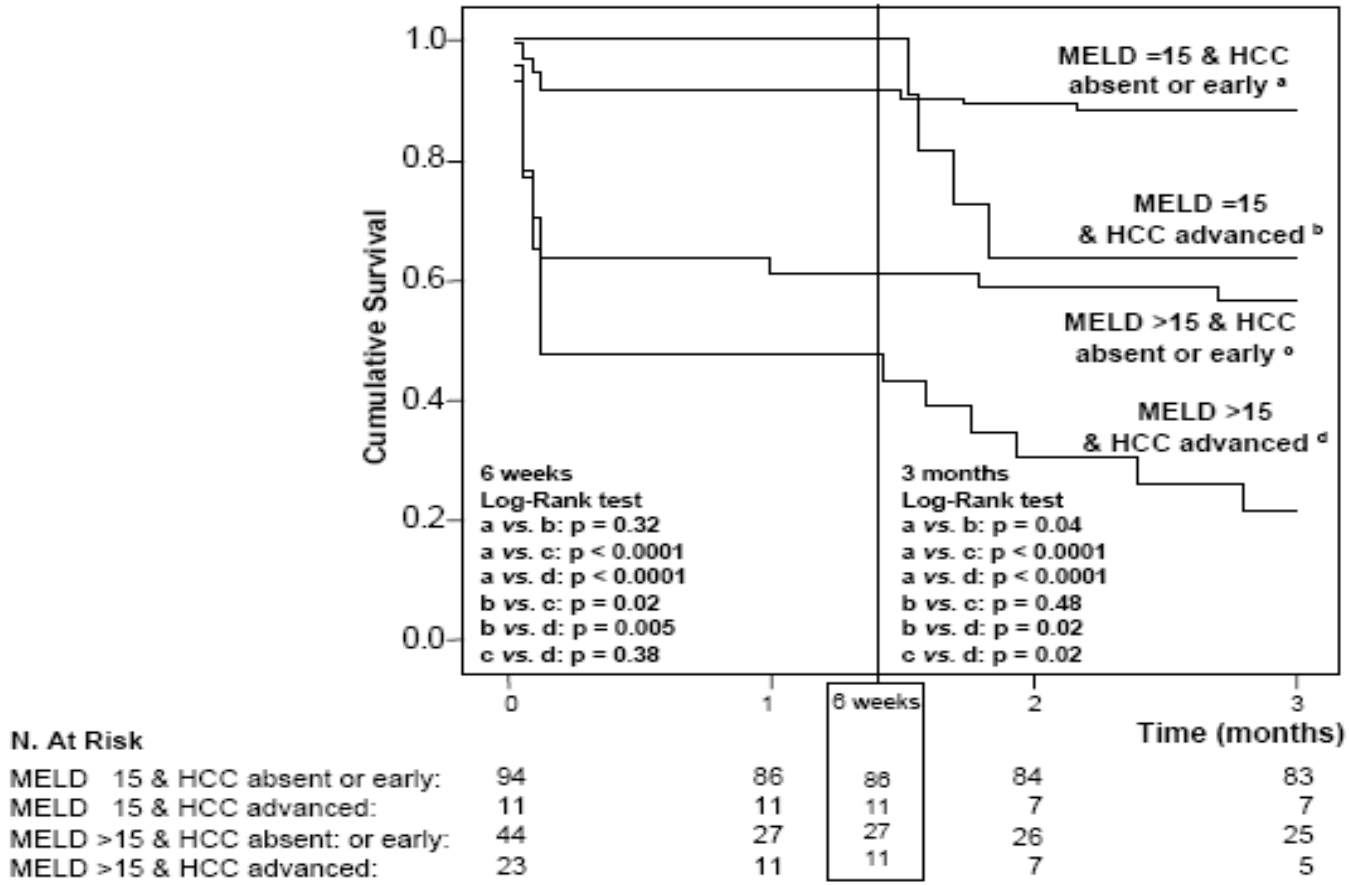
Barcelona Clinic Liver Cancer staging and transplant survival benefit for patients with hepatocellular carcinoma: a multicentre, cohort study

Lancet Oncol 2011; 12: 654–62

Alessandro Vitale[1], and Coll

does the model for end-stage liver disease score for tumour-free patients. In clinical practice, our results suggest that liver transplantation could be done, with survival benefit, in patients with hepatocellular carcinoma and advanced liver cirrhosis and in those with intermediate tumours (BCLC stages B–C), regardless of the nodule number–size criterion (BCLC stage D), provided that macroscopic vascular invasion and extra-hepatic disease are absent. The application of this new approach should lead to greater homogeneity and equity in organ allocation in liver transplantation.

Kaplan–Meier survival curves in patients stratified according to absence or presence (early or advanced) of HCC and MELD score

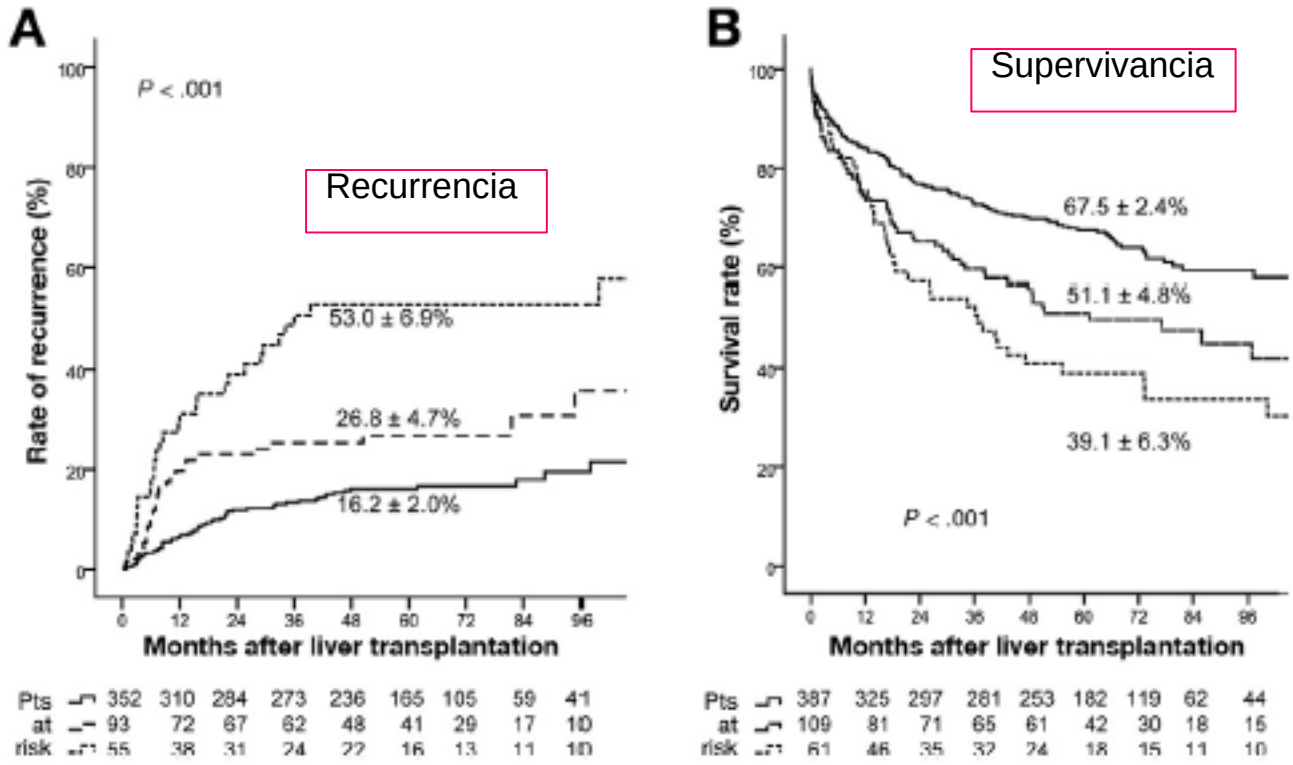


Amitrano L, et al. J Hepatol. 2005;42:820-5.

Liver Transplantation for Hepatocellular Carcinoma: A Model Including α-Fetoprotein Improves the Performance of Milan Criteria

CHRISTOPHE DUVOUX,[1,2] FRANÇOISE ROUDOT–THORAVAL,[2,3] THOMAS DECAENS,[1,2,4] FABIENNE PESSIONE,[5] HANAA BADRAN,[1] TULLIO PIARDI,[6] CLAIRE FRANCOZ,[7] PHILIPPE COMPAGNON,[8] CLAIRE VANLEMMENS,[9] JÉROME DUMORTIER,[10] SÉBASTIEN DHARANCY,[11] JEAN GUGENHEIM,[12] PIERRE–HENRI BERNARD,[13] RENÉ ADAM,[14] SYLVIE RADENNE,[15] FABRICE MUSCARI,[16] FILOMENA CONTI,[17] JEAN HARDWIGSEN,[18] GEORGES–PHILIPPE PAGEAUX,[19] OLIVIER CHAZOUILLÈRES,[17] EPHREM SALAME,[20] MARIE–NOELLE HILLERET,[21] PASCAL LEBRAY,[22] ARMAND ABERGEL,[23] MARILYNE DEBETTE–GRATIEN,[24] MICHAEL D. KLUGER,[25] ARIANE MALLAT,[1,2,4] DANIEL AZOULAY,[2,25] and DANIEL CHERQUI,[2,25] on behalf of the Liver Transplantation French Study Group

GASTROENTEROLOGY 2012;143:986–994



AFP < 100

AFP 100-1000

AFP > 1000

Figure 1. Rates of (*A*) recurrence and (*B*) overall survival rates according to α-fetoprotein level in the training cohort. AFP ≤100 ng/L (*solid line*); AFP = 100–1000 ng/L (*dashed line*); AFP >1000 ng/L (*dotted line*).

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GASTROENTEROLOGY 2012;143:986–994

Table 2. Simplified, User-Friendly Version of the AFP Model

Variables	β coefficient	Hazard ratio	Points
Largest diameter, *cm*			
≤3	0	1	0
3–6	0.272	1.31	1
>6	1.347	3.84	4
Number of nodules			
1–3	0	1	0
≥4	0.696	2.01	2
AFP level, *ng/mL*			
≤100	0	1	0
100–1000	0.668	1.95	2
>1000	0.945	2.57	3

NOTE. The score is calculated by adding the individual points for each obtained variable. A cut-off value of 2 separates between patients at high and low risk of recurrence. In this simplified version, a cut-off value of 2 selected exactly the same patients as the original Cox score cut-off value of 0.7.

death. By using a simplified version of the model, with untransformed AFP values, a cut-off value of 2 was identified. In the validation cohort, a score greater than 2 predicted a marked increase in 5-year risk of recurrence (50.6% ± 10.2% vs 8.8% ± 1.7%; $P < .001$) and decreased survival (47.5% ± 8.1% vs 67.8% ± 3.4%; $P = .002$) as compared with others. Among patients exceeding Milan criteria, a score of 2

A method for establishing allocation equity among patients with and without hepatocellular carcinoma on a common liver transplant waiting list

Alessandro Vitale[1], and Coll

Journal of Hepatology 2014 vol. 60 | 290–297

Background & Aims: The current organ allocation system for liver transplantation (LT) creates an imbalance between patients with and without hepatocellular carcinoma (HCC). We describe a model designed to re-establish allocation equity among patient groups using transplant benefit as the common endpoint.

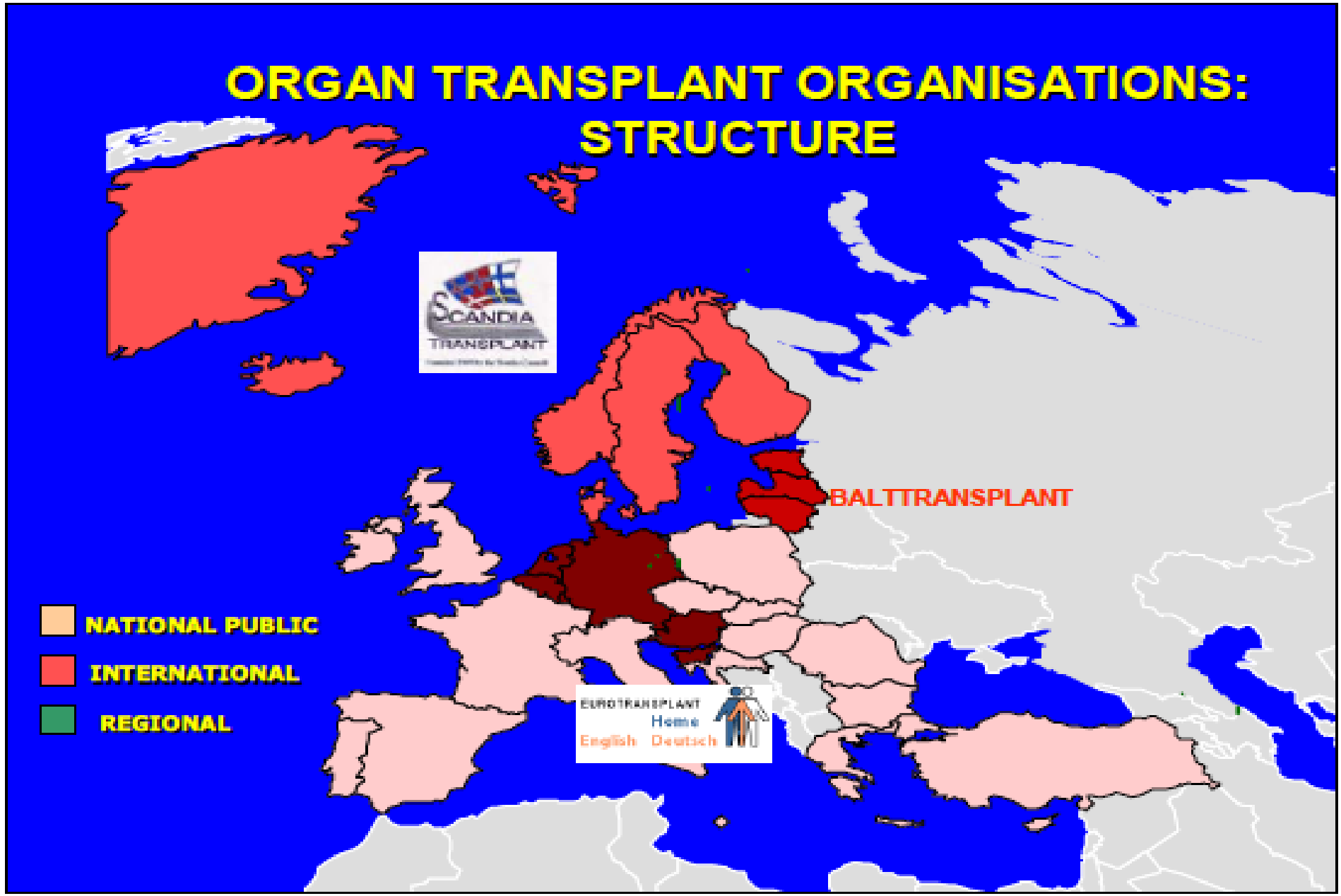
Methods: We enrolled consecutive adult patients entering the waiting list (WL group, n = 2697) and undergoing LT (LT group, n = 1702) during the period 2004–2009 in the North Italy Transplant program area. Independent multivariable regressions (WL and LT models) were created for patients without HCC and for those with stage T2 HCC. Monte Carlo simulation was used to create distributions of transplant benefit, and covariates such as Model for End-stage Liver Disease (MELD) and alpha-fetoprotein (AFP) were combined in regression equations. These equations were then calibrated to create an "MELD equivalent" which matches HCC patients to non-HCC patients having the same numerical MELD score.

Results: Median 5 year transplant benefit was 15.12 months (8.75–25.35) for the non-HCC patients, and 28.18 months (15.11–36.38) for the T2-HCC patients (p <0.001). Independent predictors of transplant benefit were MELD score (estimate = 0.89, p <0.001) among non-HCC patients, and MELD (estimate = 1.14, p <0.001) and logAFP (estimate = –0.46, p <0.001) among HCC patients. The equation "HCC-MELD" = 1.27 * MELD – 0.51 * logAFP + 4.59 calculates a numerical score for HCC patients, whereby their transplant benefit is equal to that of non-HCC patients with the same numerical value for MELD.

Conclusions: We describe a method for calibrating HCC and non-HCC patients according to survival benefit, and propose that this method has the potential, if externally validated, to restore equity to the organ allocation system.

$$\text{HCC-MELD} = 1.27^{*}\text{MELD} - 0.51^{*}\text{logAFP} + 4.59$$

Allocation in Europe


ORGAN TRANSPLANT ORGANISATIONS:
STRUCTURE
SCANDIA
TRANSPLANT
BALTTRANSPLANT
NATIONAL PUBLIC
INTERNATIONAL
REGIONAL
EUROTRANSPLANT
Home
English Deutsch

The old debate…

Center-oriented

- Better matching D/R
- Better Outcome ?
- Center Experience

Patient-oriented

- Better transparency
- Reproducibility
- No center impact

The political constraints

The allocation system is:

- **Objective**: the match list is the same no matter which duty desk officer arranges the allocation
- **Reproducible**: the same question will lead to the same answer
- **Transparent**: every step in the process can be accounted for
- **Valid**: the system is based upon valid medical and ethical criteria that are supported by consensus within the transplant community.

The match is based upon two general principles:

- Expected outcome
- Urgency (as determined by experts in an objective and transparent way)

Eurotransplant

Allocation system in France

Benefits and Problems

C. Jacquelinet, B. Audry, F. Pessione, C. Antoine, M Thuong, R. Adam

agence de la biomédecine

Current Liver Allocation Scheme (LAS)

- **LAS comprises nationwide priorities:**
  - **a national « SU » priority, given to highly urgent patients with**
    - fulminant hepatitis, Wilson's disease, early retransplantation, paediatric recipients with ischemic necrosis in biliary atresia, acute liver failure in metabolic diseases
  - **a national paediatric priority, given to recipients <18yo for donors <18yo and in case of split liver**
- **and a patient-based allocation score:**
  - **in the absence of prioritized patient, a potential BD-donor liver is offered to the patient with the highest score:**
    - when a donor is retrieved in the "local area" of a LTx Centre, the score is used as an advisory allocation tool, with the possibility of derogation to include local medical advice in the allocation decision
    - when there is no local LTx centre or no suitable local recipient, the score is used to rank all the patients of the national waiting list, as a mandatory allocation rule

Liver Allocation Score: *a patient allocation rule*

- providing an access to transplantation adapted to the type of liver disease, based on:
  - MELD for cirrhosis,
  - Waiting time for other diseases,
- Tacking into account practicability with:
  - Distance between donor and transplant centers
  - Preserving a minimal level of "local priority"

LA score : a weigthed sum of functions

AB-Liver Allocation Score $v_{1.1\ (3\ aug\ 2007\text{-}Nov\ 2009)}$ =

1000 . f_1(MELD)

+ **200** . f_2(WTime; threshold = 12 mo) . **if**(HCC TNM1)

+ **200** . f_2(WTime; threshold = 6 mo) . **if**(HCC TNM≥2)

+ **150** . f_2(WTime; threshold = 12 mo) . **if**(NCLD)

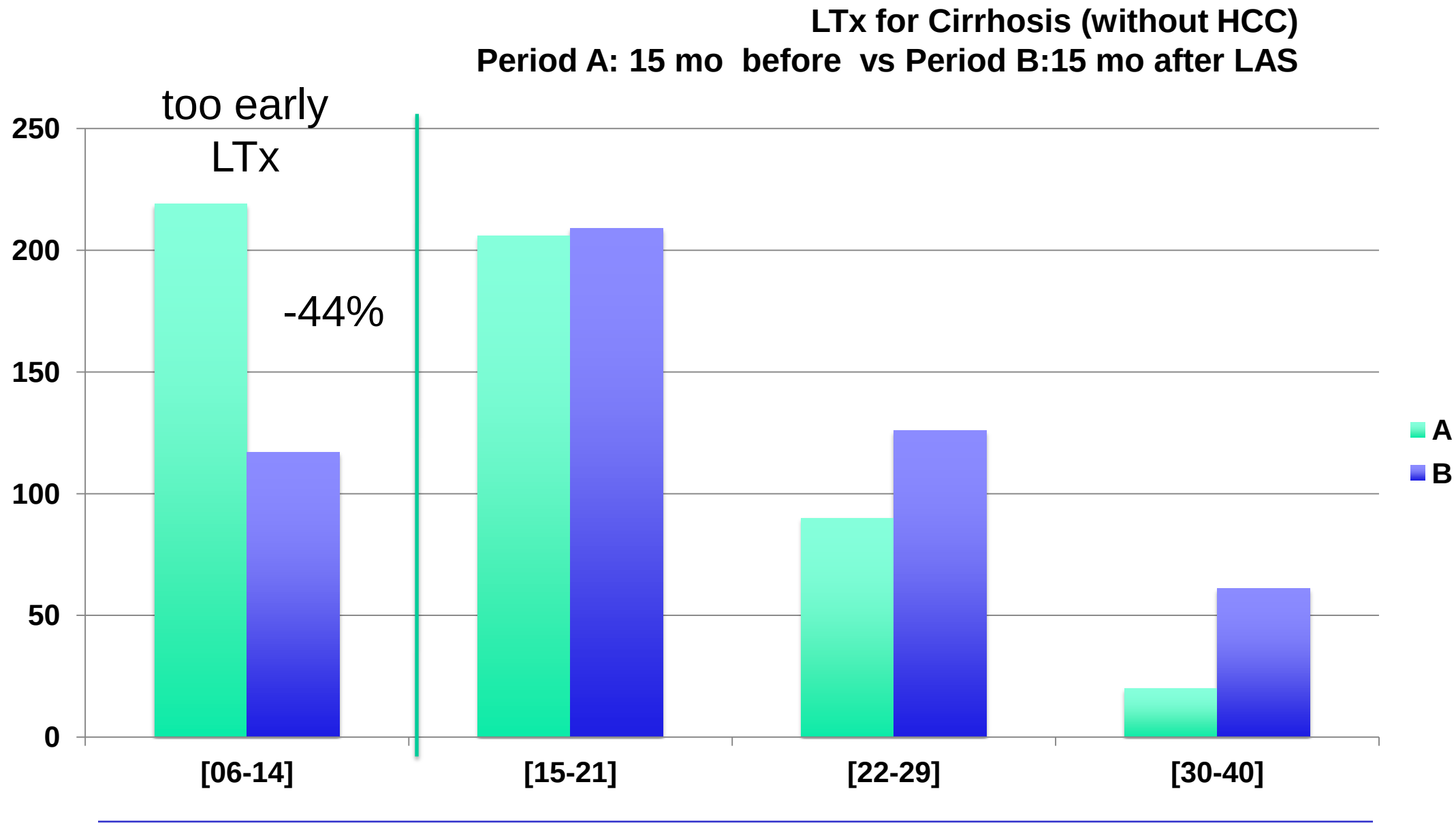
+ **80** . f_2(WTime; threshold = 6 mo) . **if**(eReTx)

+ **300** . f_3(DistanceTDC; LTC)

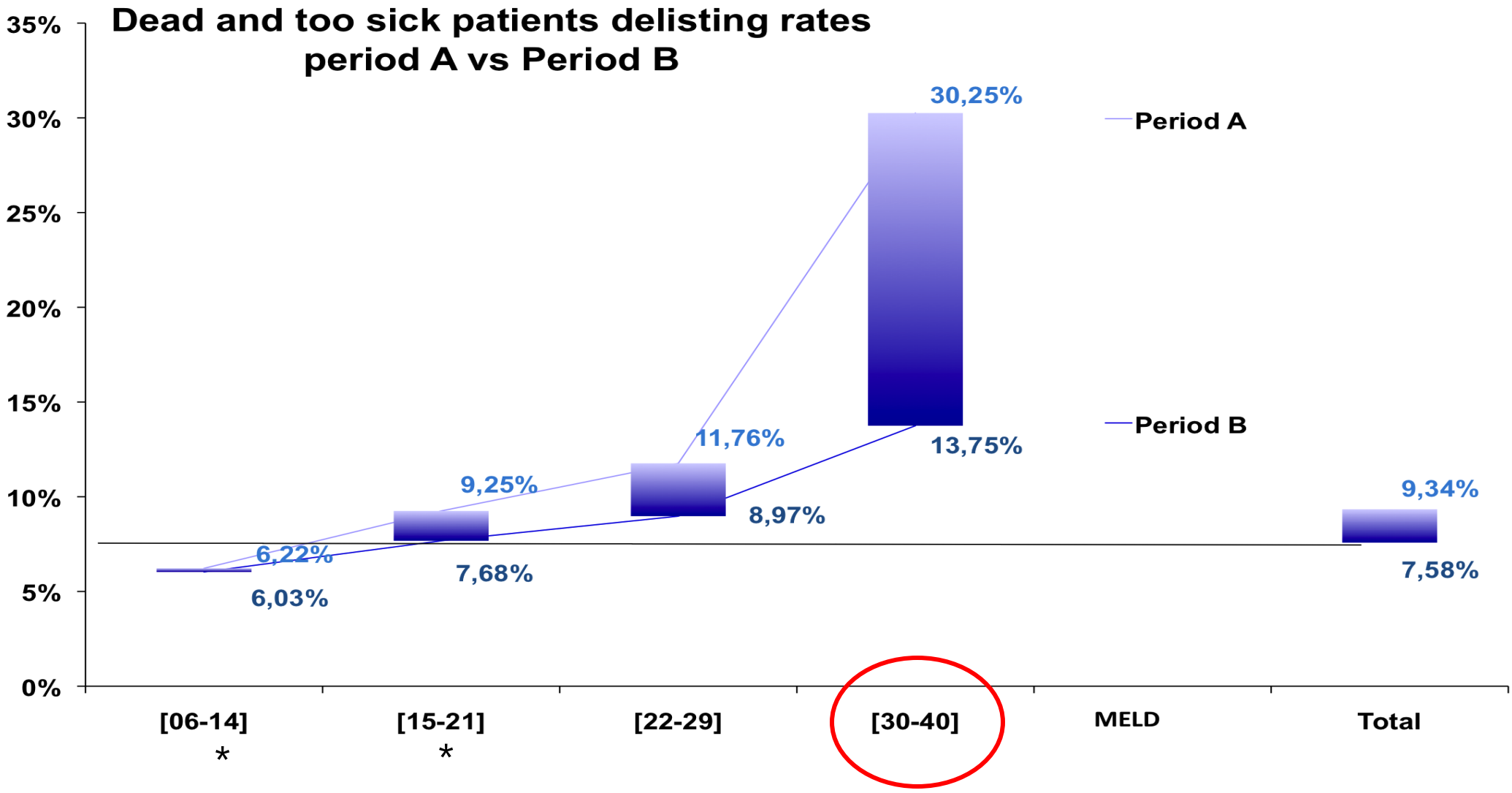
+ **1000**. $f_2(WTime_{exp}$; threshold= [0, 3, 6, 12]) . if(Priority)

Benefits: *patients point of view (1)*

- **A significant Decrease in too early LTx**
- **A significant Decrease of Mortality on the Waiting list**
- **with Improved post transplant results**
- **the value of MELD for WL mortality in Cirrhotic patients**



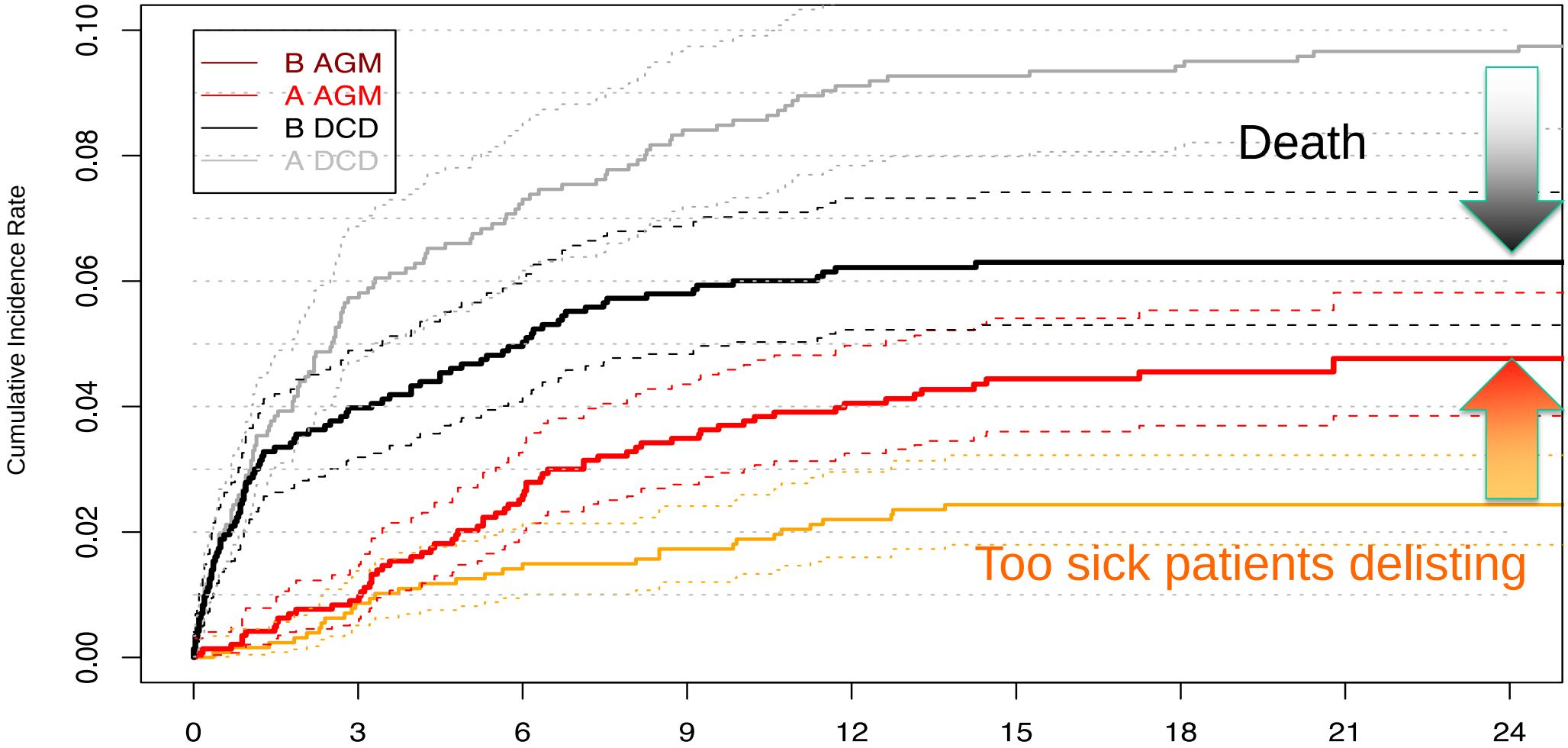
agence de la biomédecine



agence de la biomédecine

Competing Outcomes on the waiting List

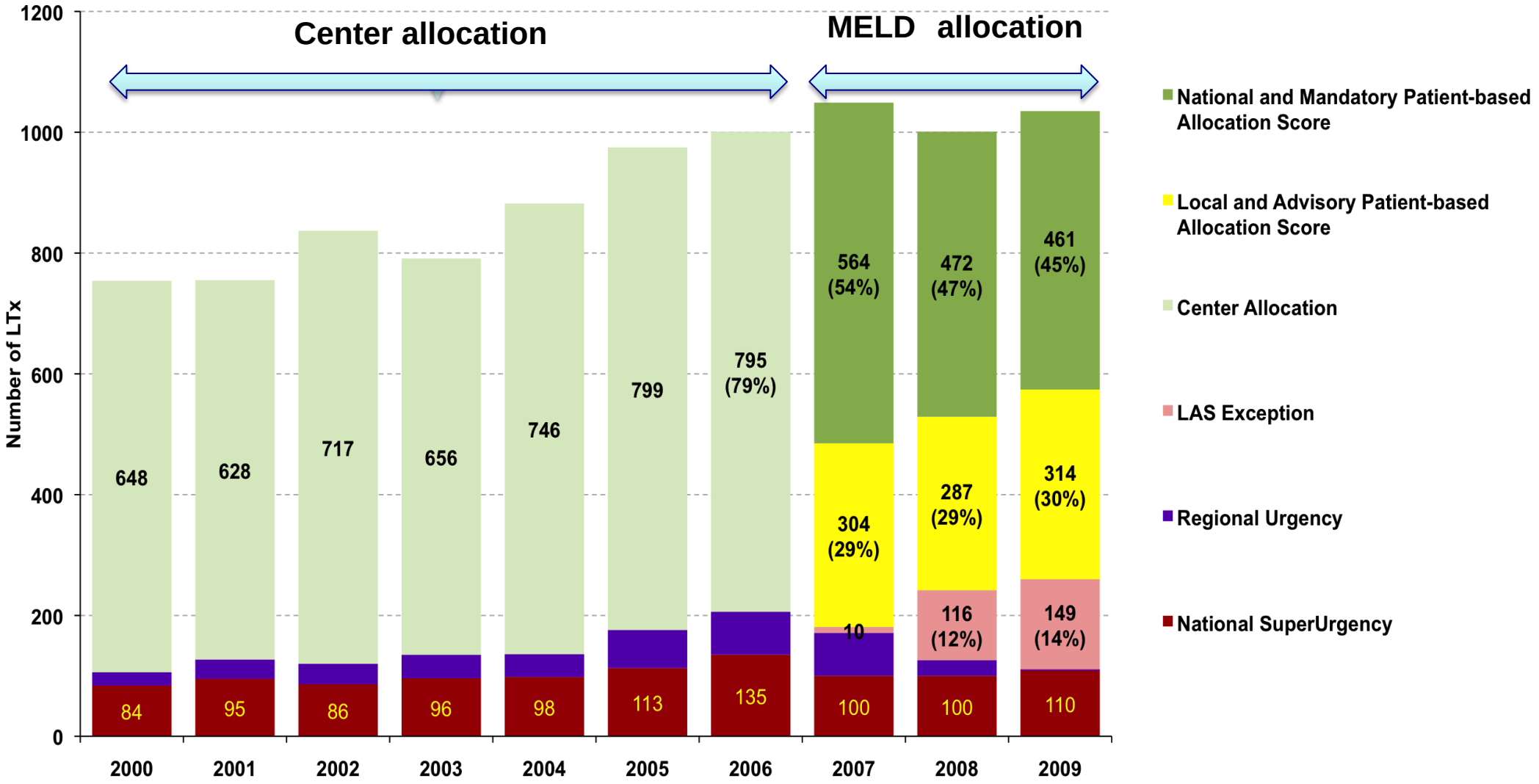
Period A: 15 mo before versus Period B:15 mo after LAS, PointDate = 27/5/2009



Risk	Gray's Stat	p-value	df
Too sick (disease unrelated)	0,918	0,3379	1
Too Sick (disease related): A vs B	**9,407**	**0,0022**	**1**
Improved	0,78	0,3772	1
Dead : A vs B	**9,713**	**0,0018**	**1**
Patient's decision	0,893	0,3447	1
Transplanted	0,018	0,8947	1

agence de la biomédecine

Evolution Liver Allocation Modalities (BD-donors)



ITALY

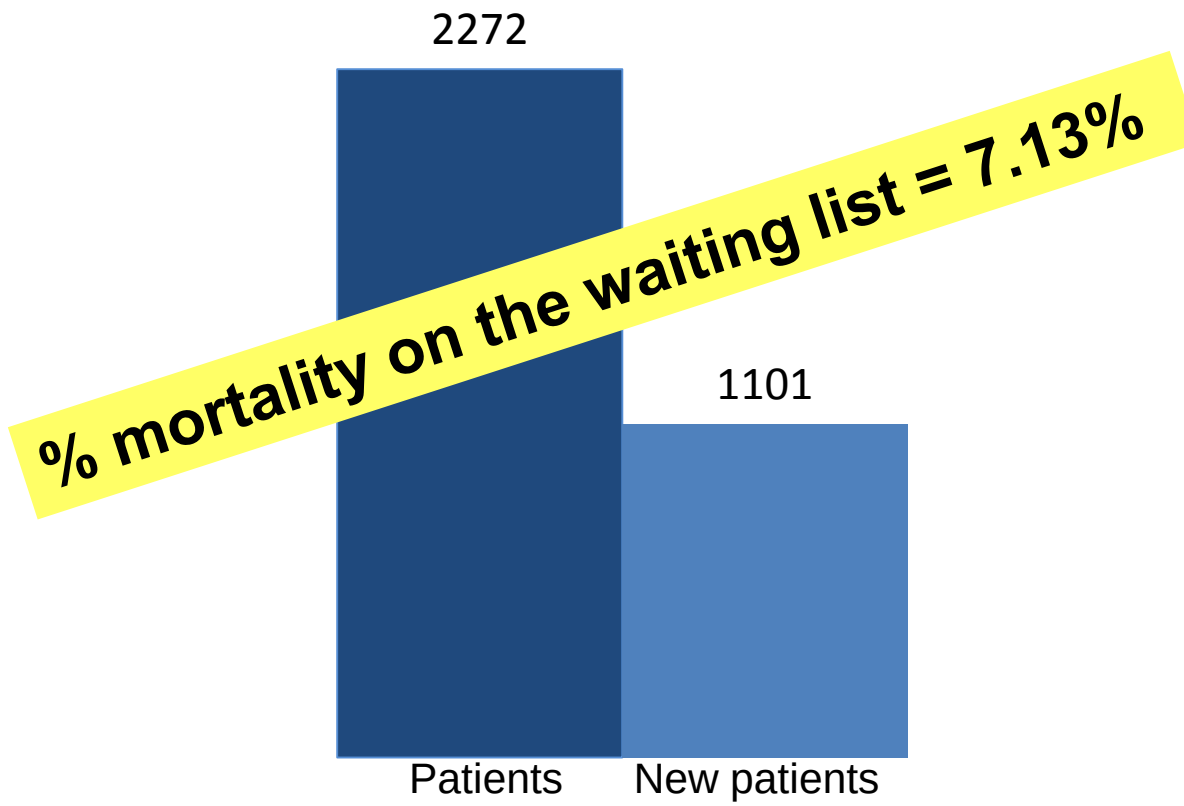
Italy's organ transplantation network is governed by the National Transplantation Center (CNT). It has 21 LT centers in 13 regions, grouped into 2 macro areas (central-northern and central-southern Italy). The current policy stems from a revision in 2012 designed to expand macro area and nationwide organ sharing according to urgency principles.

Organs are shared:

- nationwide for the most severely ill candidates classifiable as UNOS Status 1 (super-urgent);
- by macro area for patients with MELD ≥ 30; and
- regionally for patients with MELD ≤ 29 (the minimum score for listing a patient for LT is 15) .

The arbitrary cutoff at 30 was chosen because patients with MELD >30 at transplantation represented the highest decile (10%) of patients transplanted in Italy in the previous year (2011). With this allocation system, policies at local level may be heterogeneous, with a potential imbalance among different liver disease etiologies

Waiting list (1.1.2012 – 31.12.2012)



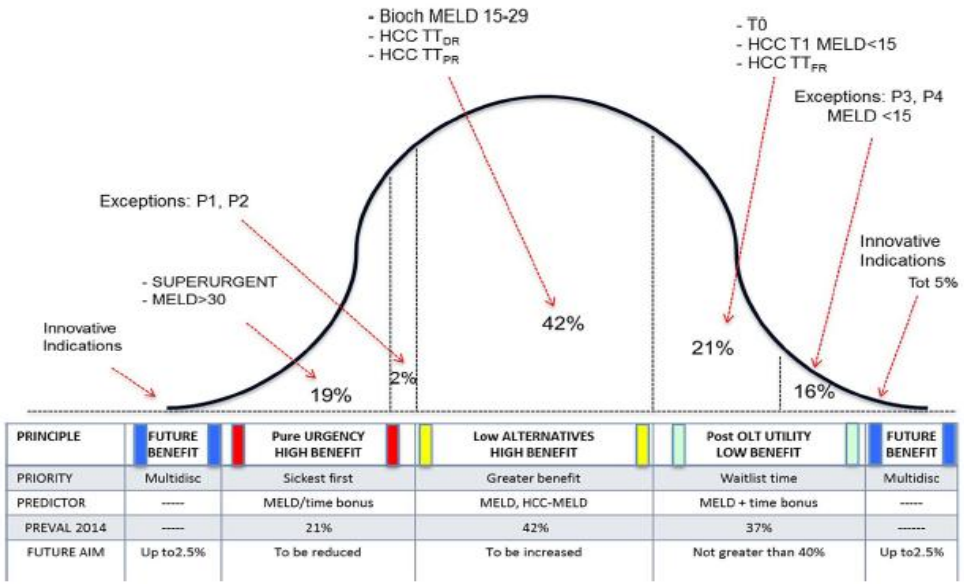
FONTE DATI: Dati Sistema Informativo Trapianti

A Multistep, Consensus-Based Approach to Organ Allocation in Liver Transplantation: Toward a "Blended Principle Model"

U. Cillo[1], P. Burra[2,*], V. Mazzaferro[3], L. Belli[4],

American Journal of Transplantation 2015;

Study of the Liver (AISF), to review the best indicators for orienting organ allocation policies based on principles of urgency, utility, and transplant benefit in the light of current scientific evidence. MELD exceptions and hepatocellular carcinoma were analyzed to construct a transplantation priority algorithm, given the inequity of a purely MELD-based system for governing organ allocation. Working groups of transplant surgeons and



PRINCIPLE	FUTURE BENEFIT	Pure URGENCY HIGH BENEFIT	Low ALTERNATIVES HIGH BENEFIT	Post OLT UTILITY LOW BENEFIT	FUTURE BENEFIT
PRIORITY	Multidisc	Sickest first	Greater benefit	Waitlist time	Multidisc
PREDICTOR	-----	MELD/time bonus	MELD, HCC-MELD	MELD + time bonus	-----
PREVAL 2014	-----	21%	42%	37%	------
FUTURE AIM	Up to2.5%	To be reduced	To be increased	Not greater than 40%	Up to2.5%

Figure 1: Ideogram of donor resource distribution among the main liver allocation principles in Italy. Location of the different

- P1: Very high priority: warrants organ sharing by macro area (central-northern or central-southern Italy, each serving a population of 20–25 million) as for patients with MELD ≥30;
- P2: High priority: organs to be shared within each region (serving populations of 1–6 million, 4 regions have more than one LT center), priority increasing with time on the waiting list (extra points for time, capping at 29)
- P3: Intermediate priority: organ sharing by region, priority increasing with time on the waiting list (extra points for time, capping at 29)
- P4: Low priority, organ sharing by region, priority increasing with time on the waiting list (extra points for time, capping at 29)
- P Multidisciplinary: Patients with particular indications

EuroTransplant

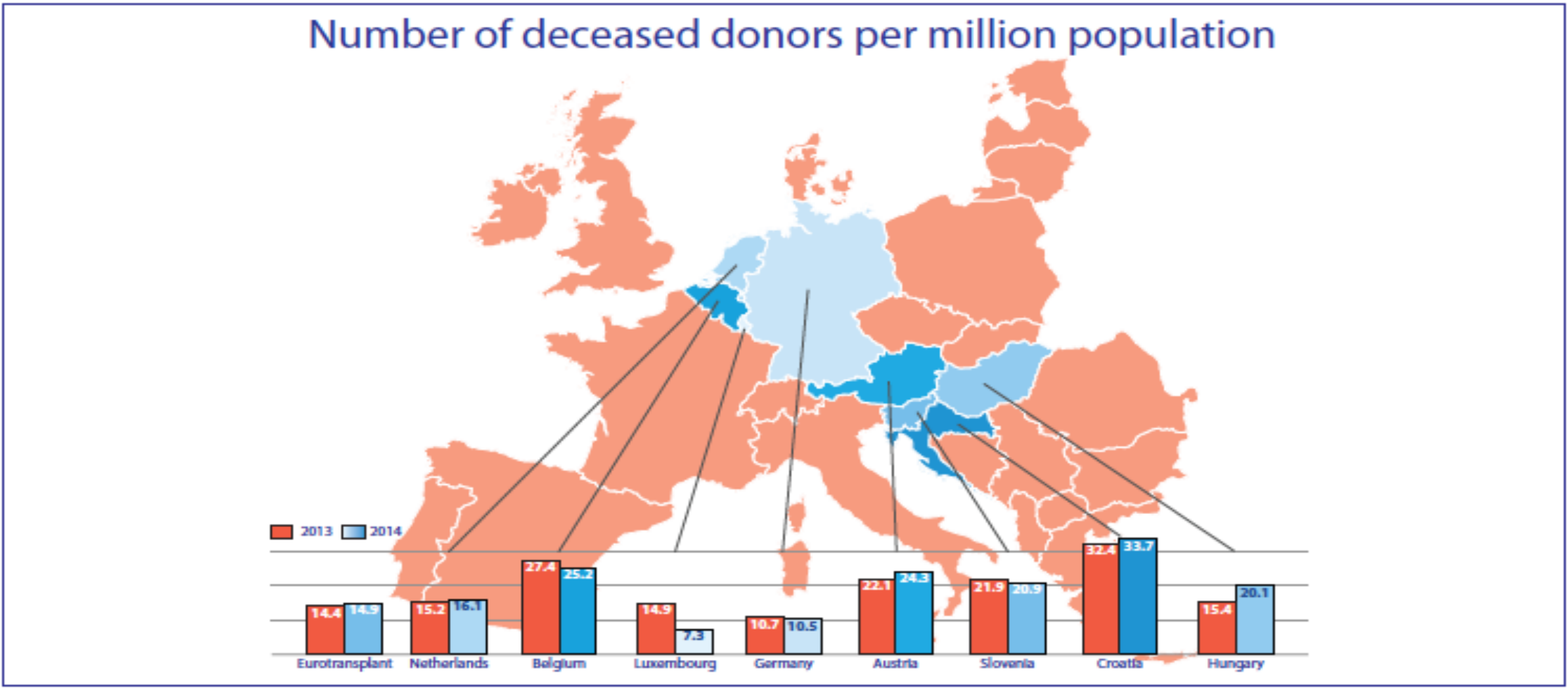


Table 4.1 Number of deceased donors used for a transplant, by donor country, from 2010 to 2014

By order of priority

1. Hyper urgent for liver failure and HAT
2. Combined thoracic plus abdominal organs
3. MELD (Lab Meld or Matched MELD) for SE and NSE

SE: Patients with Standarsd exception (SE) are given extra MELD points: mostly HCC within Milan, Hepatopulmonary hypertension and porto pulmonary hypoxia, polycystosis, Hemangioendothelioma (to fulfill precises diagnosis criteria)

NSE: Non Standard exception (NSE) Patients in whom the degree of emergency of the Tx is not reflected by the MELD and who are not SE. A file has to be submitted to auditors. If approved these patients also receive extra MELD points

Model for End-stage Liver Disease (MELD)

Overview standard exceptions per country

Diseases defined as SE	A	B/L	G	NL	SLO	CHR
Cholangiocarcinoma	✓		✓		✓	✓
Cystic fibrosis (CF)	✓	✓	✓		✓	✓
FAP	✓	✓	✓	✓	✓	✓
Hepatopulmonal syndrome (HPS)	✓	✓	✓	✓	✓	✓
Porto-pulmonary hypertension (PoPH)	✓	✓		✓	✓	✓
Primary hyperoxaluria Type 1 (PH1)	✓	✓	✓	✓	✓	✓
Polycycstic liver disease (PLD)	✓	✓	✓	✓	✓	✓
Hepatocellular carcinoma (HCC)	✓	✓	✓	✓	✓	✓
Non-metastatic hepatoblastoma	✓*	✓*	✓*	✓*	✓*	✓*
Urea cycle disorder/organic acidemia	✓*	✓*	✓*	✓*	✓*	✓*
Persistant hepatic dysfunction	✓	✓	✓	✓**	✓	✓

* same in all countries

**SE audited as NSE

Model for End-stage Liver Disease (MELD)
Overview standard exceptions per country

Diseases defined as SE	A	B/L	G	NL	SLO	CHR
Hereditary hemorrhagic teleangiectasia	✓	✓	✓	✓**	✓	✓
Hepatic hemangioendothelioma	✓	✓	✓	✓**	✓	✓
Biliary sepsis	✓	✓	✓	✓**	✓	✓
Hepatopulmonal syndrome (HPS)	✓	✓	✓	✓**	✓	✓
Primary sclerosing cholangitis (PSC)			✓	✓**	✓	✓

**SE audited as NSE

Model for End-stage Liver Disease (MELD)

Recertification schedule

MELD	lab MELD expires after	Notification before expiry	Expiry date of lab values at data entry
MELD ≥25	7 d	2 d	not older than 48 h
MELD ≤24, >18	30 d	7 d	not older than 7 d
MELD ≤18, ≥11	90 d	14 d	not older than 14 d
MELD ≤10	365 d	30 d	not older than 30 d

Como mas grave el paciente, mas frequente la nueva certificacion

Model for End-stage Liver Disease (MELD)

Missed recertifications

- Missed recertification
  - One time?
    - downgrade to immediate previous lower MELD score
    - downgrade to MELD 6 if no immediate previous lower MELD score known
  - Two consecutive times?
    - downgrade to MELD 6
- Downgrades performed at end of recertification period
- New recertification period starts at downgrade

Figure 4.7 Median waiting time to transplant (deceased donor transplants)

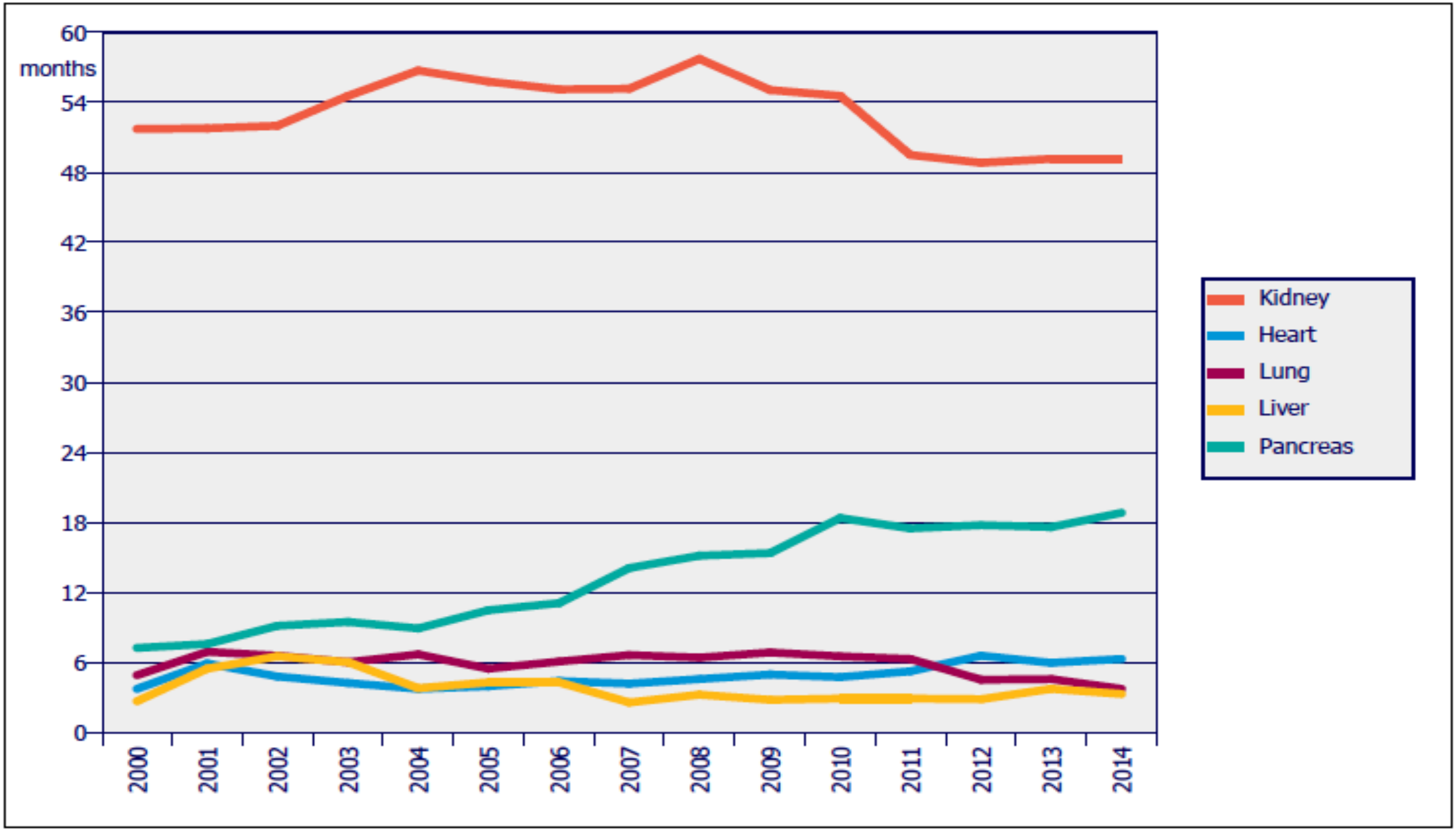


Figure 7.2 Liver waiting list, percentage of patients at year end, by urgency

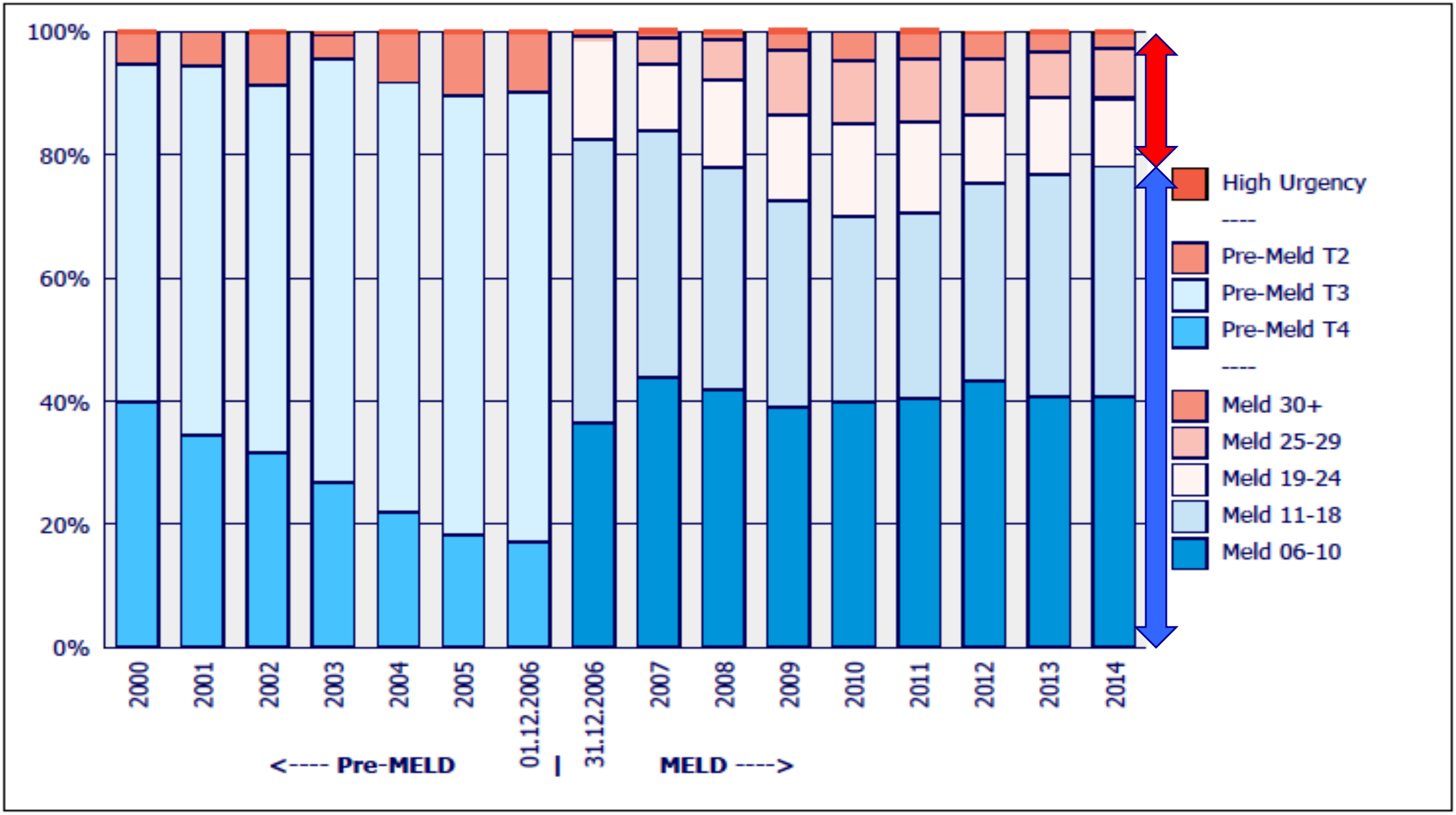
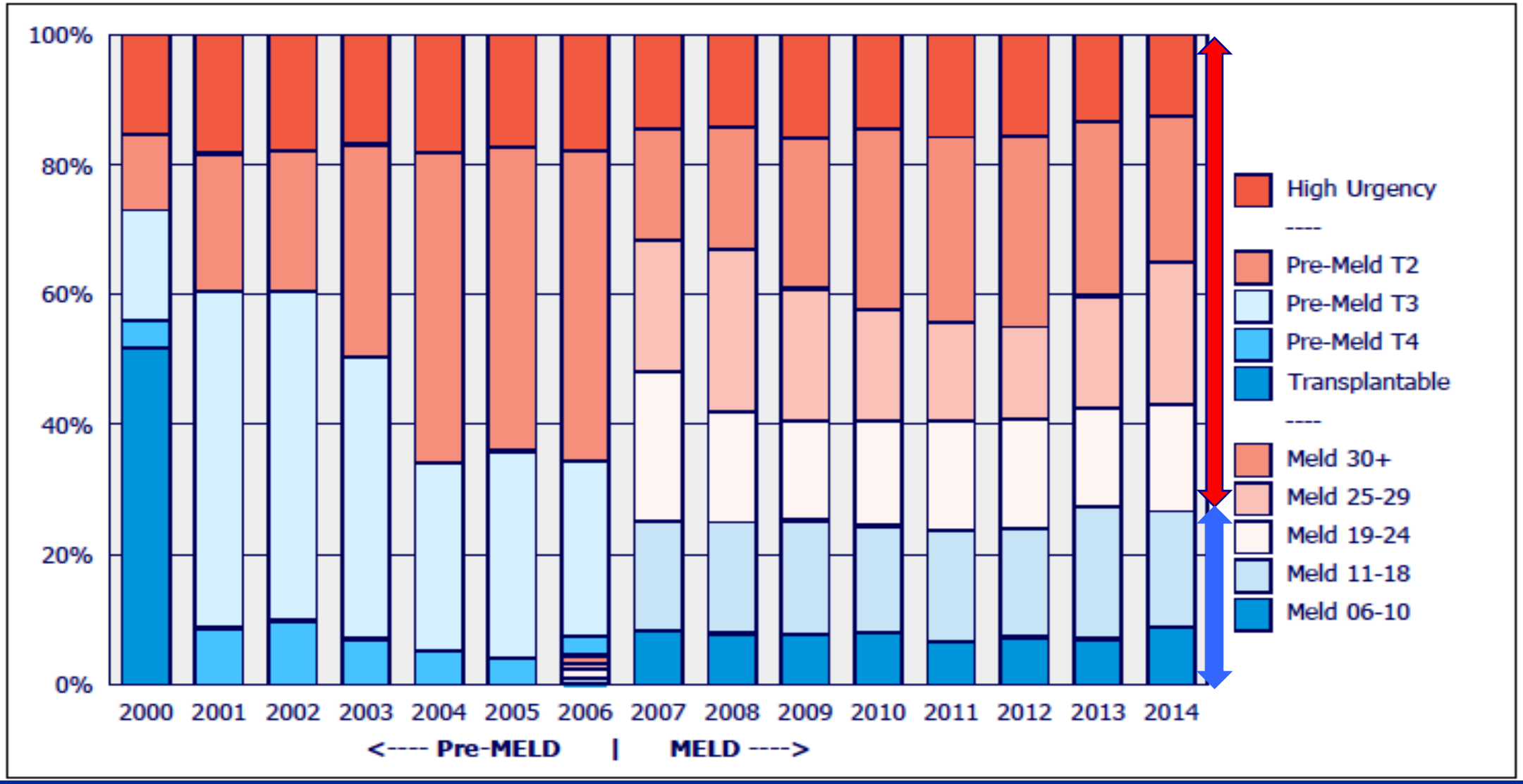
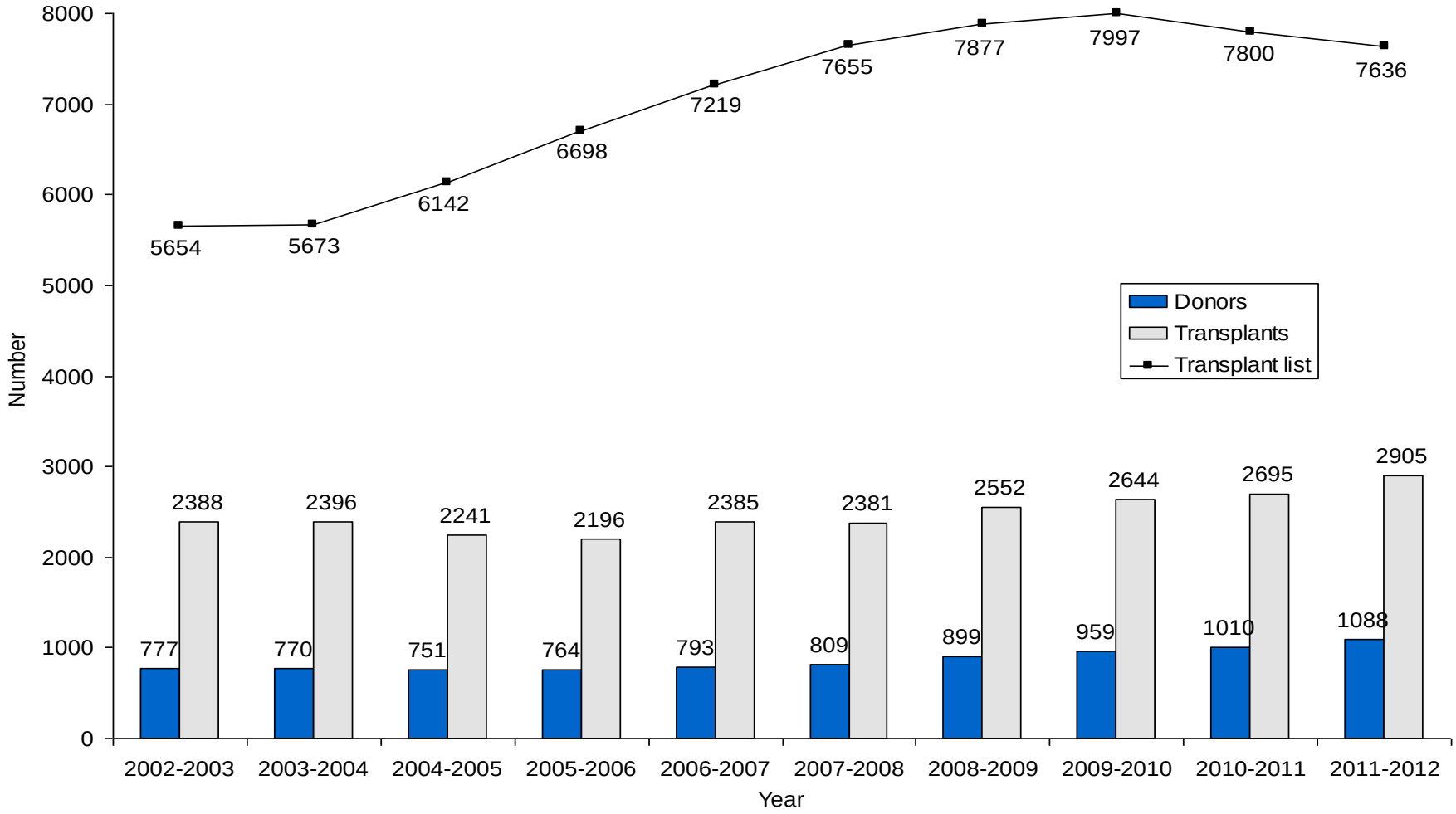


Figure 7.4 Percentage of deceased donor liver transplants, by recipient urgency at transplant



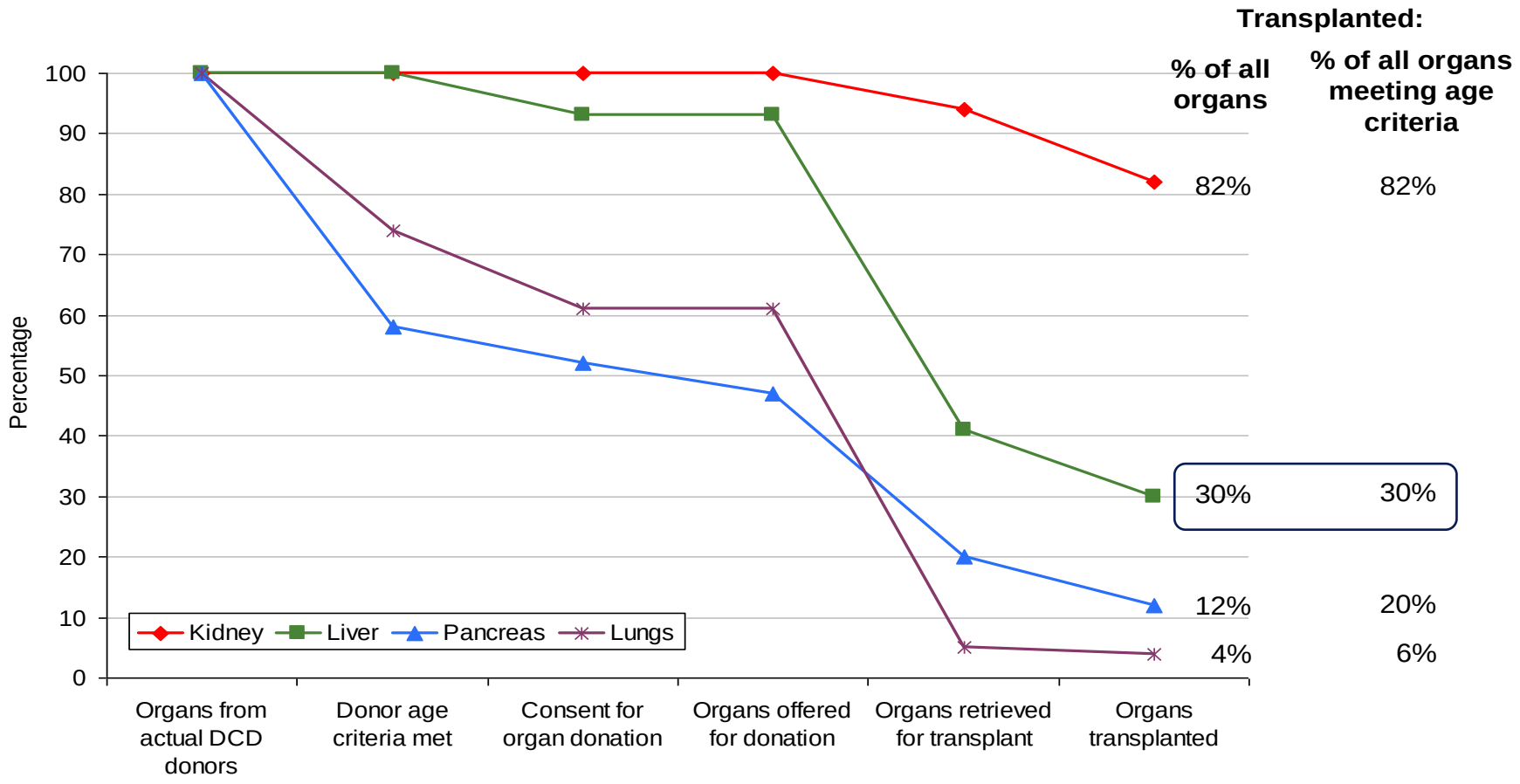
UK

Number of deceased donors and transplants in the UK, 1 April 2002 - 31 March 2012, and patients on the active transplant lists at 31 March



Source: Transplant activity in the UK, 2011-2012, NHS Blood and Transplant

Donation and transplantation rates of organs from DCD organ donors in the UK, 1 April 2011 – 31 March 2012



Source: Transplant activity in the UK, 2011-2012, NHS Blood and Transplant

UNITED KINGDOM

NHSBT : Organ procurement via a new National Organ Retrieval Service introduced in 2010

7 abdominal – 6 Thoracic retrieval teams
Travel time < 3 hours in each region

Liver Allocation : Center-oriented

- All donors reported to the NHSBT office
- Donor zones allocated to each center based on the number of new registrations on the waiting list
- Rotation of the centers
- Allocation priority at each centre ; decided by transplant Surgeons and Physicians on Call (donor/recipient factors)
- DCD Donors: Local priority
- DBD Donors : < 40 yrs, > 50 Kgs, < 5 days ITU : Split…
  Justify the reason when not done…
- Extra UK Offers : « first come, first served » basis

CONCLUSION

- El modelo ideal de allocacion de organos no existe…
- Un compromiso de urgencia, utilidad y beneficio ?…
- El MELD ha aportado mas rigor y transparencia en la lista de espera
- La mayoria de los paises europeos excepto Reino Unido lo han adoptado con modulacion de otros factores y excepciones
- No hay harmonizacion acerca del modelo que utilizar para determinar que paciente priorizar…

Lo mas importante…

Aristote:
« Tratar igualmente casos iguales y desigualmente casos desiguales »

Challenge fundamental de allocation de organos es EQUIDAD entre los pacientes heterogeneos de la lista de espera

Equidad es tratar todos los pacientes con el mismo end point

Equidad is hierarchicamente mas importante que los demas criterios, sea que se favorezca urgencia, utilidad o beneficio como end points de allocation…

« La simplicidad es la complejidad resuelta »

P Mondrian Pintor pionero del arte abstracto

The ethical constraint

Aristote:
« Treating equal cases equally and unequal cases unequally »

Fundamental challenge of organ allocation is EQUITY among the heterogeneous patients of the waiting list

Equity means treating all patients according to the same end point

Equity is hierarchically more important than all others, whether we decide to favor urgency, utility or benefit as end points for allocation…

Eurotransplant

Liver Transplantation for Hepatocellular Cancer: The Impact of the MELD Allocation Policy

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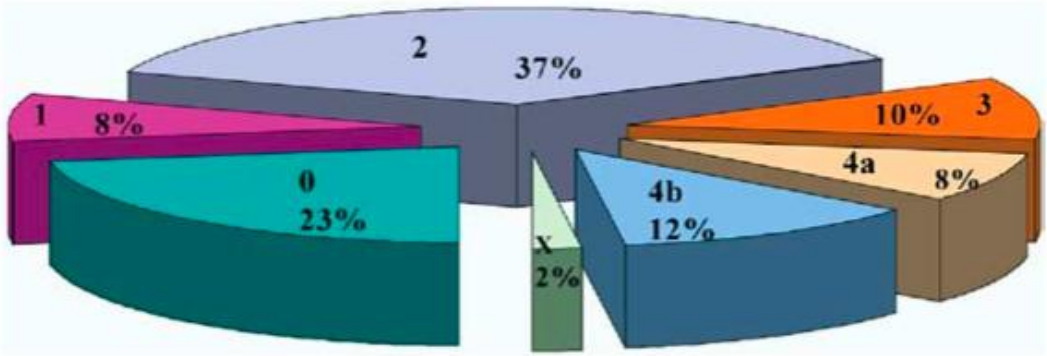

Figure 7. Staging of hepatocellular carcinoma based on explant pathology on 666 HCC patients undergoing liver transplantation. All patients had imaging studies showing stage 1 or stage 2 HCC at time of listings for liver transplantation.

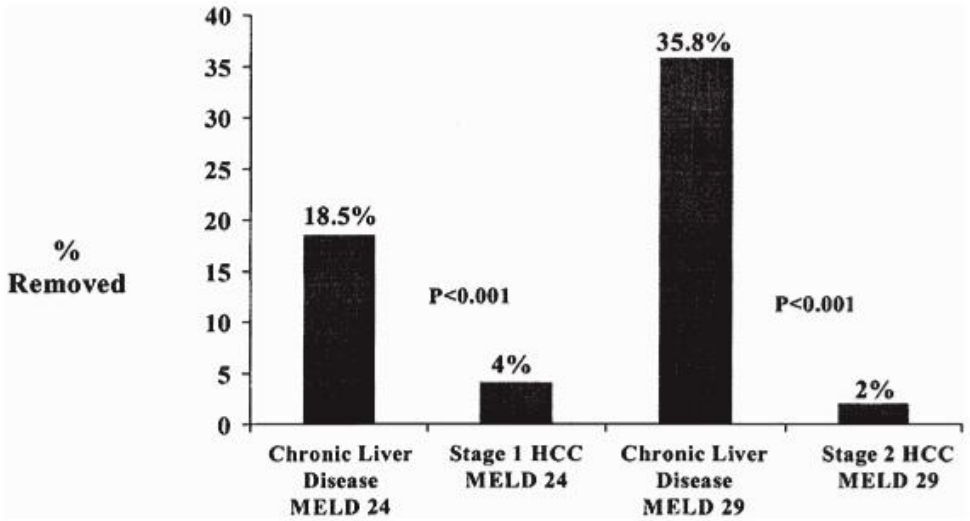

Figure 5. Percent of patients removed from UNOS waiting list because of death/being too sick or nontransplantable patient with HCC and in patients with chronic liver disease with comparable MELD scores (SRTR analysis, January 2004).