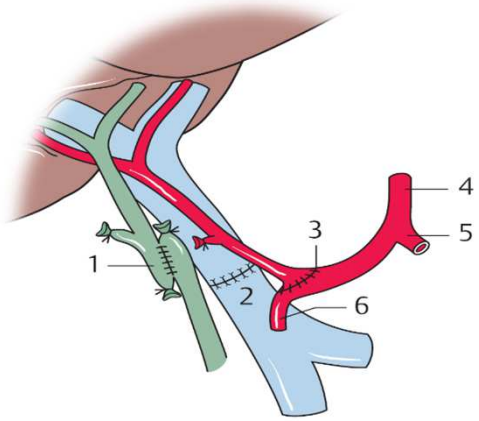

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TRANSPLANTATIONSZENTRUM

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20-years of follow up after liver transplantation: What can we learn from the past ?

Daniel Seehofer

Universitätsklinikum Leipzig, Klinik für Viszeral-, Transplantations-Thorax- und Gefäßchirurgie

University of Pittsburgh

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March 5, 2017

Thomas E. Starzl, MD, PhD, 'Father of Transplantation,' Dies at 90

The following is offered at the request, and on behalf, of the Starzl family, as well as the University of Pittsburgh and UPMC.

Contact: Gloria Kreps, UPMC
Mobile: 412-417-2582
E-mail: KrepsGA@upmc.edu

Contact: Joe Miksch, University of Pittsburgh
Mobile: 412-997-0314
E-mail: jmiksch@pitt.edu

PITTSBURGH, March 5, 2017

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1963 world's first liver transplant

1967 world's first successful liver transplant (survival > 1 year)

(50 years)

1969 first LT in Germany (Bonn)

1987/88 first LT in Berlin

1993 first LT in Leipzig

http://www.telegraph.co.uk

Issues to be adressed

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- Long term results after LT
- The evolution of organ donation and allocation
- Predicting outcome after LT
- Donor/recipient matching
- Biliary complications (NAS, AMR)

Organ Transplantation in Germany (since 1963)

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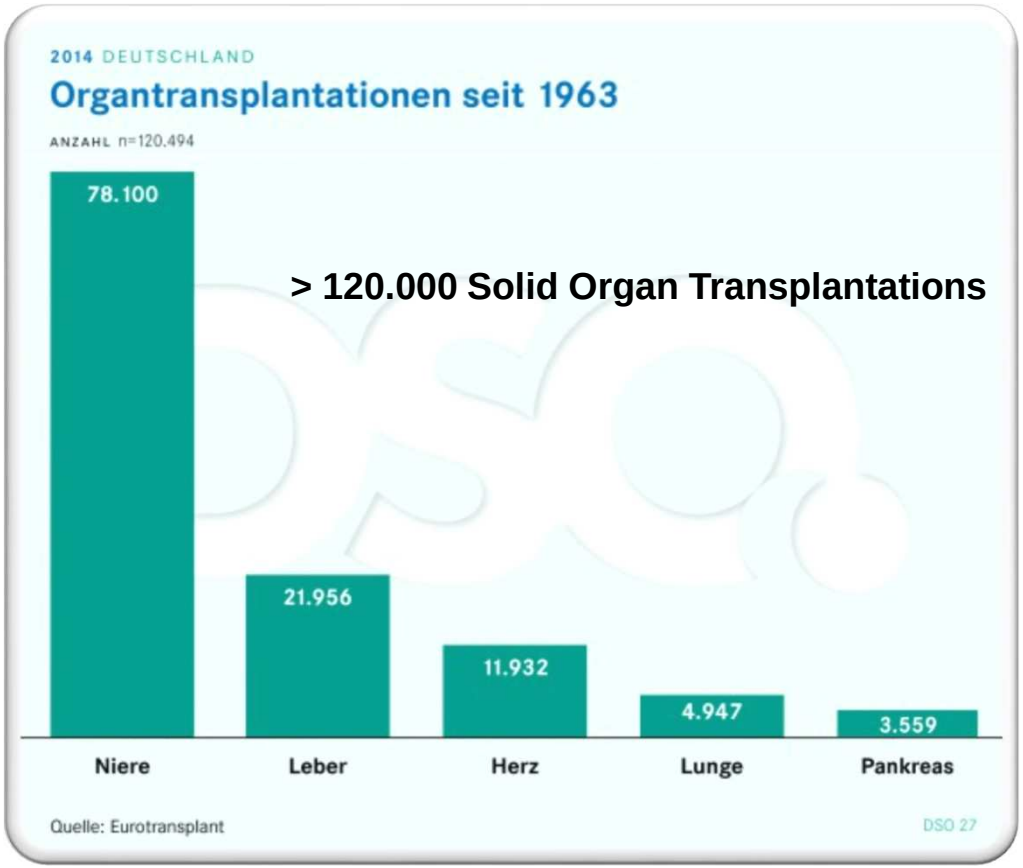
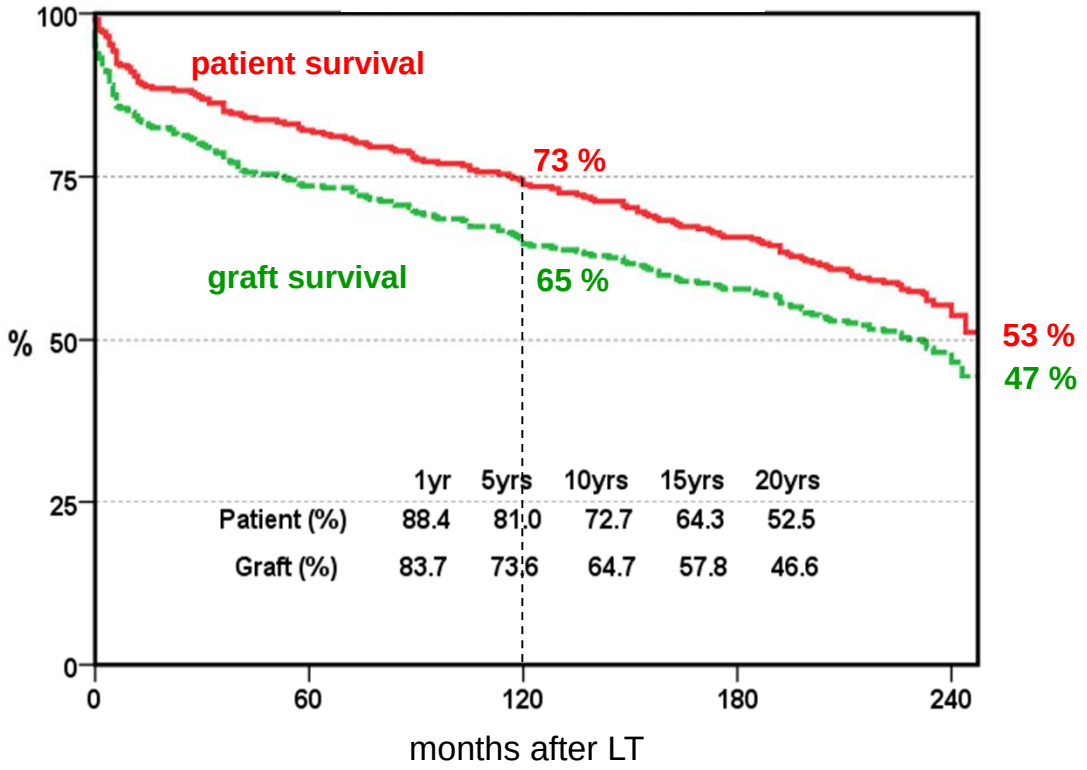


> 120.000 Solid Organ Transplantations

ELTR: 140.000 LT

20 year patient and graft survival

Berlin, LT between 1988 and 1993, n=313 patients)



Schoening WN, Am J Transplant 2013; 13: 2384

Survival after LT (1 year mortality excluded)

(age at LT > 55 years, LT between 1988 and 1993)

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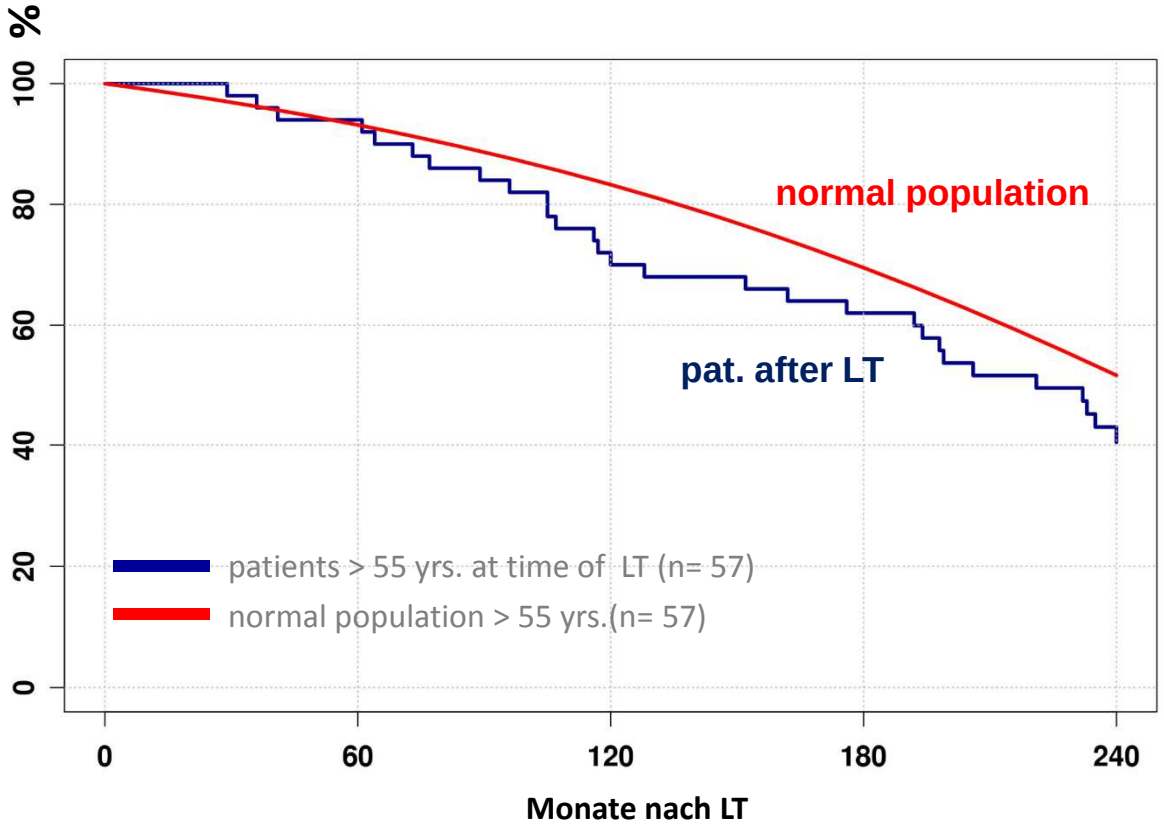
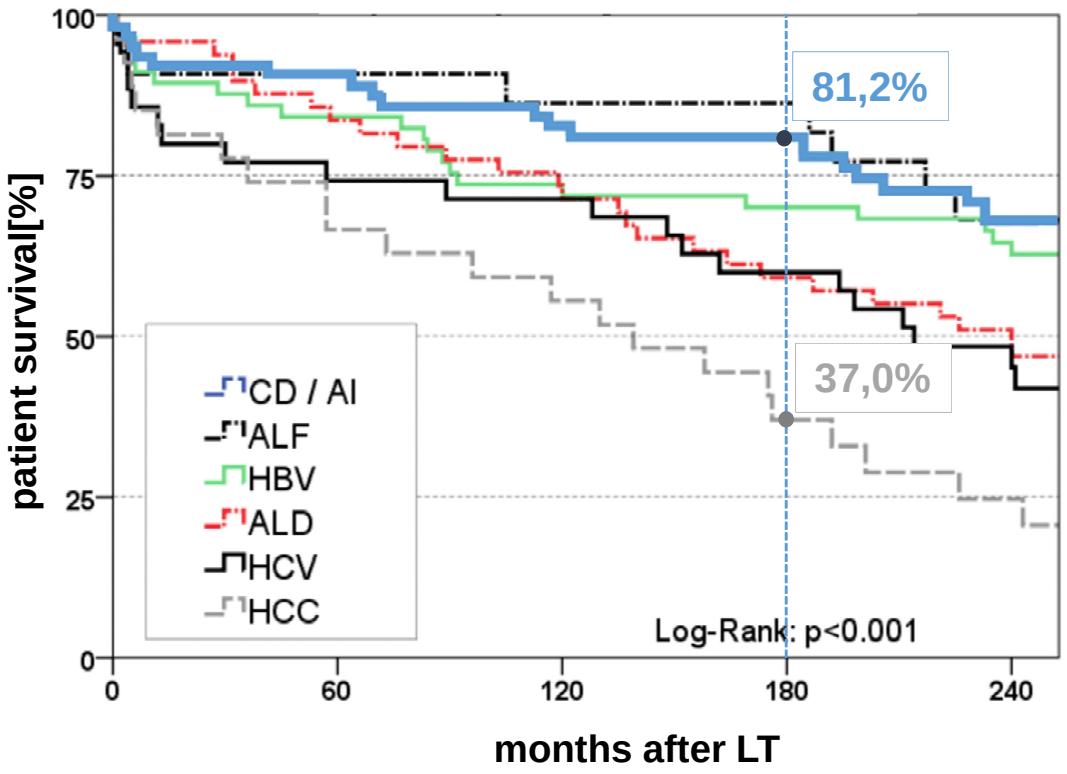


Schoening WN, Am J Transplant 2013; 13: 2384

20-year survival after LT



PBC, PSC, AIH

HCC

Schoening WN, Am J Transplant 2013; 13: 2384

Impact on BMI on long term outcome

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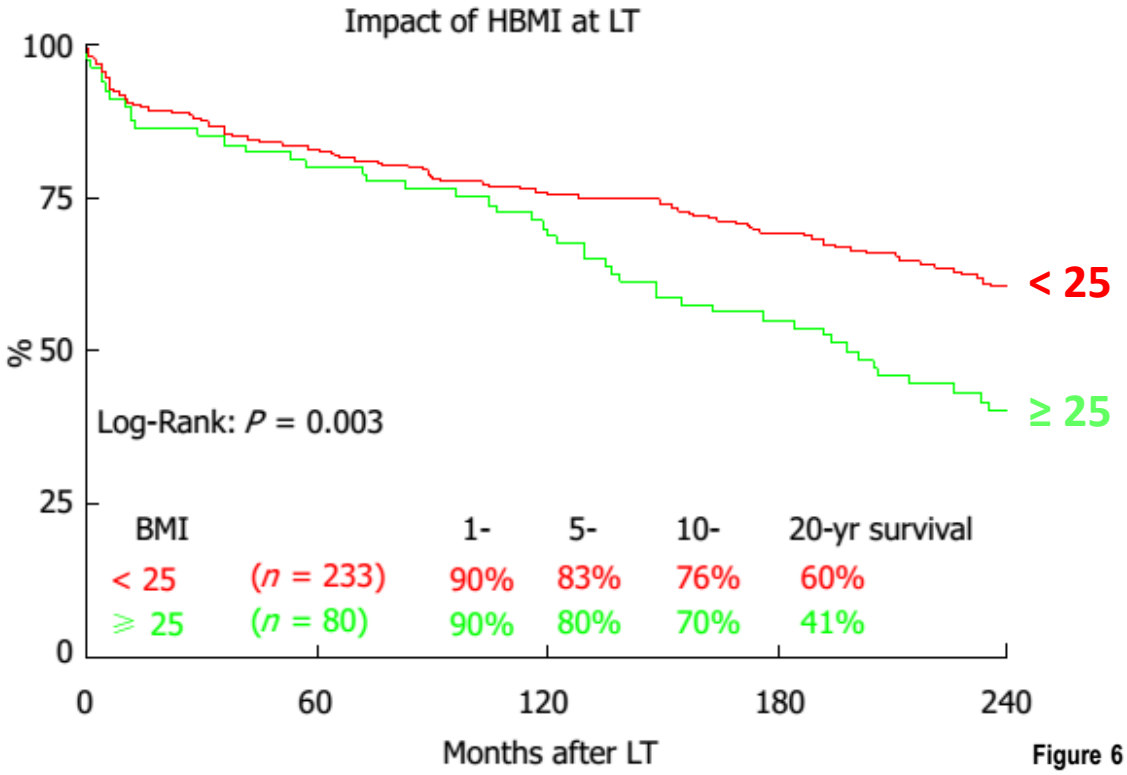

Figure 6 The impact of overweight (overweight, body-mass-index > 25) at time of liver transplantation on 20-year survival. LT: Liver transplantation; HBMI: High body mass index (> 25).

Buescher N, Seehofer D, World J Transplant 2016; 6: 599

Causes of death after LT

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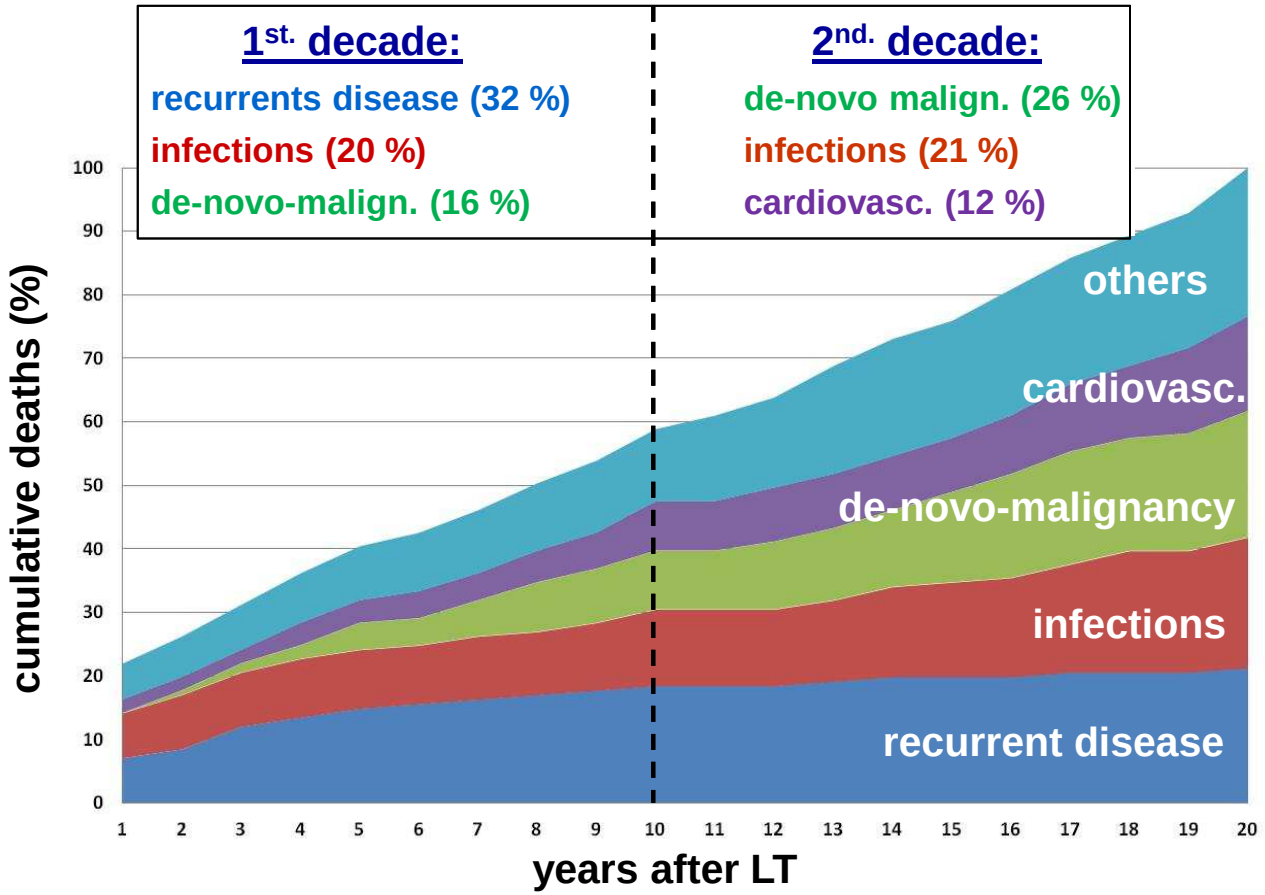

Schoening WN, Am J Transplant 2013; 13: 2384

What has changed ?

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- organ allocation (‘sickest first’)
- organ donation (rate, ECD, DCD, ...)
- primary disease (HBV, HCV -> HCC, NASH)
- ....

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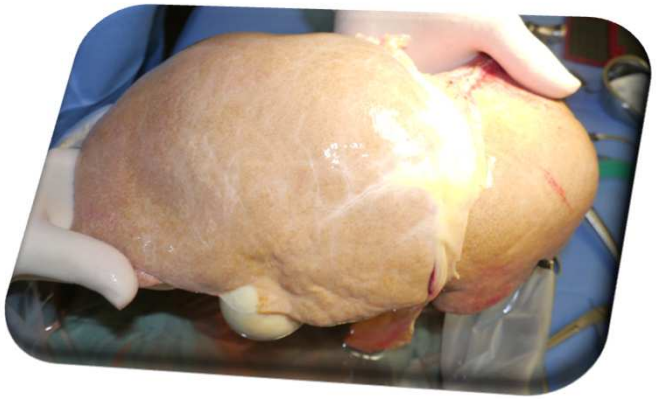

The evolution of organ donation and allocation

Organ allocation by urgency of the recipient

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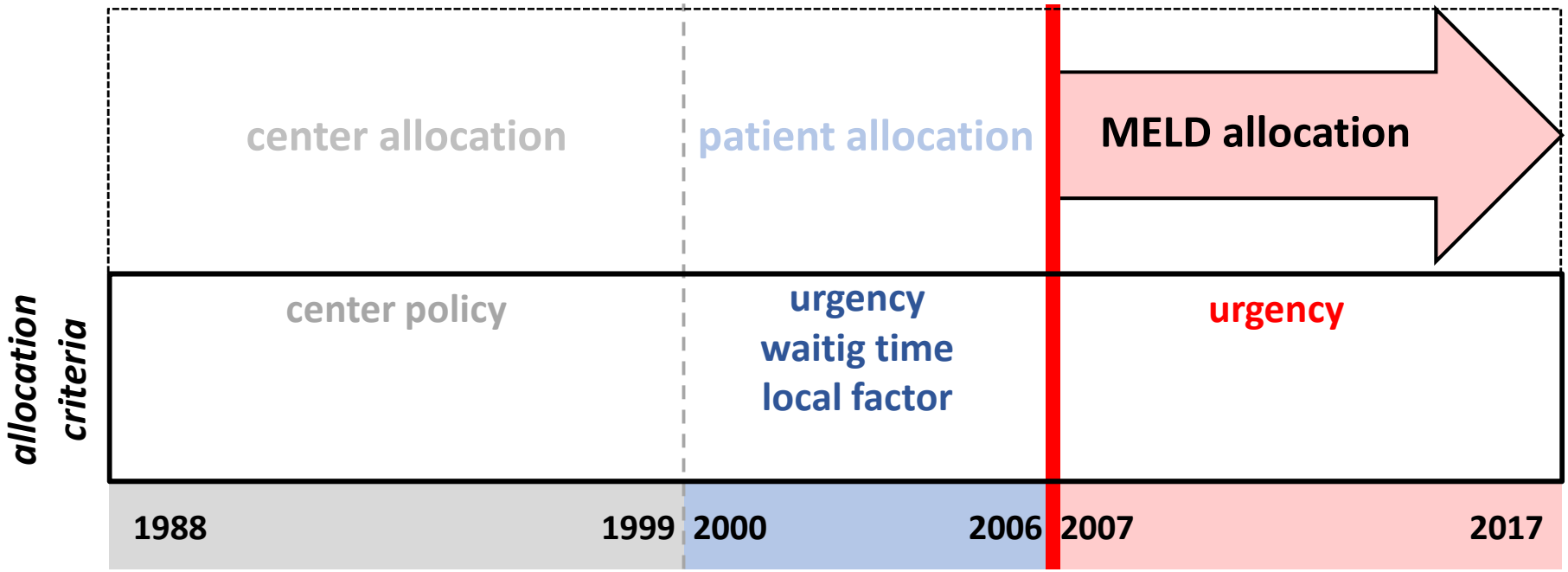
„sickest first concept“



Organ Allocation by MELD

*(**M**odel for **E**ndstage **L**iver **D**isease)*

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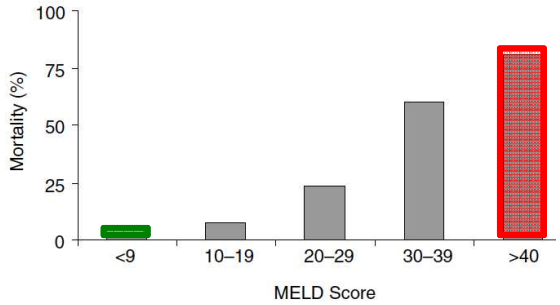
MELD = 10 x (0.957 x ln **(creatinine)** + 0.378 x ln **(total bilirubin)** + 1.12 x ln **(INR)** + 0.643

MELD and 3 months mortality

	≤9	10–19	20–29	30–39	≥40
MELD Score					
3-Month death rate	4 (6/148)	27 (28/103)	76 (16/21)	83 (5/6)	100 (4/4)
CTP Score		A	B		C
3-Month death rate		4 (3/77)	14 (13/93)		51 (35/69)

Note: values expressed as percentages (number/total). Source: Kamath et al., 2001 (13).



Urgency of the recipient

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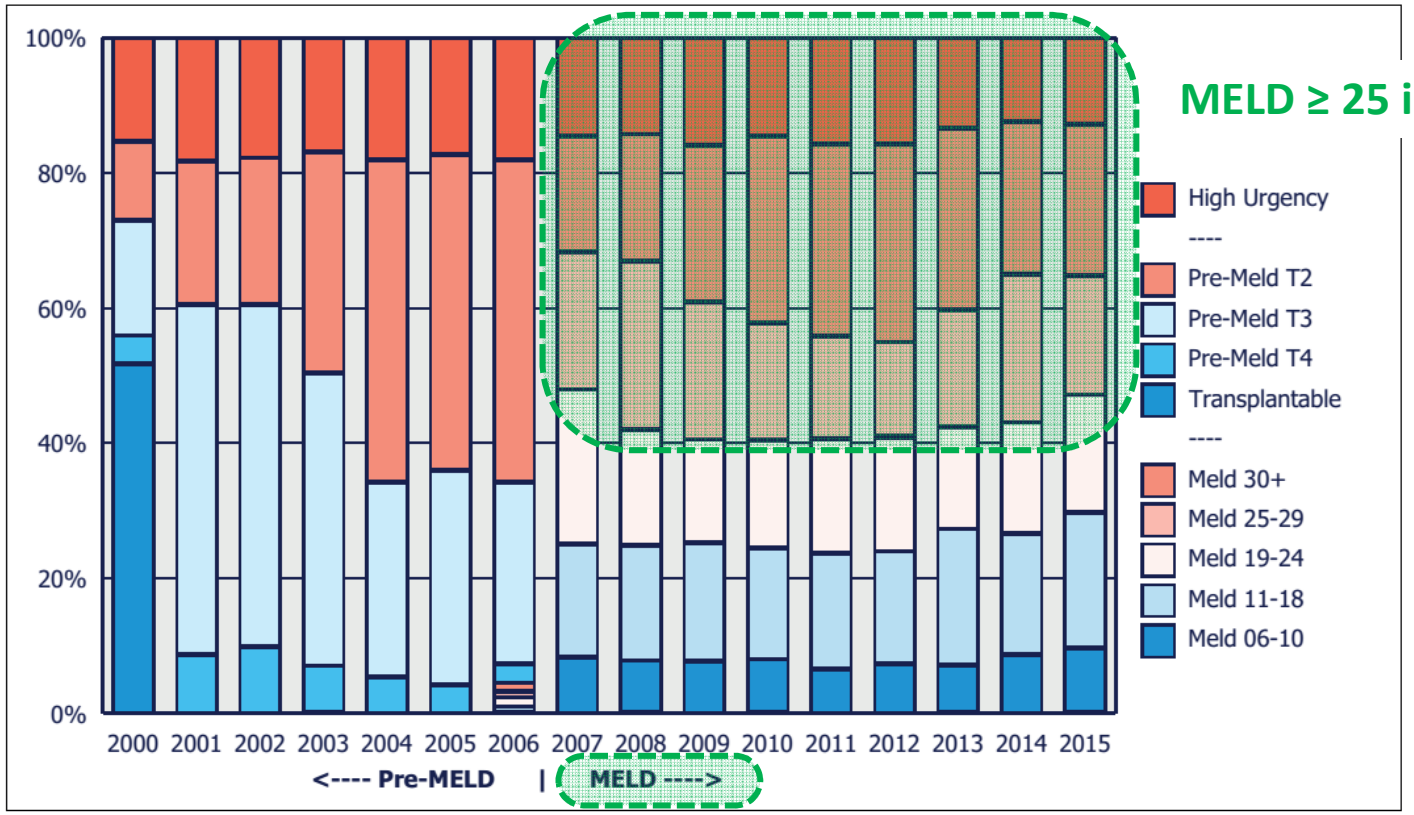
Figure 7.4 Percentage of deceased donor liver transplants, by recipient urgency at transplant



MELD ≥ 25 in 60% of LT

1 year survival after LT in different MELD categories

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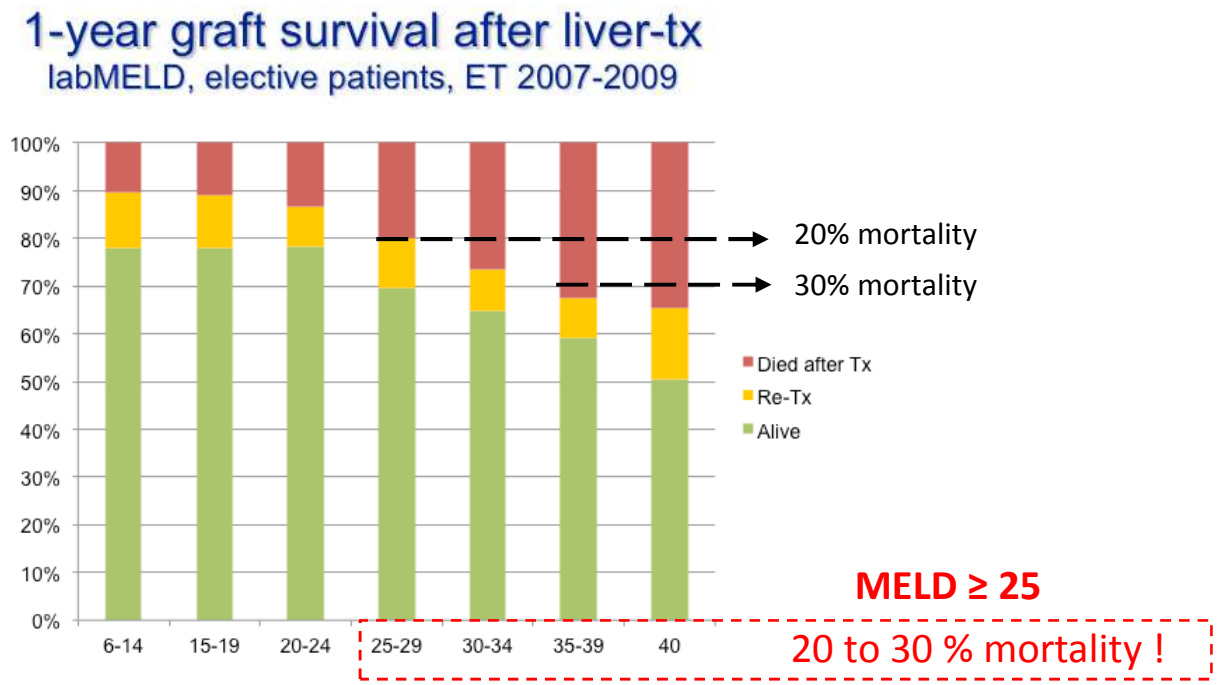

=> less deaths on the waiting list but inferior results after LT !

Urgency of the recipient by country

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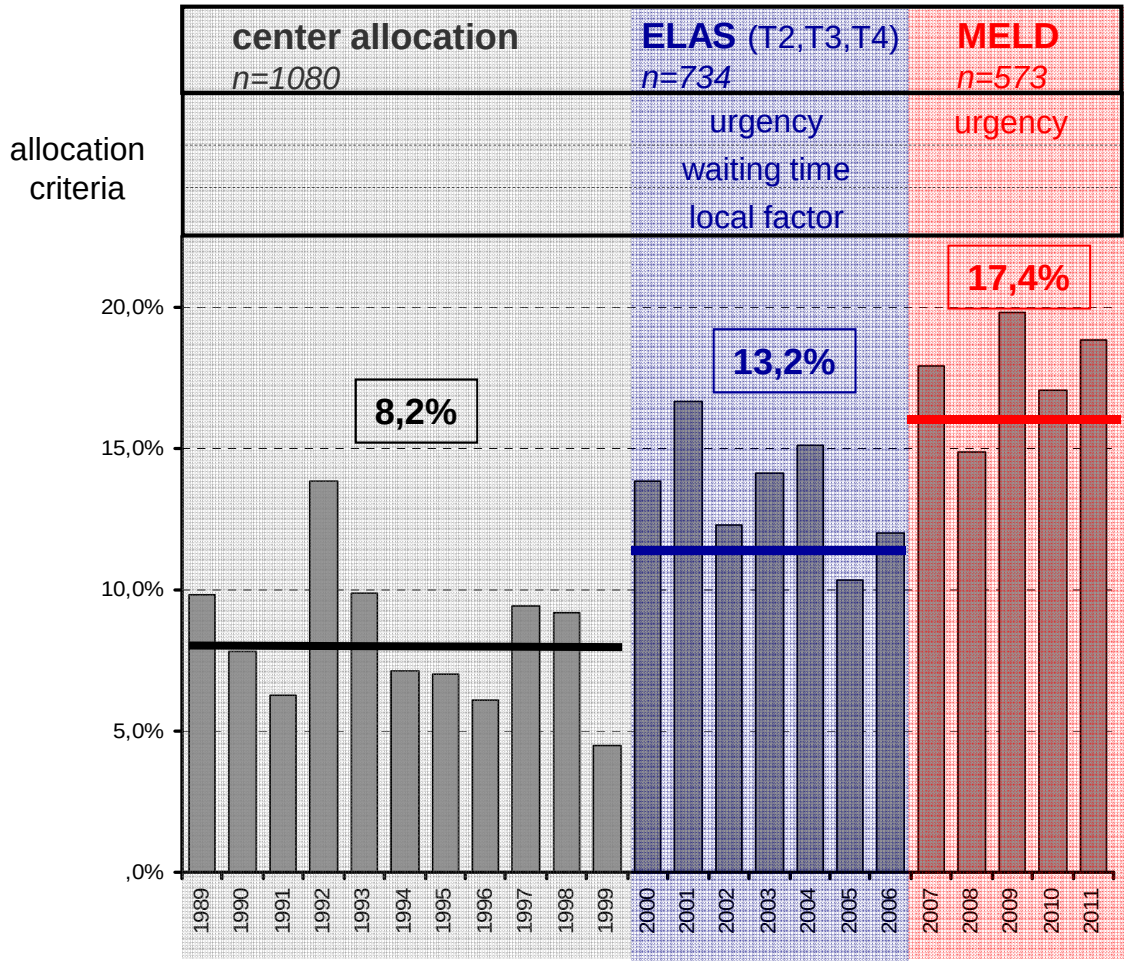
Liver-only transplants (deceased donor) in 2016, by country, by characteristic

MELD score	A	B	D	H	HR	NL	SLO	Total
Unknown	1	2	7		3	1	1	15
06-10	29	9	40	30	4	4	3	119
11-18	48	34	120	37	39	19	14	311
19-24	40	44	115	6	52	51	1	309
25-29	5	72	155		9	25	3	269
30+	8	52	231		6	18	1	316
High urgency	16	28	134	4	8	27	3	220
Total	147	241	802	77	121	145	26	1559

MELD > 25 **20 %** **65 %**

1 year mortality after LT



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Seehofer D, Chirurg 2013

Organ Donation in the ET region and Germany

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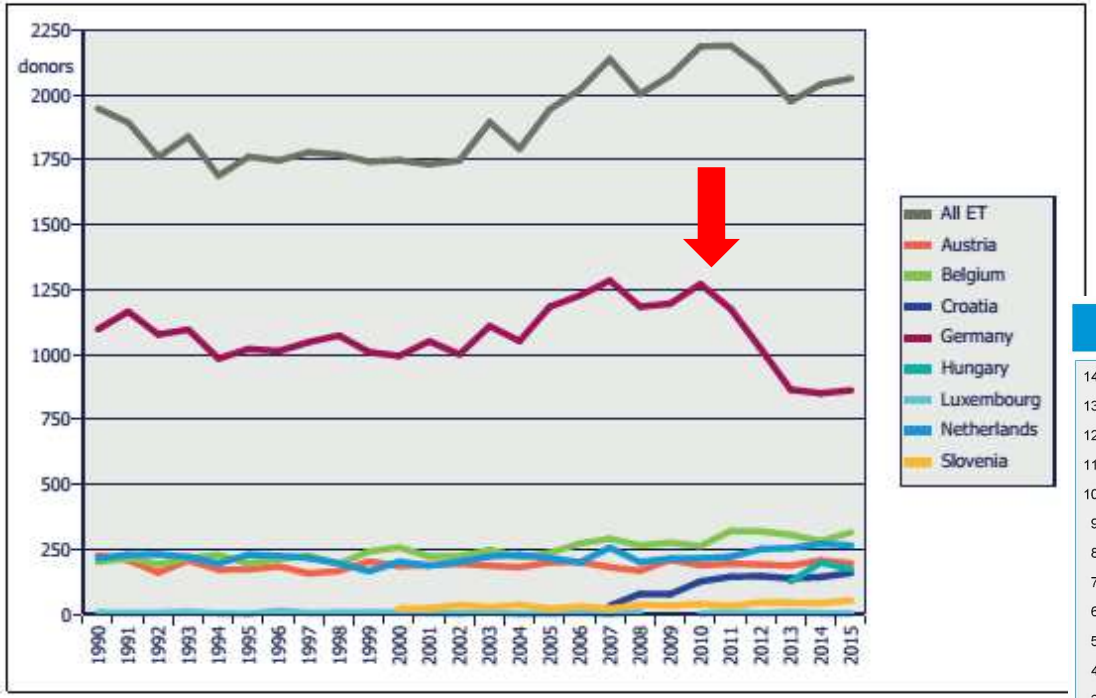
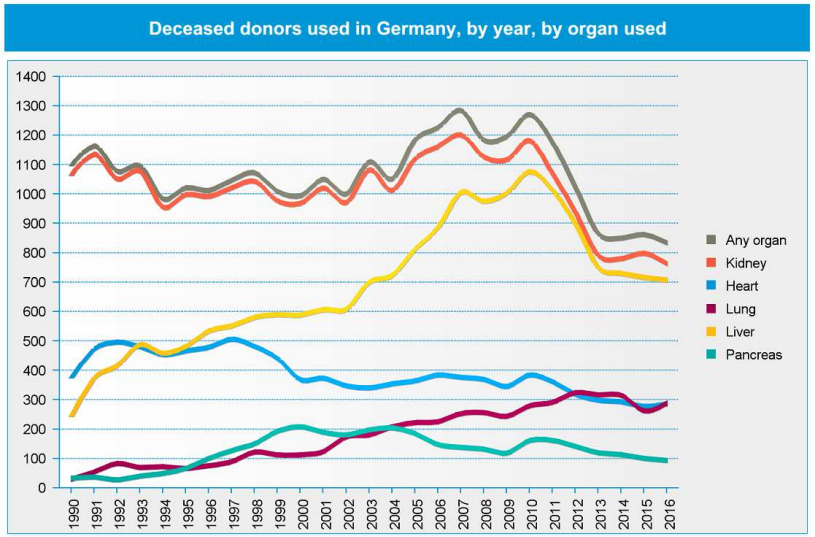


Donors in the Eurotransplant region by country

donated organs in Germany



Organ Donation in the Eurotransplant Region

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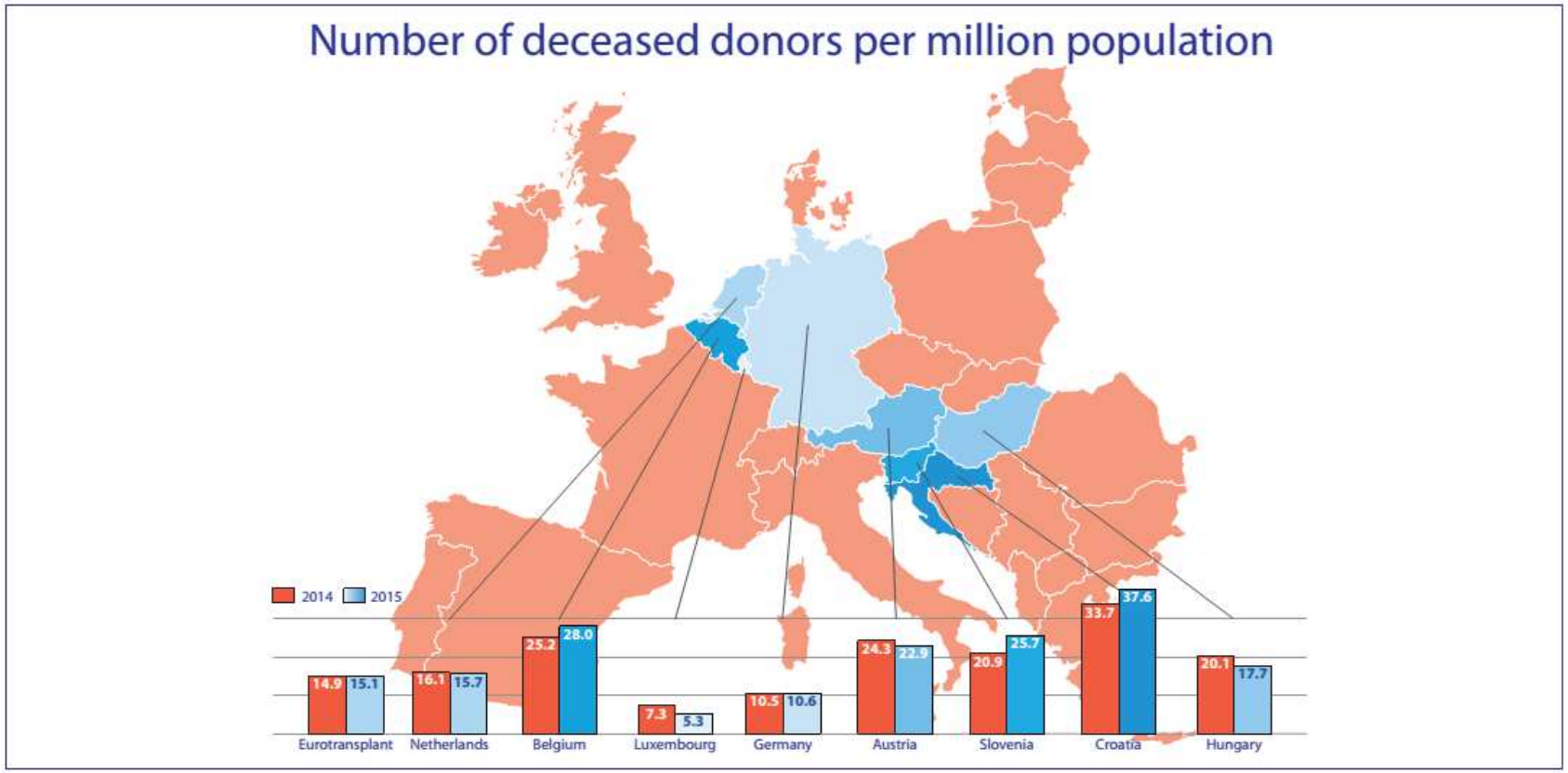

Eurotransplant: median donor age

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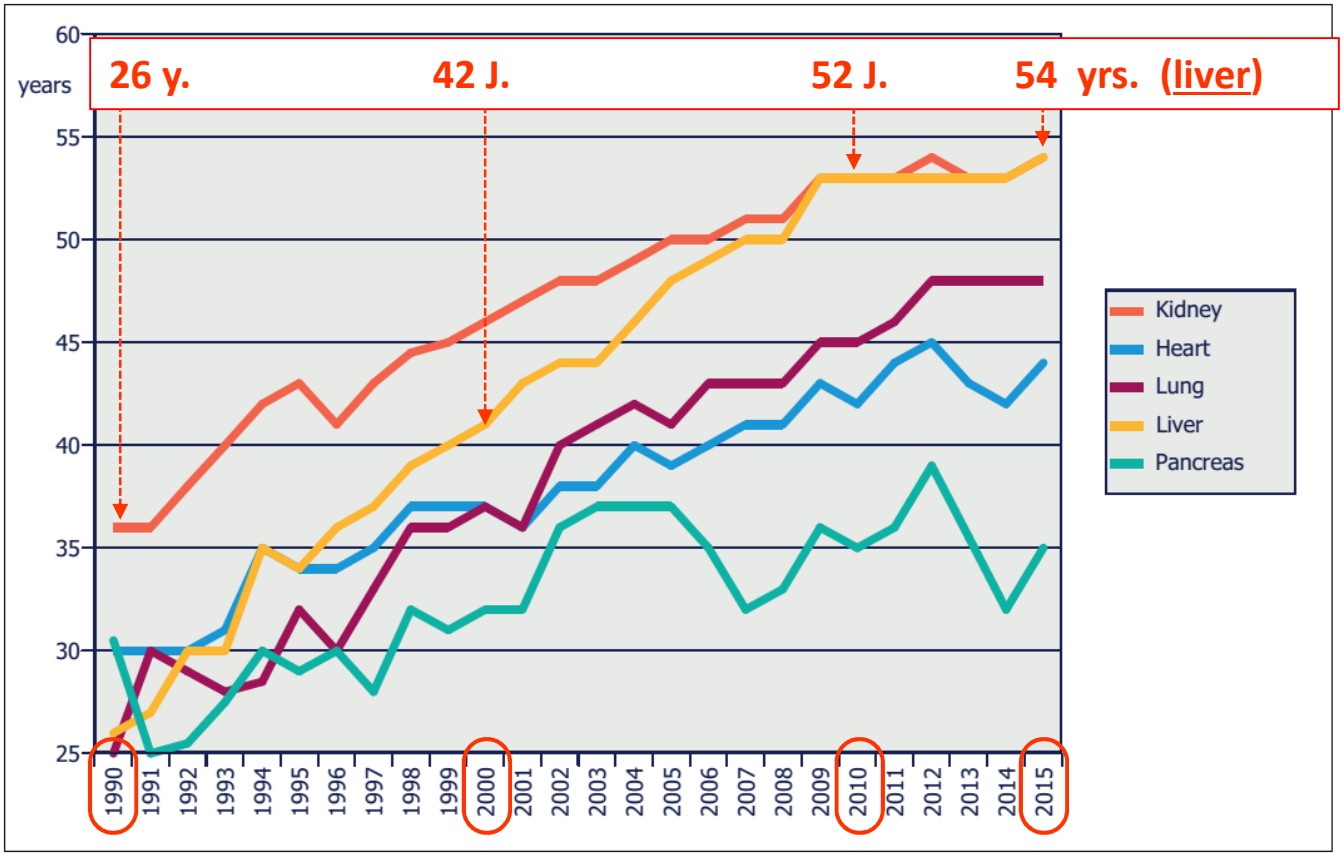

Extended Criteria Donors (ECD)

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ECD are grafts with impaired quality due to different reasons:

- presence of macrosteatosis >30%
- cold ischemia time >12 hours
- donor warm ischemia time >30 minutes
- grafts >70 years
- donation after cardiac death (DCD)
- ....

Organ Quality - ET-DRI

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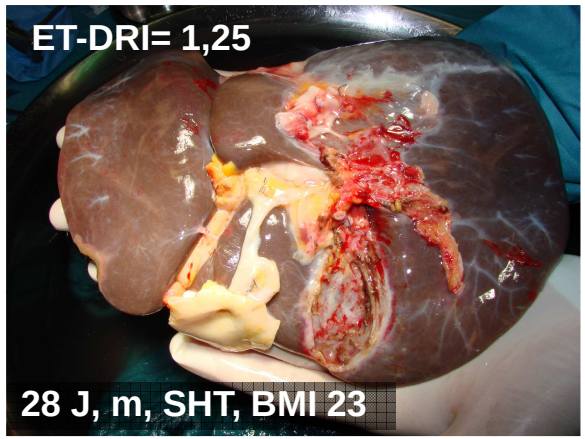

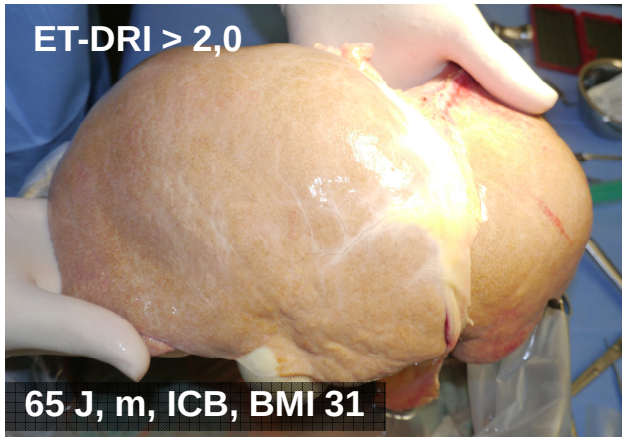

	1989-1999	2000-2006	2007-2011 (MELD)
ET-DRI (M + SD)	1,4 ± 0,29	1.71, ±0,40#	1,89 ± 0,46#

 # < 0,05 vs. 1989-1999

ET-DRI Kategorie	1,0 - 1,2	1,2 1- 1,4	1,41-2,0	> 2,0
n=	100	135	363	134
initial non-function (INF, %)	**3,0 %**	**4,4 %**	**8,0 %**	**11,9 %**

Schöning W, Seehofer D (unpublished data)

Outcome after LT: donor and recipient factors

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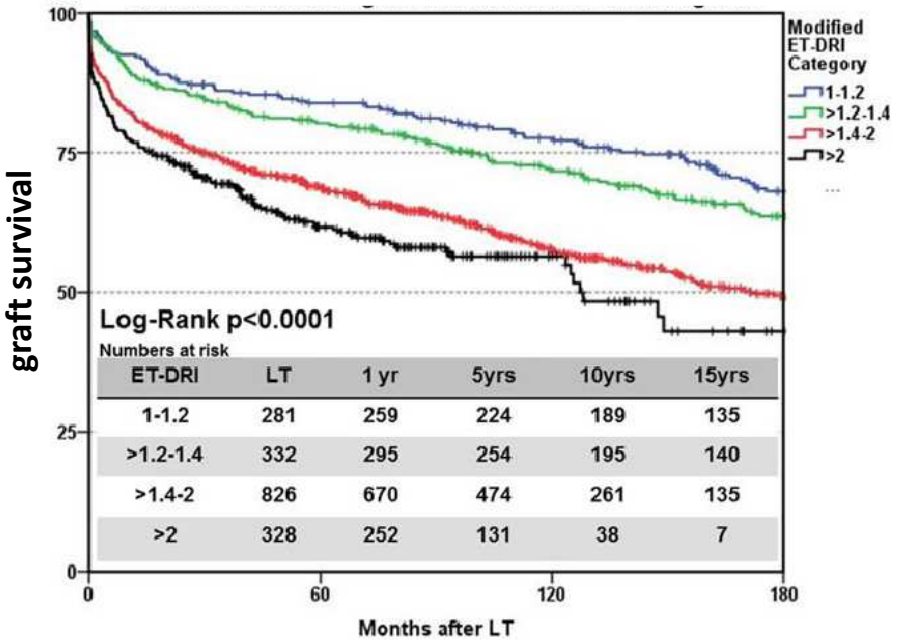
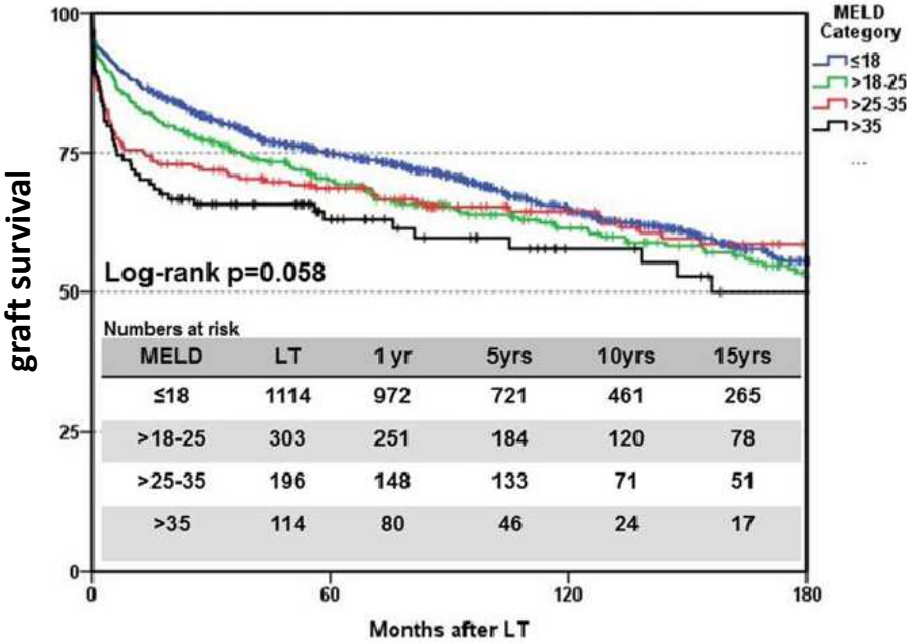
Donor Risk Index (ET-DRI)



Numbers at risk

ET-DRI	LT	1 yr	5yrs	10yrs	15yrs
1-1.2	281	259	224	189	135
>1.2-1.4	332	295	254	195	140
>1.4-2	826	670	474	261	135
>2	328	252	131	38	7

labMELD of recipient

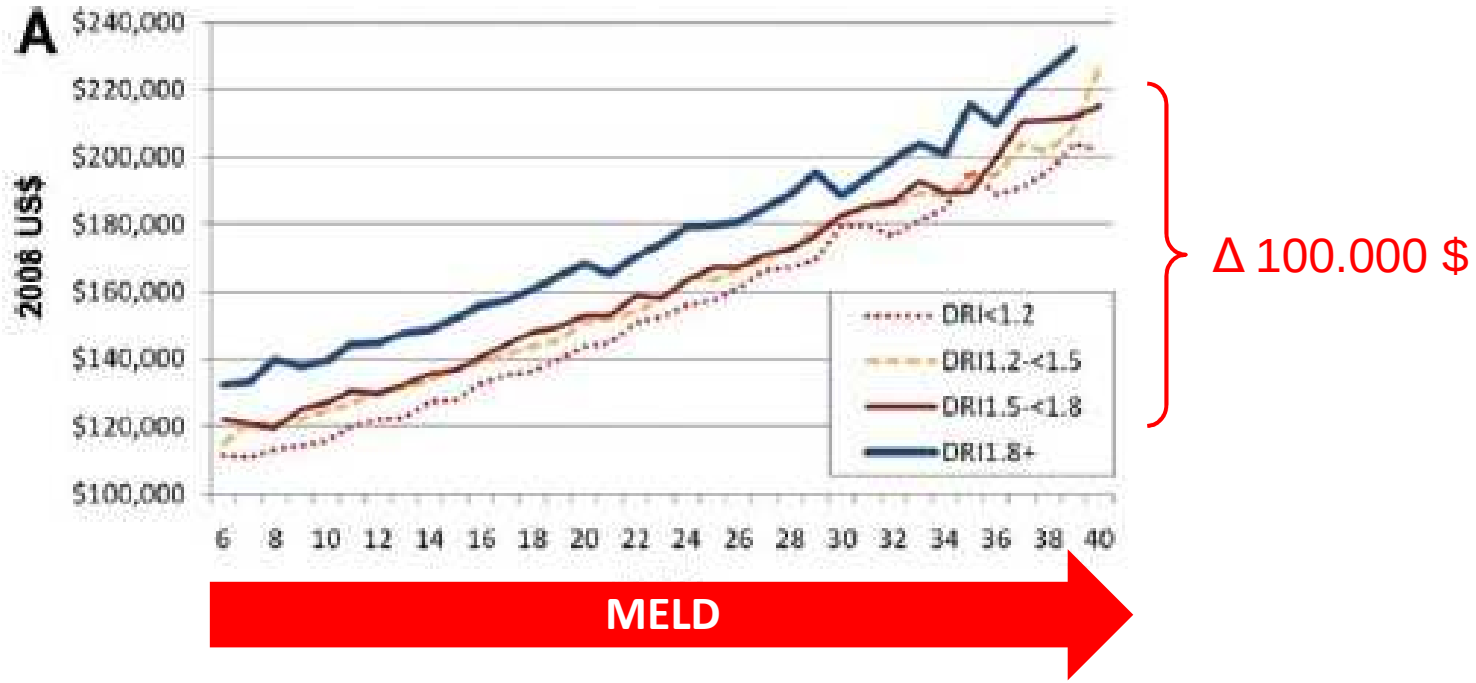


Numbers at risk

MELD	LT	1 yr	5yrs	10yrs	15yrs
≤18	1114	972	721	461	265
>18-25	303	251	184	120	78
>25-35	196	148	133	71	51
>35	114	80	46	24	17

Schoening W, Seehofer D, Clin Transplant 2016: 30: 508

Costs of LT are determined by MELD score



Salvalaggio PR, et al. Liver Transplantation 2011

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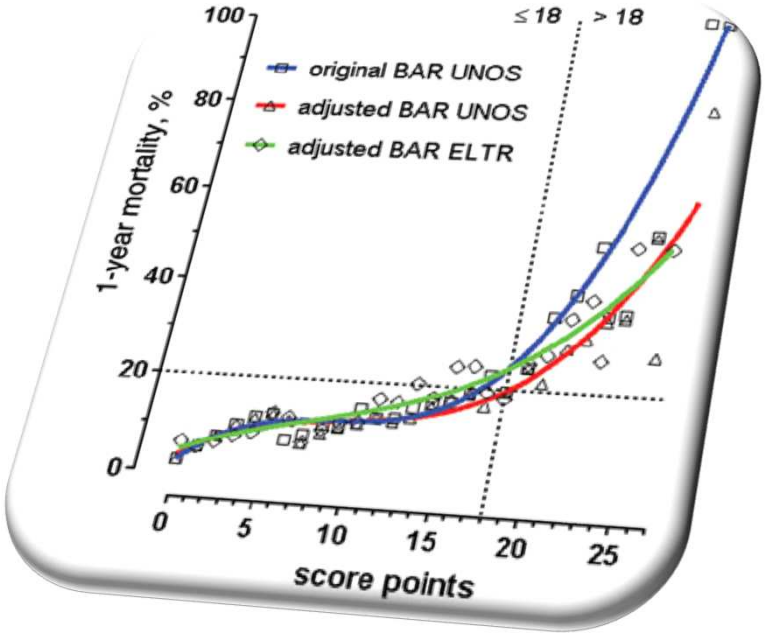

Predicting outcome after LT

Σ What has changed ?

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- less organs (shortage !)
- organ quality decreasing
- urgency of recipients increasing
- age of donors and recipients increasing
- comorbidities increasing

evolving problem: who is too sick for transplantation and who is too sick for ECD organs ?

Risk Assessment by the Balance of Risk (BAR) Score

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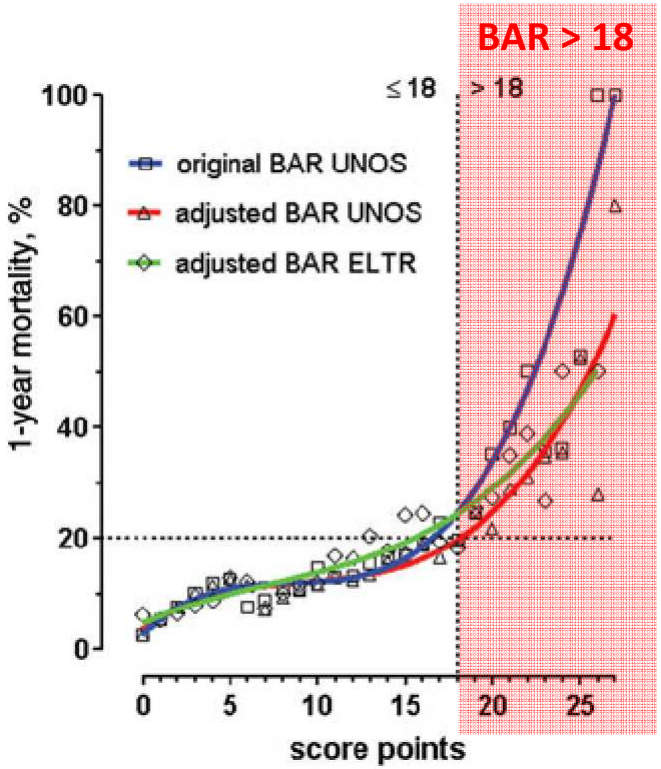
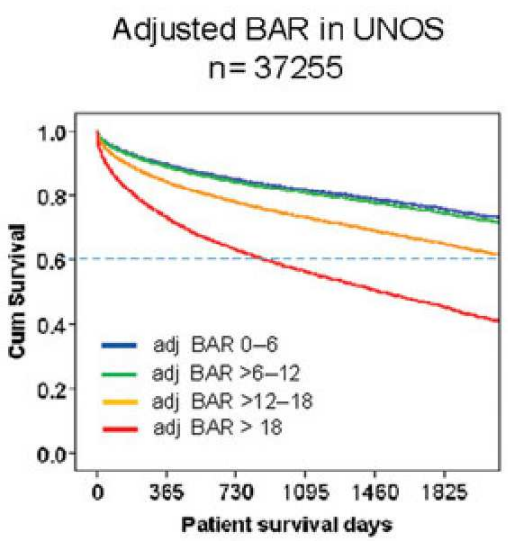
Predictor	Category	Adjusted BAR
Recipient age	≤40	0
	>40–60	1
	>60	3
Laboratory model for end-stage liver disease score at transplantation	6–15	0
	>15–25	6
	>25–35	11
	>35	16
Re-transplantation	No	0
	Yes	5
Cold ischemia	0–6	0
	>6–12	1
	>12	1
Donor age	≤40	0
	>40–60	1
	>60	2

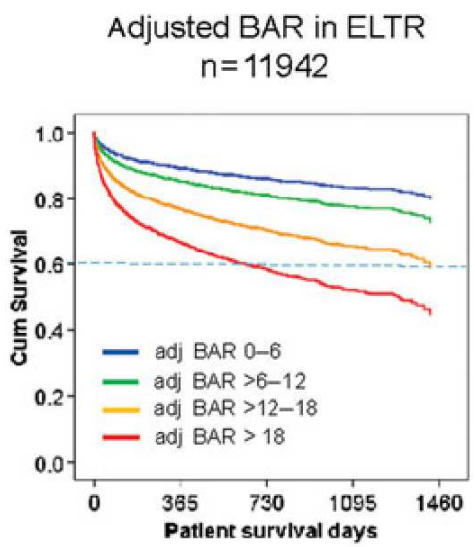
cut-off: 18

Dutkowski P, Ann Surg 2012, 256

Risk Assessment by the Balance of Risk (BAR) Score







Dutkowski P, Ann Surg 2012, 256

BAR-score and steatosis of the graft

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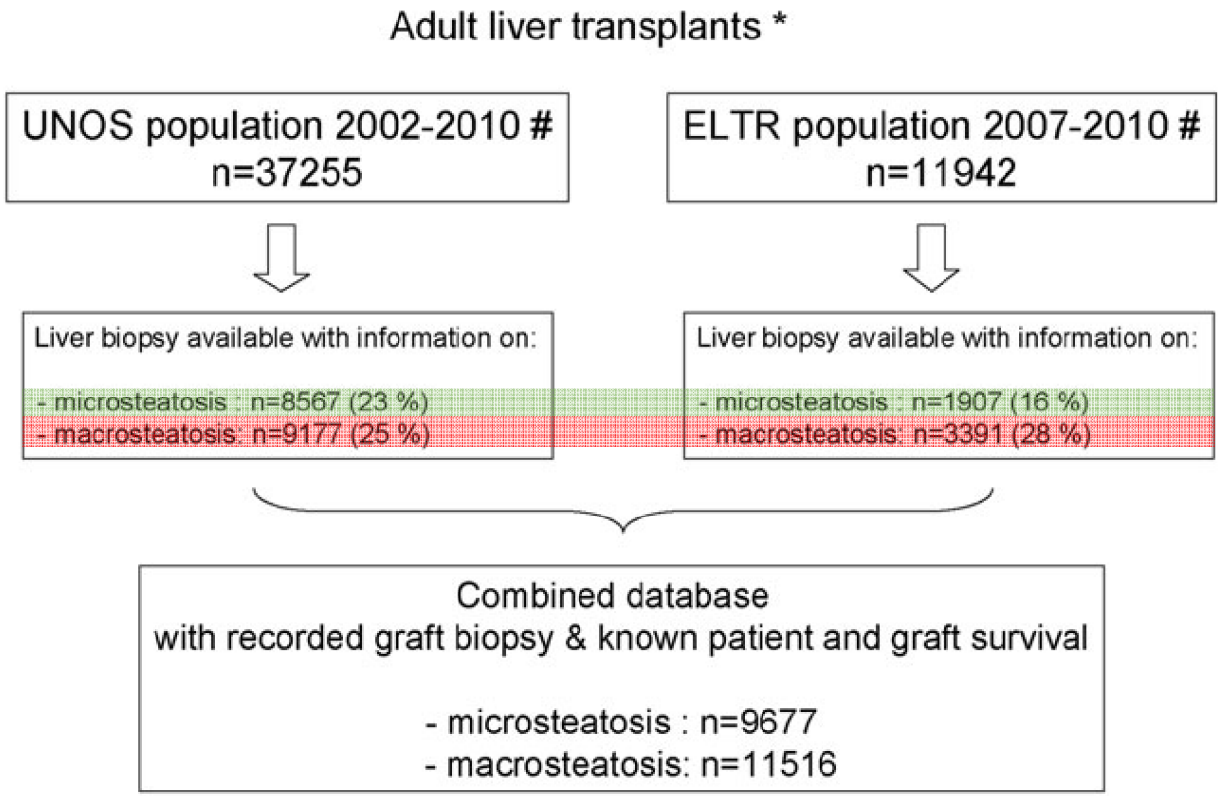

Dutkowski P, Ann Surg 2012, 256

BAR-score and microsteatosis of the graft

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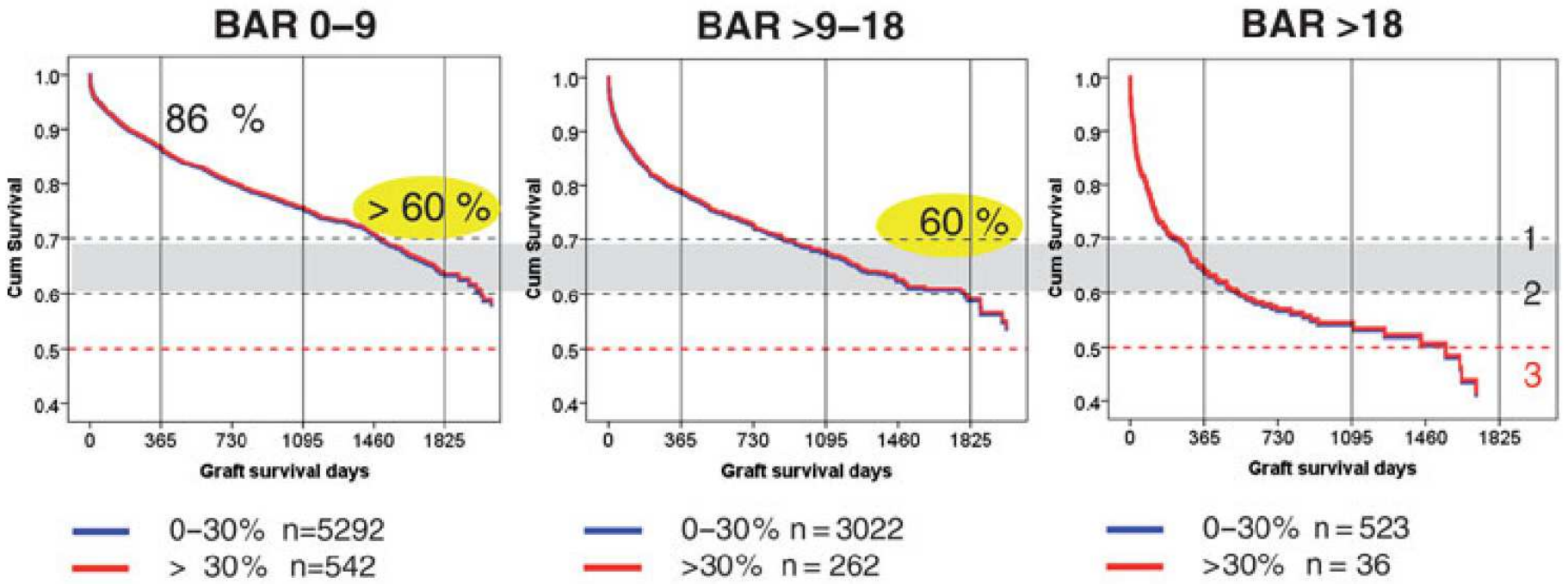

0-30% microsteatosis

> 30% microsteatosis

Dutkowski P, Ann Surg 2012, 256

BAR-score and macrosteatosis of the graft

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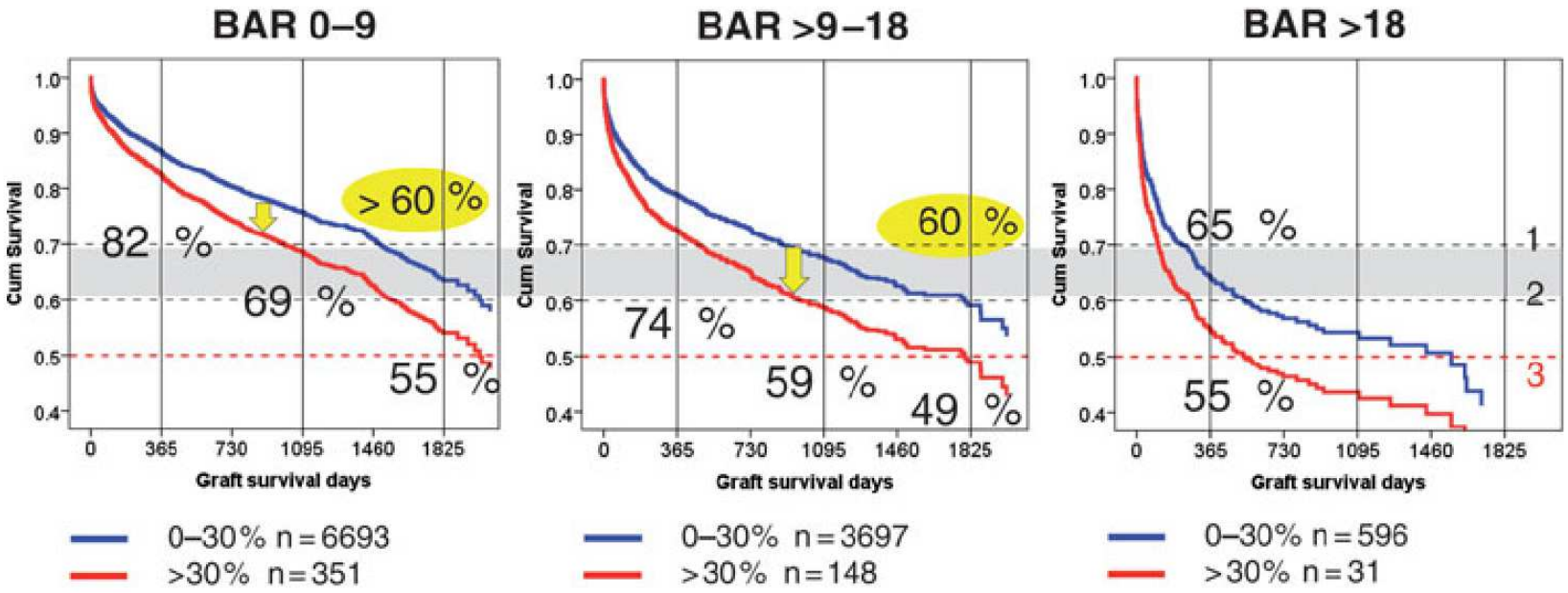

0-30% macrosteatosis

> 30% macrosteatosis

Dutkowski P, Ann Surg 2012, 256

Biliary complications

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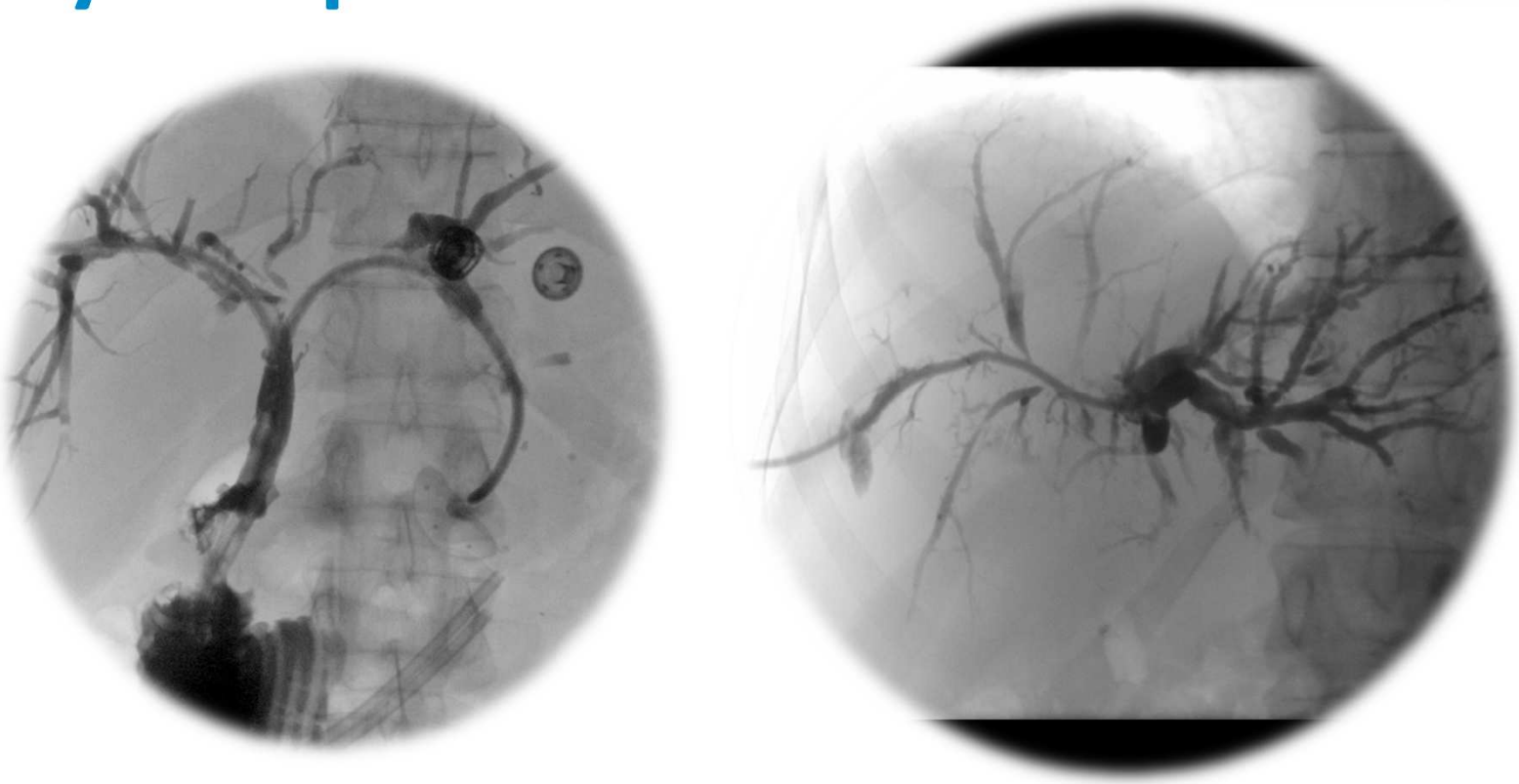

Non-anastomotic biliary strictures

Non-anastomotic biliary strictures

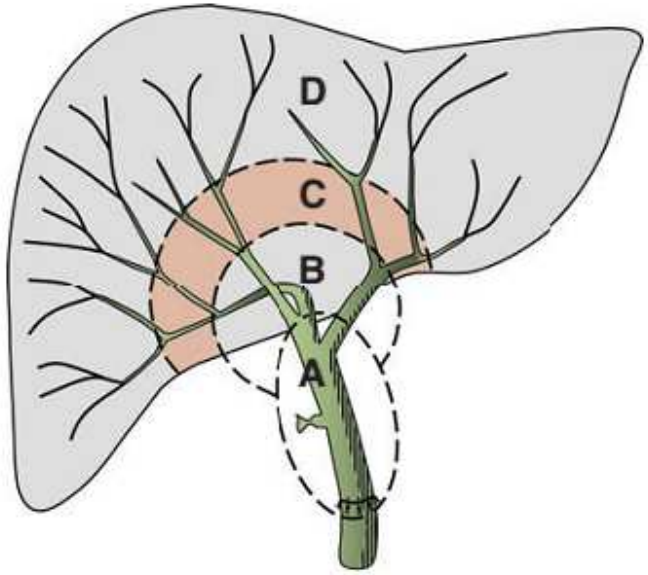

Figure 3: Classification of the anatomic regions of the biliary tree affected by nonanastomotic biliary strictures (according to Buis et al. [54]): hilar bifurcation (zone A), ducts between the first- and second-order branches (B), between second- and third-order branches (C) and in the periphery of the liver (D). Especially the extent of intrahepatic affection predetermines treatment success, whereby severe involvement of zone C is most critical.

Etiology

immunological:

- ABO incompatibility
- chronic rejection
- (recurrent) PSC

microangiopathy (injury of the peribiliary plexus)

- prolonged cold /warm ischemia
- circulatory instability of the donor

macroangiopathy:

- heaptic artery thrombosis

Seehofer D, Am J Transplantation 2013; 13: 253

Protection of the intrahepatic biliary tree by contemporaneous portal and arterial reperfusion: results of a prospective randomized pilot study

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- randomization of 80 consecutive LTs between 2008 - 2011 from heart beating donors were randomized to sequential (SPAr) or contemporaneous portal- arterial CPAr reperfusion
- non-anastomotic biliary strictures were diagnosed in **23 %** (nine cases) versus **0 %** ($p = 0.0008$) of the patients respectively in SPAr and CPAr

Table 1 Characteristics of the nine patients diagnosed with non-anastomotic biliary strictures in the SPAr group

Pts #	Donor age	Steatosis (%)	MELD	Type of graft	CIT (min)	WIT (min)	Arterial ischemia (min)	DGF	Reperfusion syndrome	HAT	Treatment	Outcome
1	57	0	22	Whole	533	41	67	No	No	No	PTC	Alive WGF
2	67	0	28	Whole	582	48	96	No	No	No	PTC	Alive WGF
3	21	0	10	Split	775	32	65	Yes	No	No	PTC	Alive WGF
4	68	15	6	Whole	305	35	75	No	No	No	PTC	Alive WGF
5	45	10	12	Whole	605	45	135	Yes	No	No	PTC	Alive WGF
6	60	0	12	Whole	342	30	65	No	No	No	PTC	Alive WGF
7	59	5	18	Whole	320	30	120	No	No	No	PTC	Alive after re-OLT
8	48	0	8	Whole	275	50	80	No	No	No	PTC	Alive WGF
9	42	0	25	Whole	635	25	52	No	Yes	No	PTC	Alive after re-OLT

Baccarani U, Updates Surg (2012) 64:173–177

Antibody-mediated rejection (AMR)

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- AMR caused by DSA is a risk factor for decreased graft survival after **kidney** transplantation
- the presence of DSA in **heart** and **lung** transplants is associated with a worse graft survival

- the **liver** appears relatively resistant to DSA-mediated injury
- The **impact** of donor-specific anti-HLA antibodies (DSA) on short- and long-term liver transplant (LT) **outcome** is **not** clearly defined
- in the setting of DSA persistence after LT, no significant clinical impact in the first year post-transplantation has been described
- **antibody-mediated adverse consequences are increasingly recognized**, after ABO-compatible liver transplant (LT)
- recent reports indicate that **some LT** recipients who develop *de novo* DSA result in lower graft survival and patient survival

Cuadrado A, World J Gastroenterol 2015; 21: 11016

Resistance of the liver to AMR

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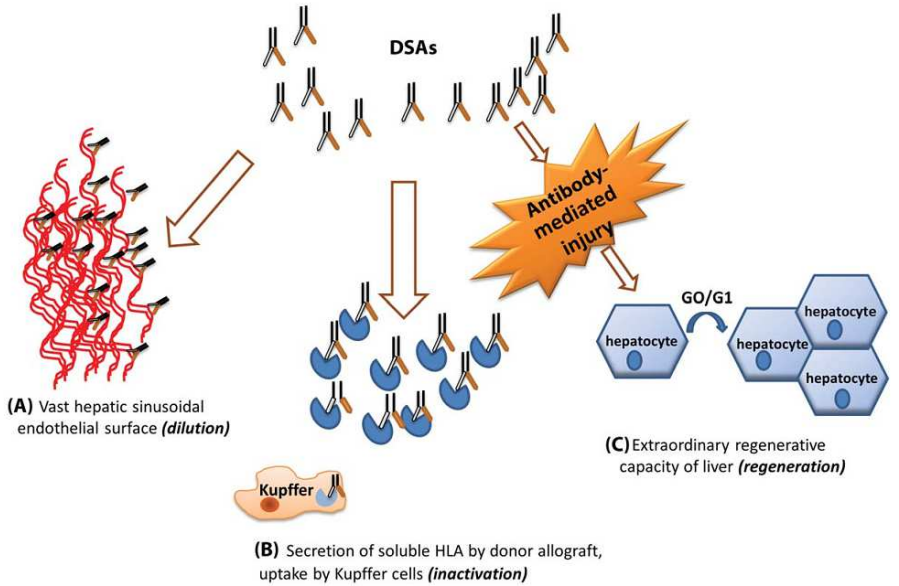
Proposed mechanisms:

- secretion of **soluble HLA** class I
- **Kupffer cell phagocytosis** of platelet **aggregates** and immune-complexes limits complement activation
- l**imited distribution of HLA class II expression** in the microvasculature
- the great liver restorative and **regenerative capacity**
- a **large endothelial surface** that is capable of **absorbing** circulating Abs.



Taner, Liver Transplantation 2014

Cuadrado A, World J Gastroenterol 2015; 21: 11016

Prevention and treatment of liver allograft antibody-mediated rejection and the role of the 'two-hit hypothesis'

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- 'two-hit' hypothesis: a **coexistent insult upregulates** HLA class II target antigens on the microvascular endothelium
- this may explain why **suboptimal donors** might suffer from acute AMR and those with chronic complications (e.g., recurrent original disease, e.g. HCV) might be more susceptible to chronic AMR
- **Chronic** liver allograft AMR is characterized by **low-grade chronic inflammation** and **progressive fibrosis** with DSA,

Kim PTW; Curr Opin Organ Transplant 2016, 21:209

HLA-expression in different liver cells und normal and inflammatory conditions

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Table 1: Expression of ABH and MHC antigens in human liver under normal circumstances versus inflammatory conditions (normal → inflamed liver)

Antigen	HC	BEC	LSEC	KC	HSC	HA/PV/CV Endothelium	DC	Portal microvascular endo.
AB	–	+	+	–	–	+++	–	++
H	–	++	+	–	–	+++	–	++
MHC A,B	± → +	+++	++	++	+→++	++	++	++
MHC DR	– → +	– → ++	– → ++	+→++	+→++	– →++	++→+++	± (variable)→+++
MHC DP	– → +	– → +	– → +	+→++	– →±	– →++	++→+++	±→++
MHC DQ	– → –	± → –	± → –	+→++	– →±	–→±	++→+++	±→++

Data compiled from references (201–206,209). More work is needed in study class II expression in specific compartments.
A, B, H, classic blood group antigens; BEC, biliary epithelial cells; CV, central vein; DC, dendritic cells; HA, hepatic artery; HC, hepatocytes; KC, Kupffer cells; LSEC, liver sinusoidal endothelial cells; PV, portal vein; HSC, hepatic stellate cells.

Demetris AJ, American Journal of Transplantation 2016; 16: 1653

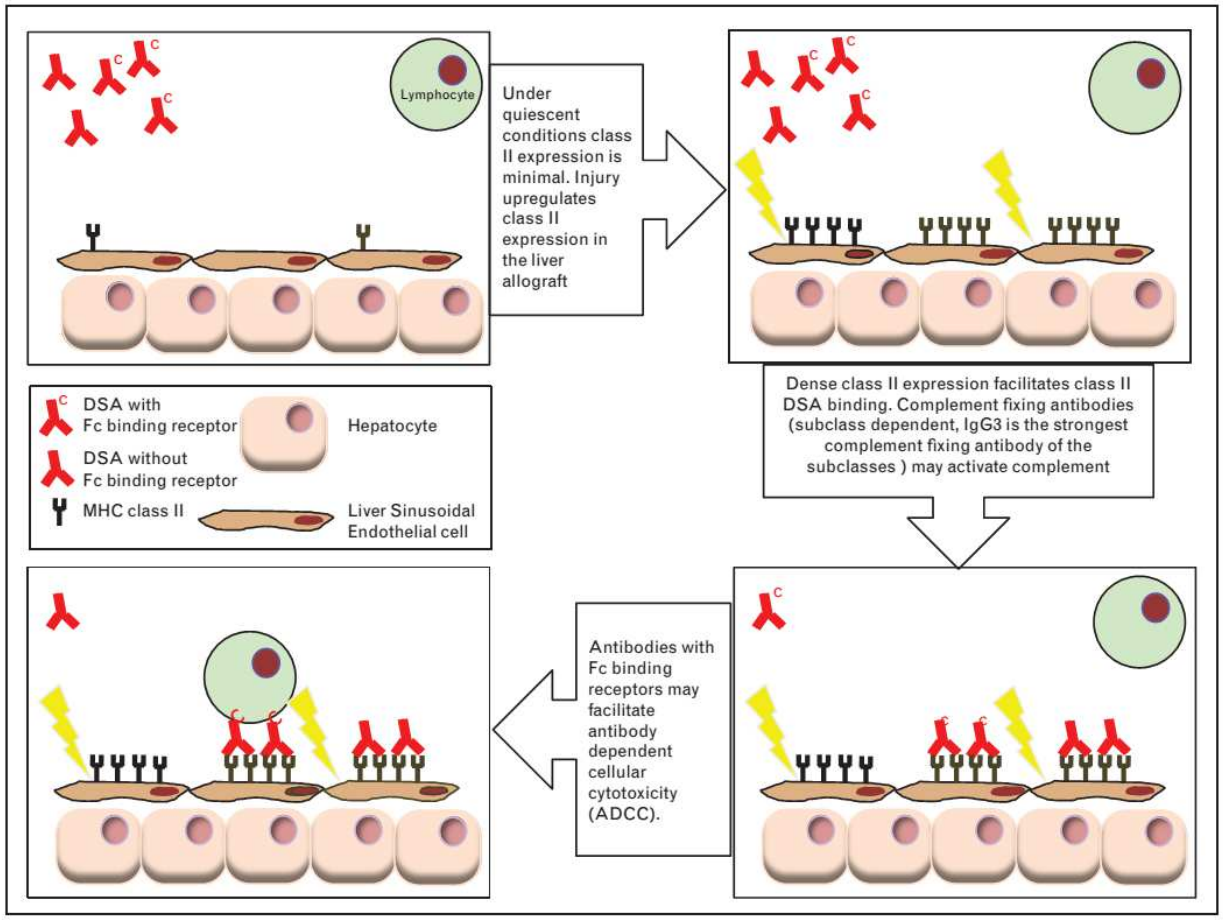

FIGURE 1. Two-hit hypothesis of liver allograft antibody-mediated rejection.

Kim PTW; Curr Opin Organ Transplant 2016, 21:209

Progression of AMR in the kidney

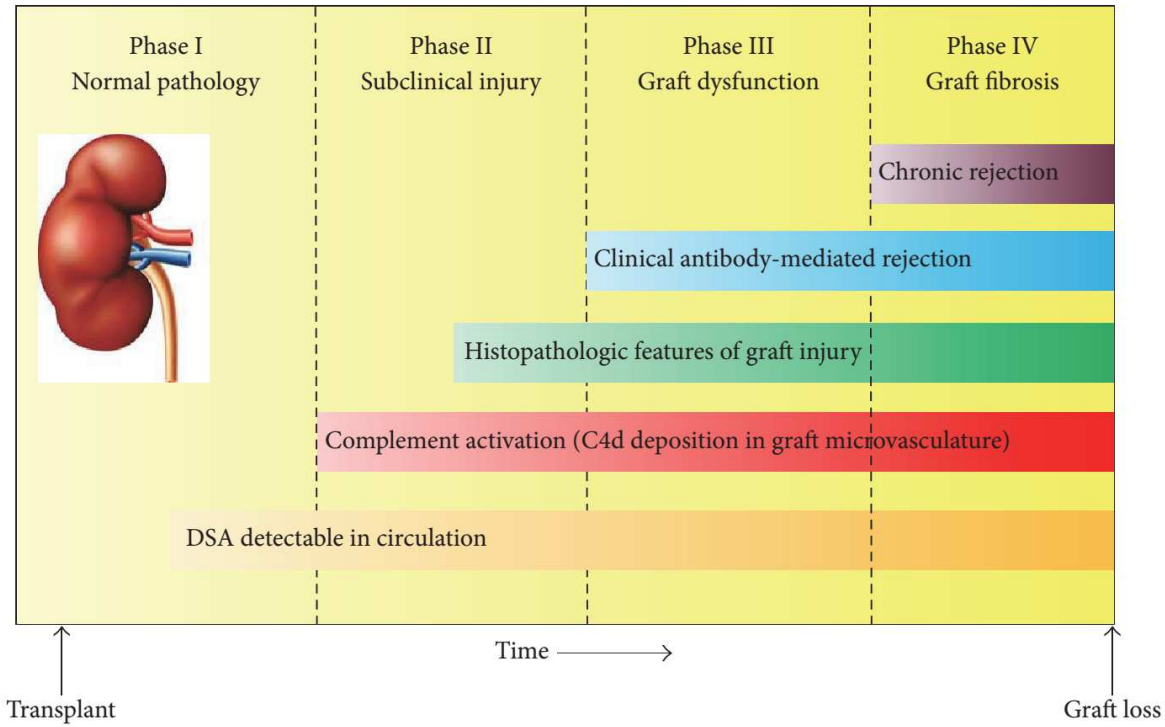

FIGURE 1: Natural progression of antibody-mediated rejection in renal transplantation. DSA, donor-specific antibody.

Cheng EY, Journal of Immunology Research 2017, Article ID 3234906

AMR in the liver - the ‚two hot hypothesis‘

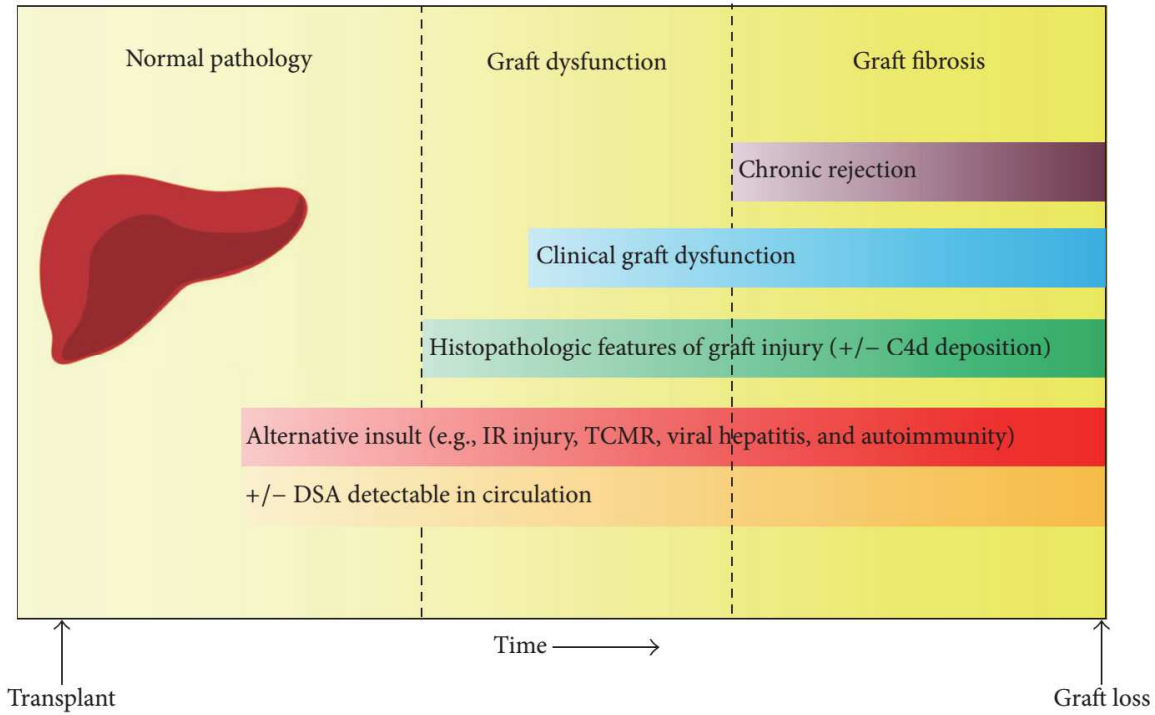

FIGURE 2: Proposed sequence of events leading to the development of chronic rejection in liver transplantation. DSA, donor-specific antibody; IR, ischemia-reperfusion; TCMR, T-cell-mediated rejection.

Cheng EY, Journal of Immunology Research 2017, Article ID 3234906

Possible Reasons for Negligence of AMR in LT in the past

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- **organ quality** in the past excellent
- Features of **TCMR** are also present in a majority of acute AMR cases, which previously hampered the recognition of acute AMR in liver allografts
- **Standard 'rejection' therapy** with steroids on the backbone of tacrolimus-based immunosuppression (with or without thymoglobulin) has likely successfully treated **mild acute AMR** or c**ombined low-grade AMR and TCMR for many decades**
- idiopathic graft failure as diagnosis **accepted**

Acute Antibody mediated Rejection (AMR)

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Occurence (rare - overall incidence 0.3–2% after LT)

- most often in patients with preformed MFI greater than 15 000 despite serial dilutions or high-titer DSA
- late presentations in the setting of nonadherence

Diagnosis

- DSA in serum
- exclusion of other causes of a similar injury
- **diffuse C4d staining in tissue** (to avoid overdiagnosis)
- plus a microvascular injury seen as endothelial cell hypertrophy, portal eosinophilia, and a capillaritis (monocytes and eosinophils in the lumen of portal capillaries).
- Microvascular inflammation is infrequently found but specific for acute AMR.
- Clinically patients have a delayed peak in aminotransferases, thrombocytopenia from consumption, and increased circulating immune complexes [29].

?

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DSA and graft fibrosis

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- 8.1% of a cohort of 749 LT recipients developed **de novo DSA** one year after transplantation (most of them against HLA-II, especially HLA-DQ)
- 75% of the patients who developed de novo DSA had **biliary complications**

Table 1 Association of graft fibrosis and concomitant anti-human leukocyte antigen class II donor-specific anti-human leukocyte antigen antibodies

Ref.	No. of patients	Positive for HLA Abs	Transplant type	Follow-up. median (yr)	Time detection DSA	Method detection DSA	MFI
Miyagawa-Hayashino *et al*[78]	79	32	LD	11	After LT	SAB	> 5000
Salah *et al*[58]	114	5	LD	2	After LT	SAB	> 5000
O´Leary *et al*[60]	507	46	DD	6.4	Pre and after LT	SAB	> 5000
Grabhorn *et al*[72]	19	16	LD + DD	4.5	After LT	SAB	> 5000
Iacob *et al*[79]	174	34	LD + DD	ND	After LT	SAB	> 5000

Cuadrado A, World J Gastroenterol 2015; 21: 11016

Summary

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- LT reveals **excellent results** under optimal conditions (donor/recipient)
- Changes in organ donation and allocation have brought about **new issues** for the LT community, especially in countries with **organ shortage** (usage of ECD donors, donor-recipient matching, risk scores, futility, ...)
- the **biliary system** remains an “Achilles heel” of LT, also in the long term after LT and NAS represent a common feature of distinct injuries including AMR
- **AMR** is increasingly recognized and investigated after LT und the actual conditions. However broadly accepted **standards** are still lacking.

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Open questions ....

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- significance of pre- and posttransplant DSA
- risk-stratification of patients for acute and chronic AMR
- diagnosis of acute AMR and chronic AMR
- potential ways to prevent and treat acute and chronic AMR
- ....

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Thank You !