

Early Liver Transplantation in Severe Alcoholic Hepatitis: How will it look like in 2018?

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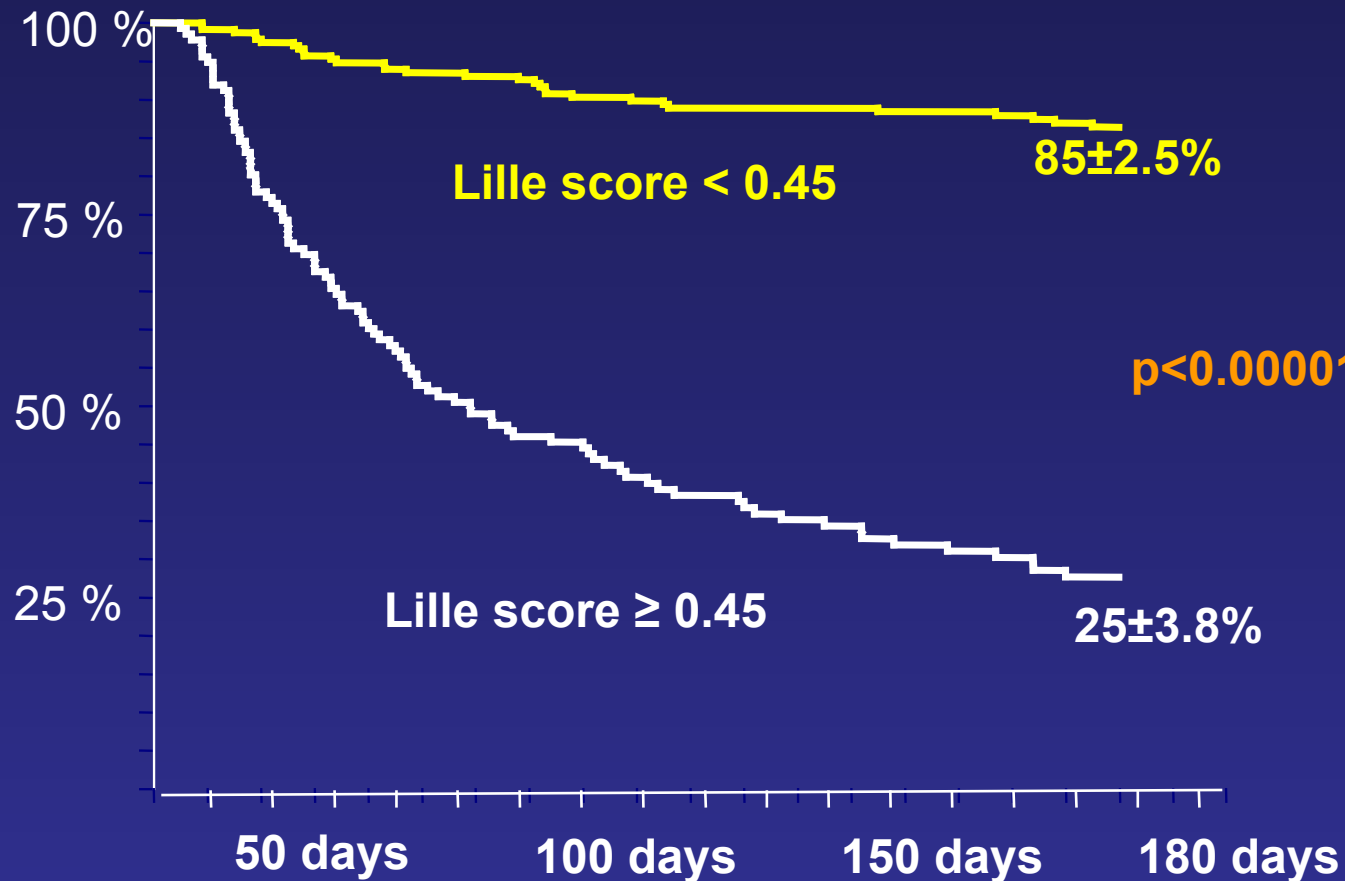


Moving toward the Response Guided therapy

Lille model: a tool for new strategies

Evaluation of Lille model on overall patients (n=438)

<http://www.lillemodel.com>



**Alcohol consumption is not
restricted to patients transplanted
for ald**

Alcohol use post liver transplantation

ALD versus non-ALD

Abstinence < 6 months OR: 7.8; 95 % CI: 4-15.3; $p < 0.05$

The 6-Month Rule:

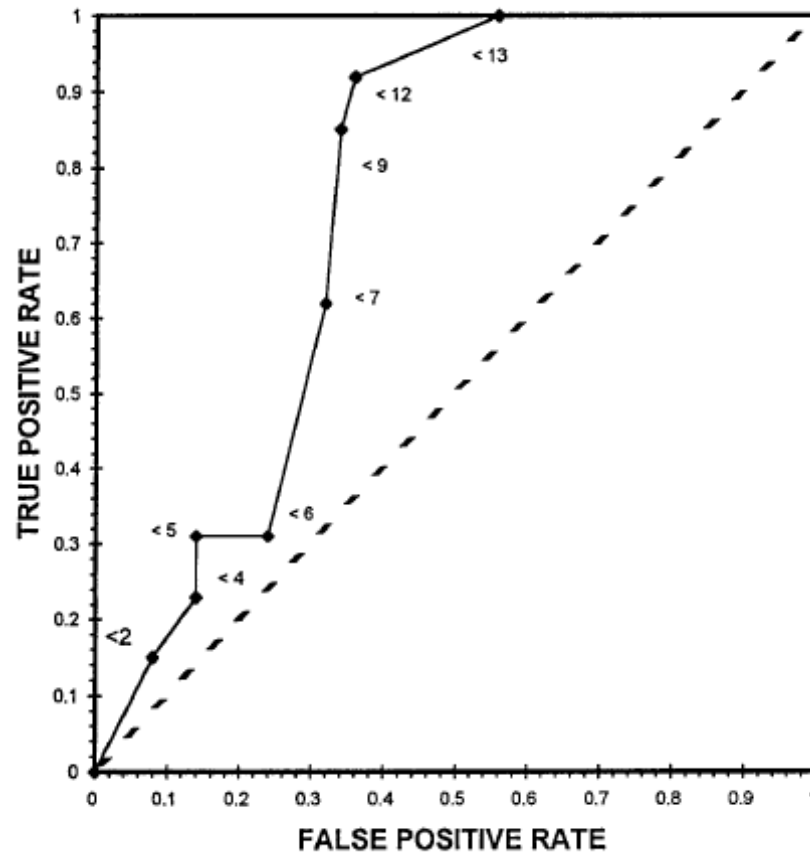
Where are the data?

Background

The 6-month: a questionable criterion in the setting of severe alcoholic hepatitis

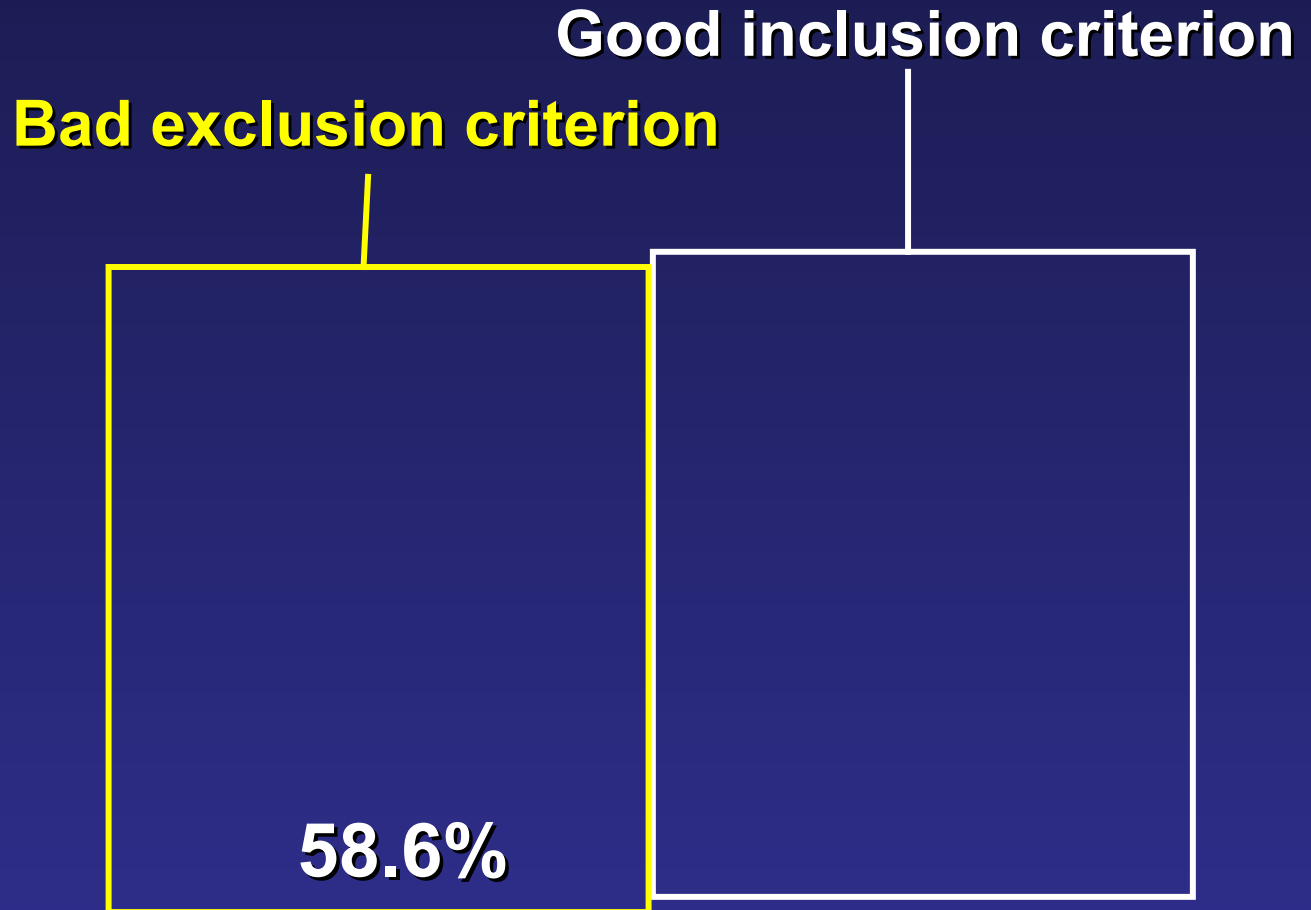
- The 6-month period of abstinence is presumed:
 - a) to identify subsets of patients likely to maintain abstinence after liver transplantation.
 - b) to permit some patients to recover from their liver disease and obviate the need for liver transplantation

6month rule: where are the data?



Liver transplantation for alcoholic liver disease: bias, beliefs, 6-month rule,

6month rule: where are the data?



Foster PF, Hepatology 1997

6-month Abstinence: Is it Justified by the Evidence?

- Allen vs. Mansour case, Michigan court in 1986
- Medicaid 2-year abstinence requirement for LT
- “Arbitrary and unreasonable”
 - High operative risks
 - May not survive the waiting period
- WITHOUT enough 6-month evidence, expert opinions

Allen vs. Mansour 86–73429. Federal Supplement, 681, 1232–9. District Court for the Eastern District of Michigan, Southern Division, 1986

Where Do We Come From ?

LIVER TRANSPLANTATION 12:998-1011, 2006

Consensus Conference: Indications for Liver Transplantation, January 19 and 20, 2005, Lyon-Palais Des Congrès
Text of Recommendations (Long Version)

The Jury stated:

- wait-and-watch strategy using the 6-month criterion may be unfair for some non-responders with 70- 80% probability of dying during this period
- recommended pilot studies evaluating early liver transplantation in non-responders

ORIGINAL ARTICLE

Early Liver Transplantation for Severe Alcoholic Hepatitis

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Didier Samuel, M.D., Ph.D., Jérôme Dumortier, M.D., Ph.D., Julia Salleron, M.S.,
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Sébastien Dharancy, M.D., Ph.D., Alexandre Louvet, M.D., Ph.D.,
Emmanuel Boleslawski, M.D., Ph.D., Valerio Lucidi, M.D., Thierry Gustot, M.D., Ph.D.,
Claire Francoz, M.D., Christian Letoublon, M.D., Denis Castaing, M.D.,
Jacques Belghiti, M.D., Vincent Donckier, M.D., Ph.D.,
François-René Pruvot, M.D., and Jean-Charles Duclos-Vallée, M.D., Ph.D.

Early LT in Alcoholic hepatitis

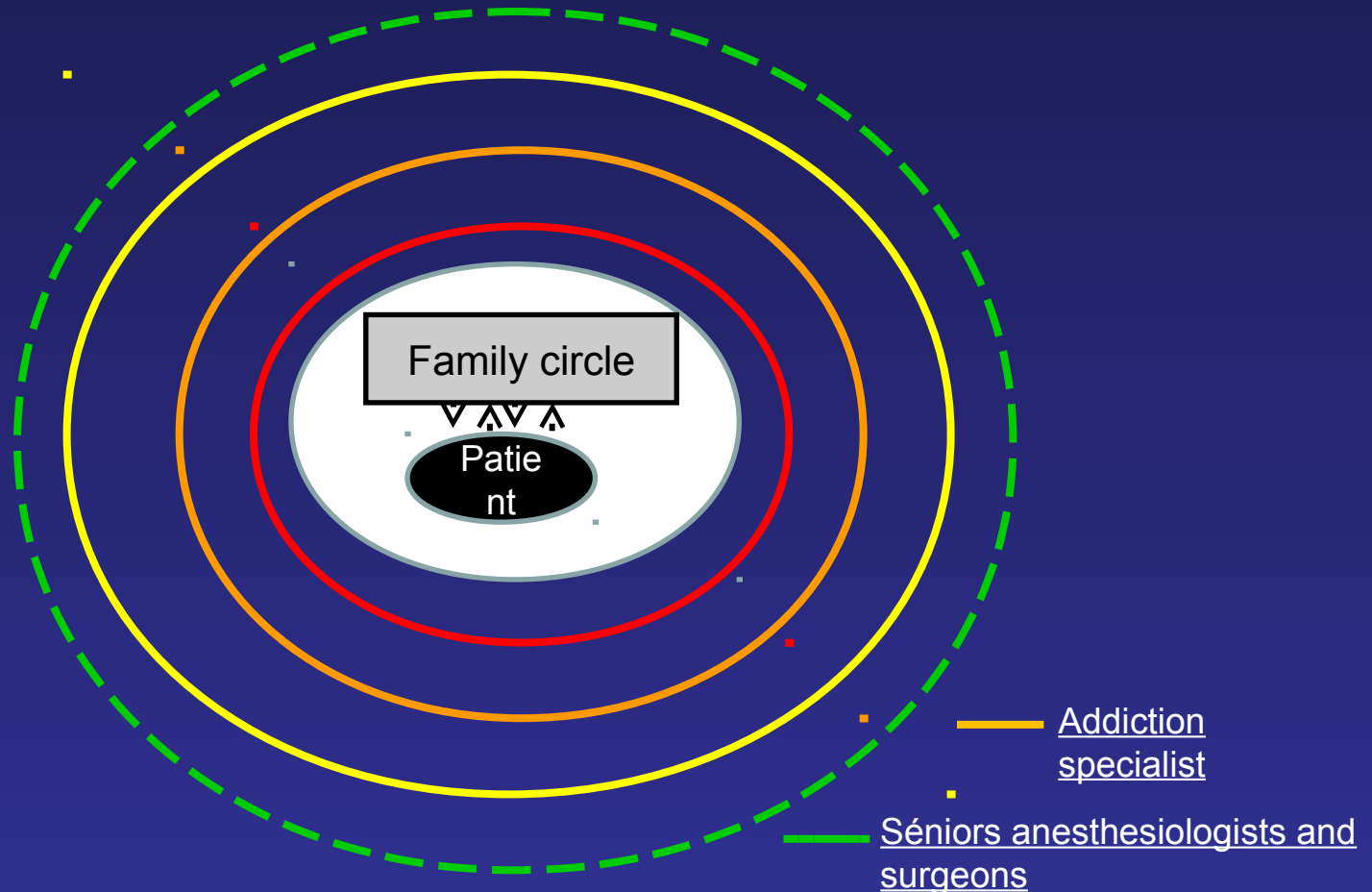
Methods

- Early liver transplantation in non-responders undergoing their first event of liver disease
- Non responders were identified using Lille score ≥ 0.45 or worsening of liver function by day 7.
- Patients were drastically selected using those criteria:
 - absolute consensus of paramedical and medical staff
 - no co-morbidities
 - social integration
 - supportive family members
 - psychiatric evaluation and addictive profile

PHRC QuickTrans-HAA

Algorithm (1)

- Intervention of 4 decision circles:



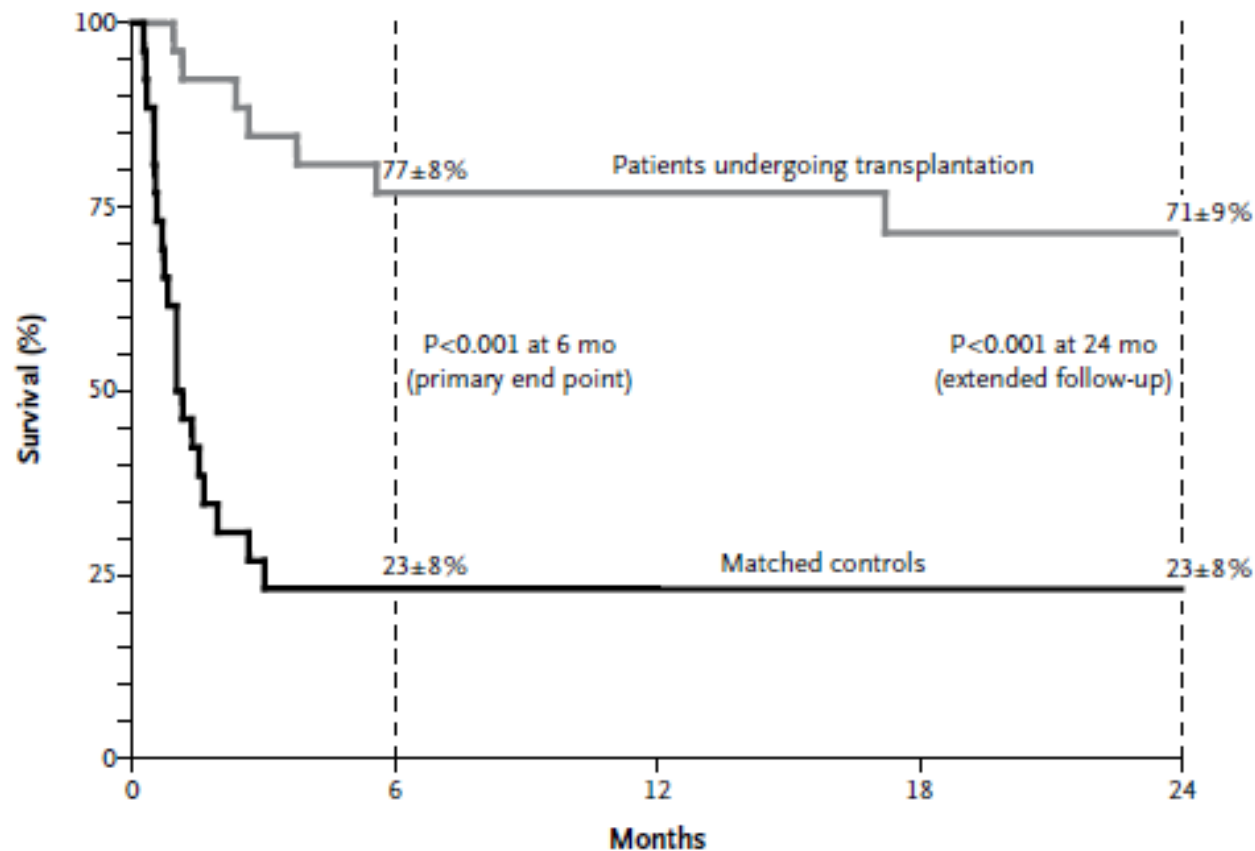
Early LT in Alcoholic hepatitis

*

*** Maximum of Lille score is 1**

Mathurin P, N Engl J Med 2011

Early LT in Alcoholic hepatitis



No. at Risk

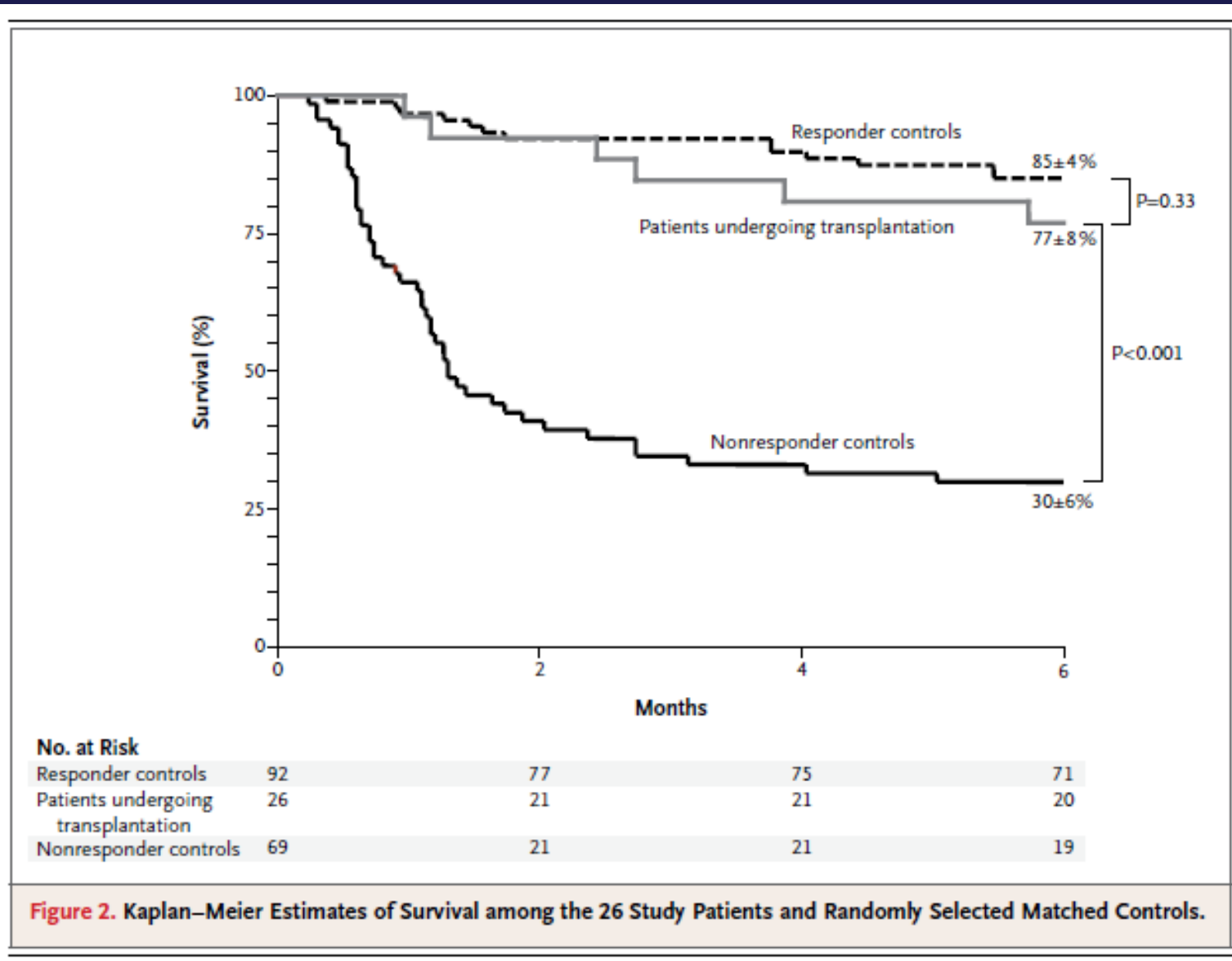
Patients undergoing transplantation	26	20	15	14	13
Matched controls	26	6	6	5	4

Figure 1. Kaplan–Meier Estimates of Survival in the 26 Study Patients and the 26 Best-Fit Matched Controls.

Early Transplantation shift survival of unresponsive to responders

- Final combined database included a total of 651 patients. Matching was performed using the global optimal algorithm
- For matching criteria, we used the following pre-established ranges: age (+/- 10 years), gender, Maddrey function (<60; 60-90 and >90) and Lille score (+/-0.15)
- The overall optimal algorithm was able to select 3 unresponsive matched controls for 20 transplanted patients, 2 unresponsive matched controls for 3 transplanted patients and only 1 unresponsive matched control for 3 transplanted patients.
- The overall optimal algorithm was able to select 4 responsive matched controls for 21 transplanted patients, 2 responsive matched controls for 3 transplanted patients and only 1 responsive matched control for 2 transplanted patients

Early LT in Alcoholic hepatitis



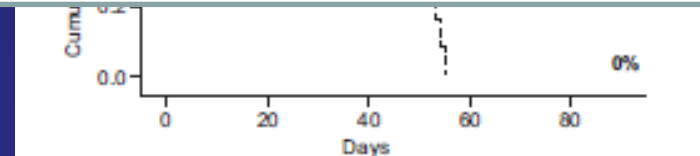
Aspergillus infection:

A Specific Outcomes After Liver Transplantation for alcoholic hepatitis ?

In transplanted 4 out of 5 deaths due to aspergillus infection



MELD score ≥ 24 at day 0 and ICU admission Independent predictive factors of Aspergillus



T Gustot, J Hepatol 2014

Data On Alcohol Relapse in patients transplanted for severe alcoholic hepatitis

- No alcohol relapse within the 6 month period
- 3 patients resumed alcohol consumption during data collection
 - at 720, 740 and 1140 days
 - Despite counseling from addiction specialist, 2 patients remained daily consumers (30 g/day and > 50 g/, respectively) whereas 1 had occasional consumption (approximately 10g/week)

Early LT in Alcoholic hepatitis

- 2 centers have prospective data base of severe alcoholic hepatitis
 - 14 out of 18 transplanted patients were referred by community hospitals
 - whereas only 4 patients (1.83%) were directly selected by the 2 centers from their own recruitment
- Proportions of eLT among the total number of procedures, and number of procedures for alcoholic liver disease, were 26/891 [2.92%] and 26/315, [8.25%], respectively

**Organ donation and early LT:
does it matter?**

Unsettled issues

- In an era of organ shortage, use of liver transplants in severe AH may negatively affect the public attitude on transplantation and organ donation
- This may cause reluctance on the part of clinicians to modify guidelines for alcoholic patients
- However, healthcare practitioners must inform the public that patients with self-inflicted disease warrant the same access to medical resources as other patients

Effects of early liver transplantation on organ donation

An online survey created and distributed using Amazon Web Service's mechanical Turk

Table 1: Respondent racial/ethnic composition, prior experiences

Category that best describes respondent's prior experiences with transplantation

No prior involvement with transplantation	414	82%
Family member of organ donor(s)	7	1.4%
Family member of organ recipient(s)	20	4.0%
Organ donor ³	45	8.9%
Healthcare professional (not physician) not involved with transplantation	11	2.2%
Nurse involved with transplantation	3	0.60%
Physician who is not involved with transplantation	3	0.60%
Physician involved with transplantation	0	0%

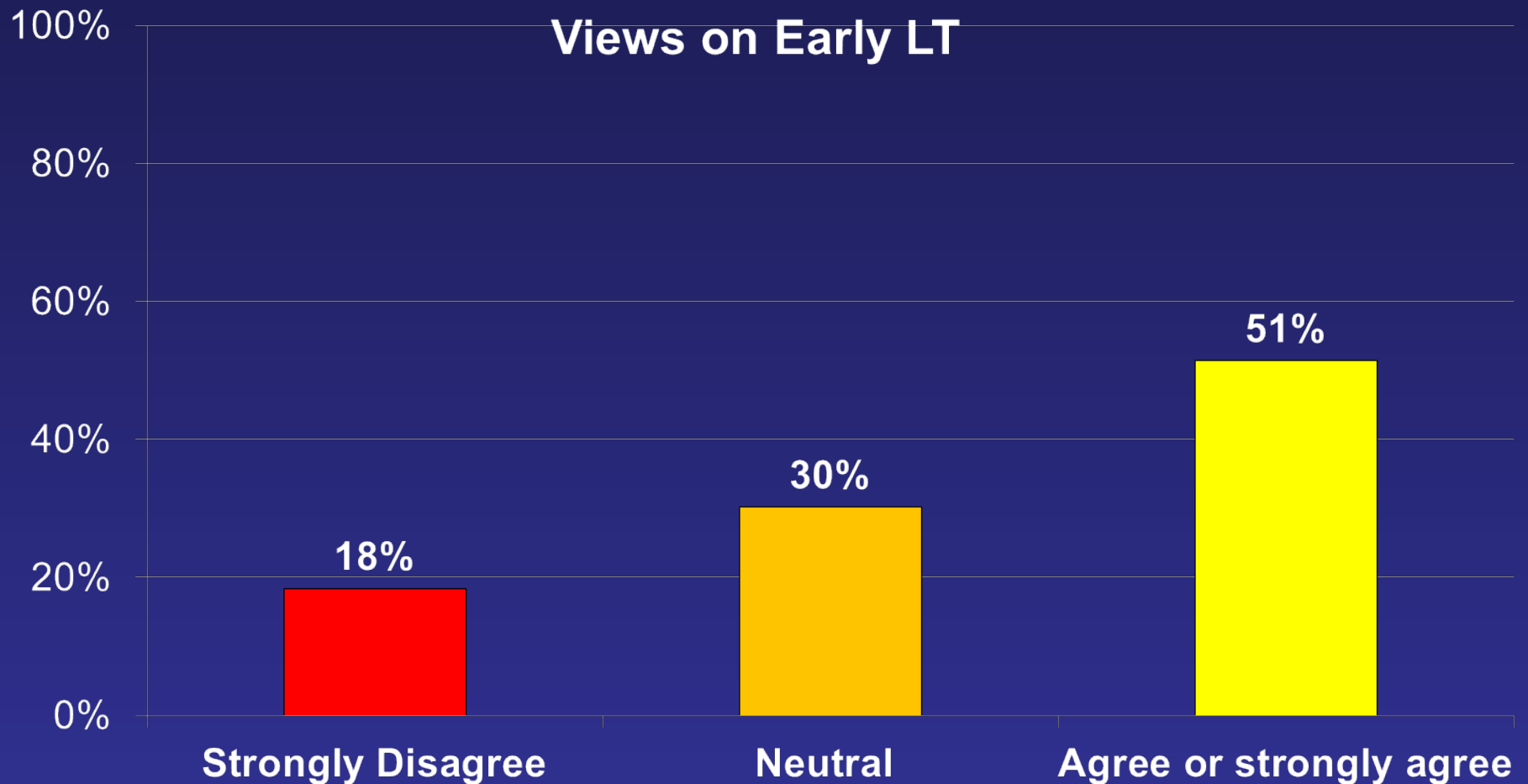
Effects of early liver transplantation on organ donation

An online survey created and distributed using Amazon Web Service's mechanical Turk

Action taken to indicate donor intent

Not taken any action	18	5.2%
Indicated on driver's license	285	84%
Talked to family about wishes to donate	31	9.1%
Indicated on advanced directive or living will	5	1.5%
Placed name on donor registry	12	3.5%

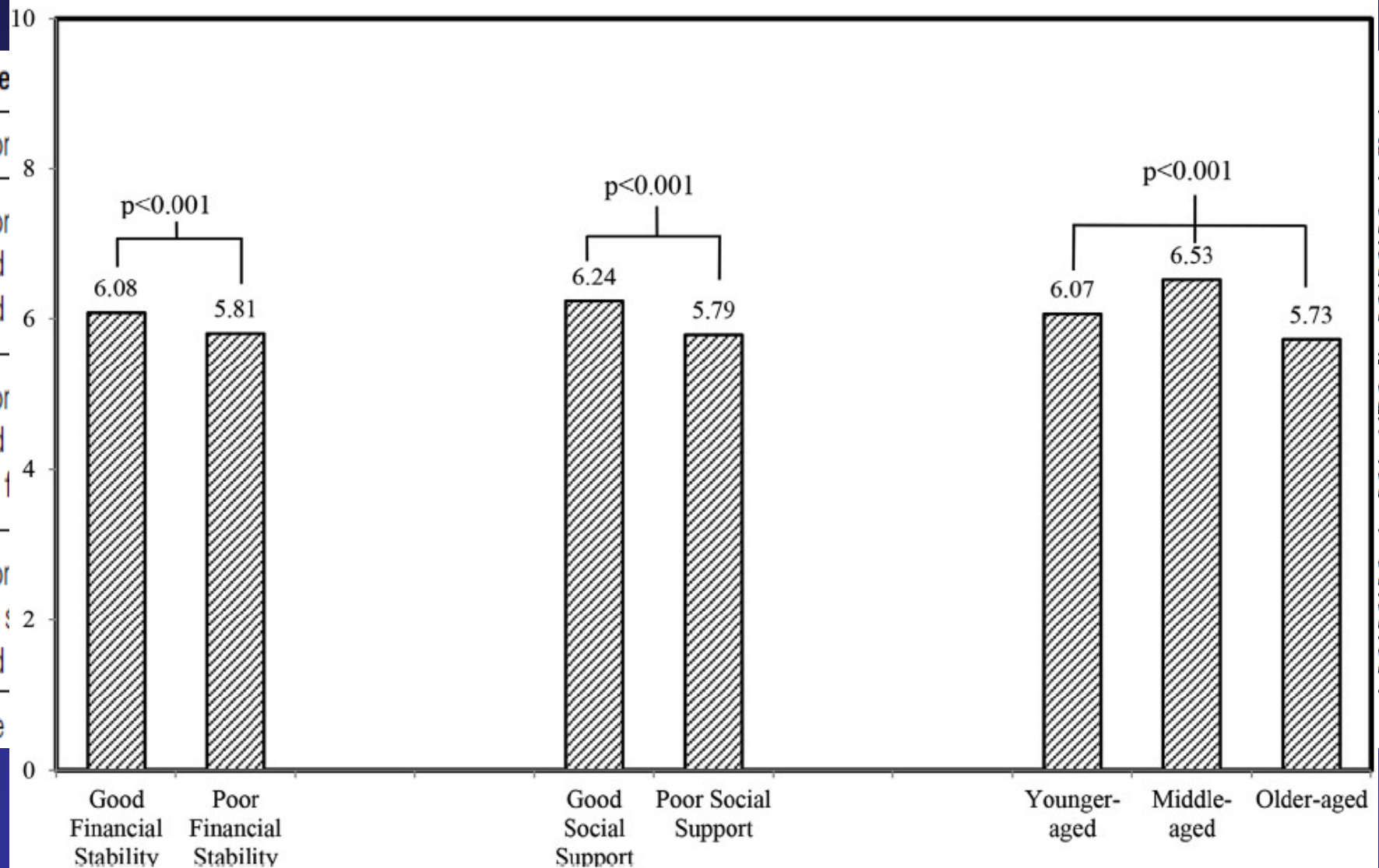
Effects of early liver transplantation on organ donation



Stroh G, American Journal of Transplantation 2015;

Effects of early liver transplantation on organ donation

Mean Approval Ratings of eLT Candidates by Selection Factors



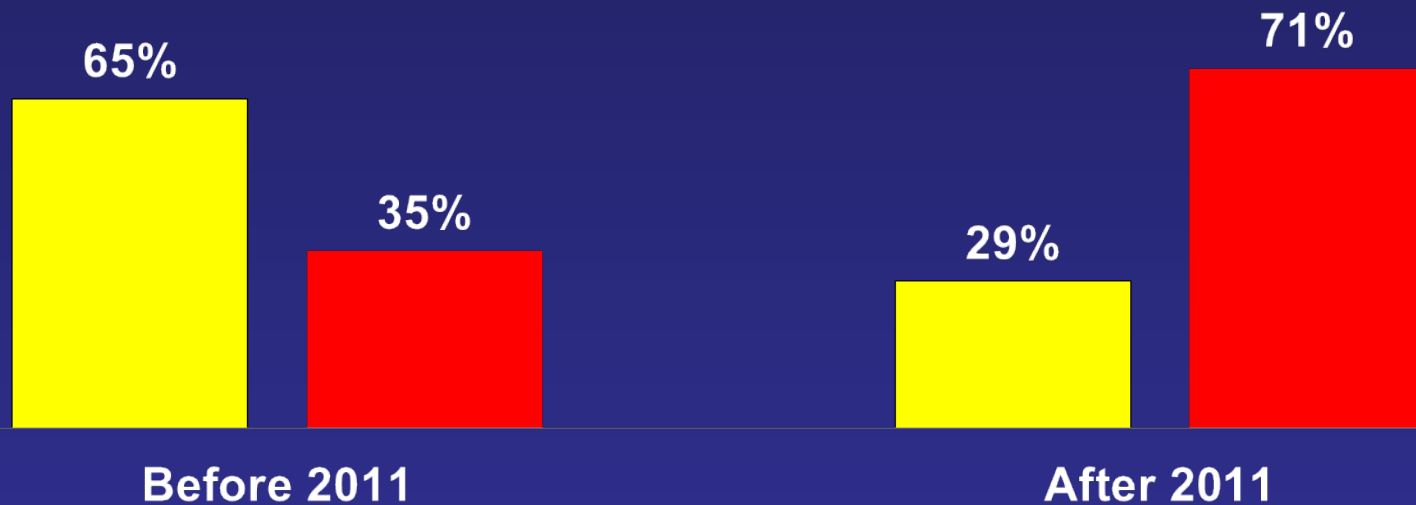
**Scientific Societies need to
homogenize their guidelines
according to data**

Experts have to work at a homogenization of rules: European example

France

Practices of French Transplant Centers

■ Never Performed ■ Performed at least 1 procedure

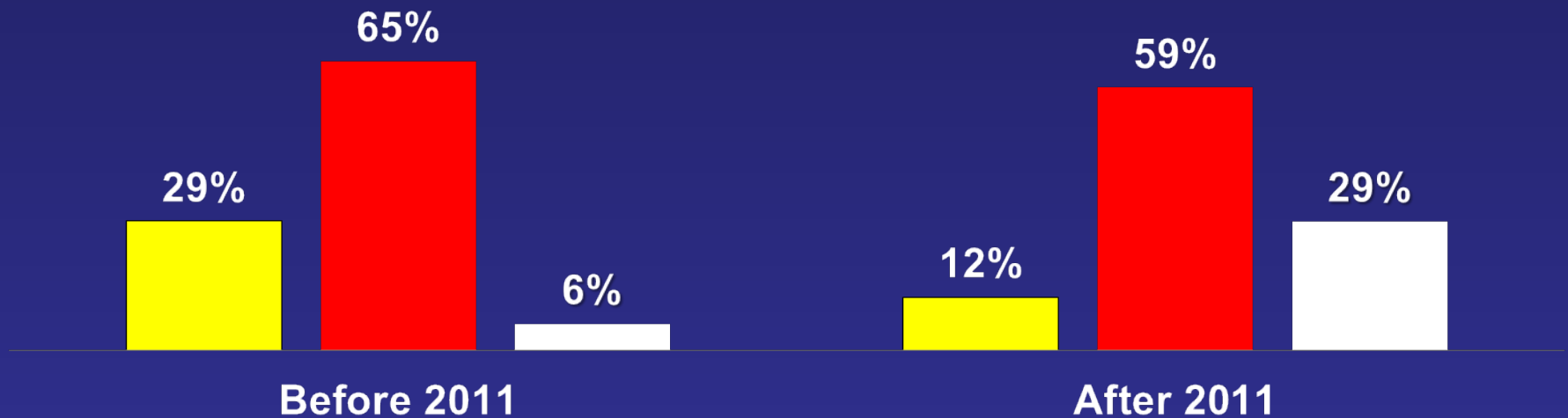


Experts have to work at a homogenization of rules: European example

France

Practices of French Transplant Centers

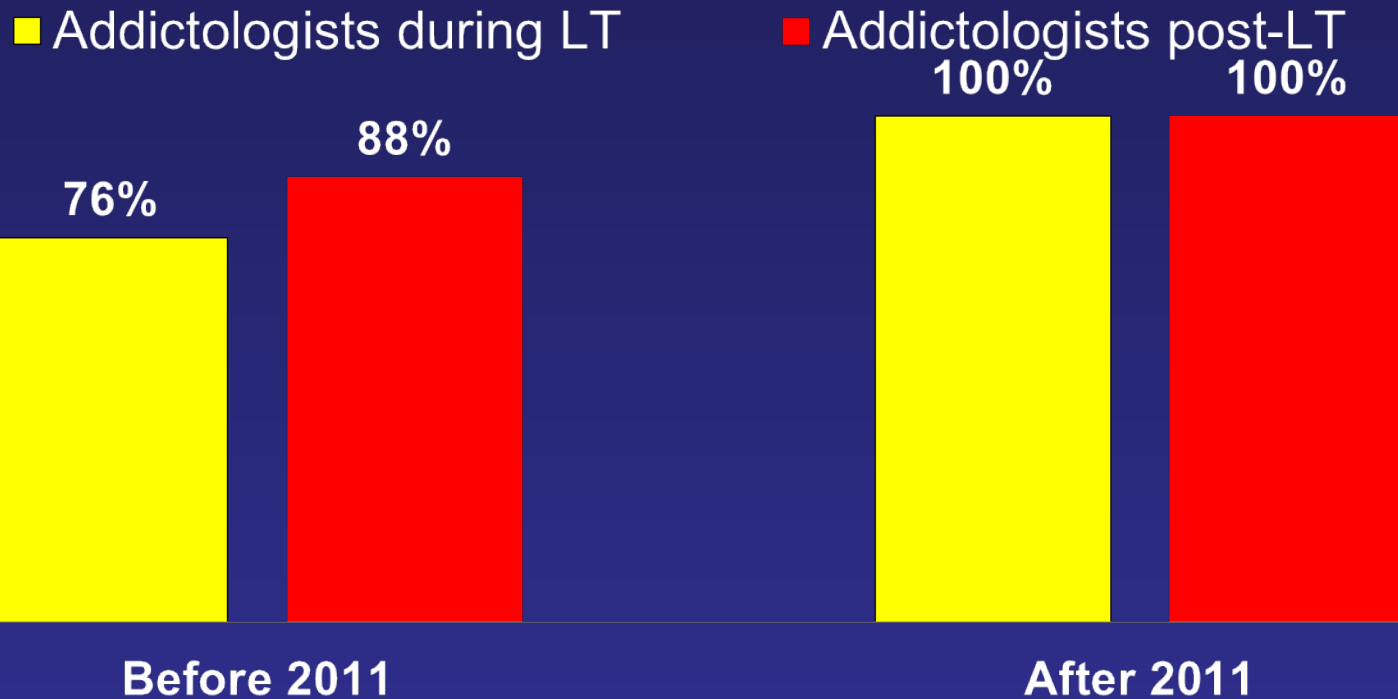
■ Use 6-month rule ■ 3-6 abstinence rule ■ 1-3abstinence rule



Experts have to work at a homogenization of rules: European example

France

Practices of French Transplant Centers



Experts have to work at a homogenization of rules: European example

Germany

Updated legal guidelines for LT in Germany:

- in exceptional cases transplant centers may request wait-listing for alcoholic patients abstinent for less than 6 months
- The request needs to be addressed to a committee of specialists at the Bundesärztekammer
- These exceptional cases are defined underlies the responsibility of the requesting transplant center and the ethical judgment of the committee

Experts have to work at a homogenization of rules: European example

Italy

Acute alcoholic hepatitis, end stage alcoholic liver disease and liver transplantation: An Italian position statement

Gianni Testino, Patrizia Burra, Ferruccio Bonino, Francesco Piani, Alessandro Sumberaz, Roberto Peressutti, Andrea Giannelli Castiglione, Valentino Patussi, Tiziana Fanucchi, Ornella Ancarani, Giovanna De Cerce, Anna Teresa Iannini, Giovanni Greco, Antonio Mosti, Marilena Durante, Paola Babocchi, Mariano Quartini, Davide Mioni, Sarino Aricò, Aniello Baselice, Silvia Leone, Fabiola Lozer, Emanuele Scafato, Paolo Borro

In a case of severe AAH, not responding to medical therapies

- LT is mandatory, even without achieving abstinence
- Italian pilot study started in 2017: around 6 patients have been transplanted for severe alcoholic hepatitis not-responding to medical therapy

Experts have to work at a homogenization of rules: European example

UK

before Brexit [do not worry before and after everything is open to discussion including earlyTH ...]

NHSBT's James Neuberger told the Guardian: 'We transplant humans, not angels

transplant centres (Bathgate AJ, Lancet 2006)

Since 2014

The NHS Blood and Transplant Service is to offer alcoholics suffering from severe liver disease transplants for the first time

Experts have to work at a homogenization of rules: European example

Clinical Practice Guidelines

 **EASL** EUROPEAN
ASSOCIATION
FOR THE STUDY
OF THE LIVER | **JOURNAL OF
HEPATOLOGY**

EASL Clinical Practice Guidelines: Management of Alcoholic Liver Disease

European Association for the Study of the Liver

In patients with severe ASH not responding to medical therapy, early LT is an efficient option but additional studies are required

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Experts have to work at a homogenization of rules: Canadian example

ORIGINAL ARTICLE

Liver transplantation for alcoholic liver disease among Canadian transplant centres: A national study

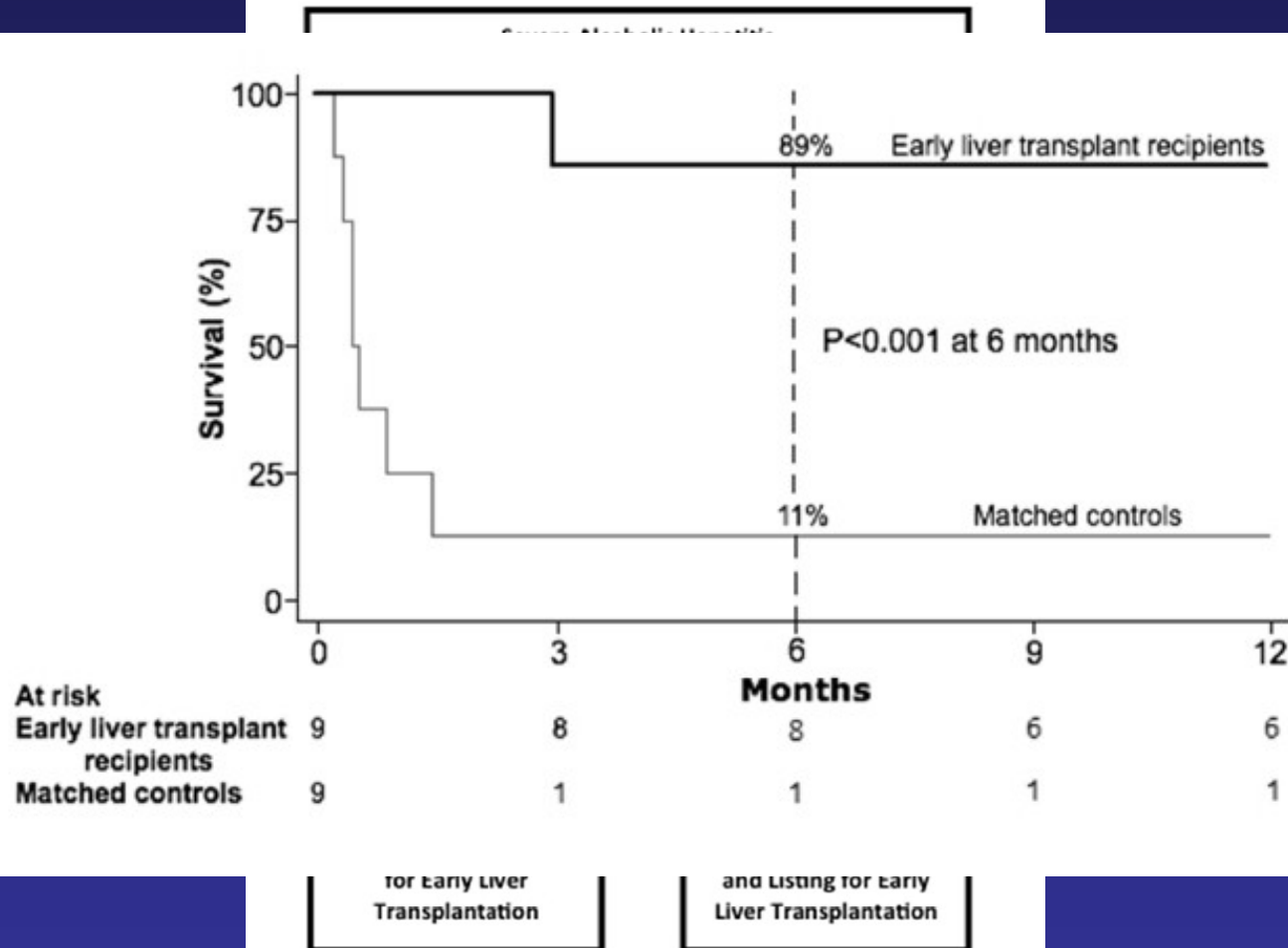
Natasha Chandok MD MPH FRCPC¹, Mohammed Aljawad MD FRCPC¹, Angela White PhD²,
Roberto Hernandez-Alejandro MD FRCPS³, Paul Marotta MD FRCPC¹, Eric M Yoshida MD FRCPC⁴

Can J Gastroenterol Vol 27 No 11 November 2013

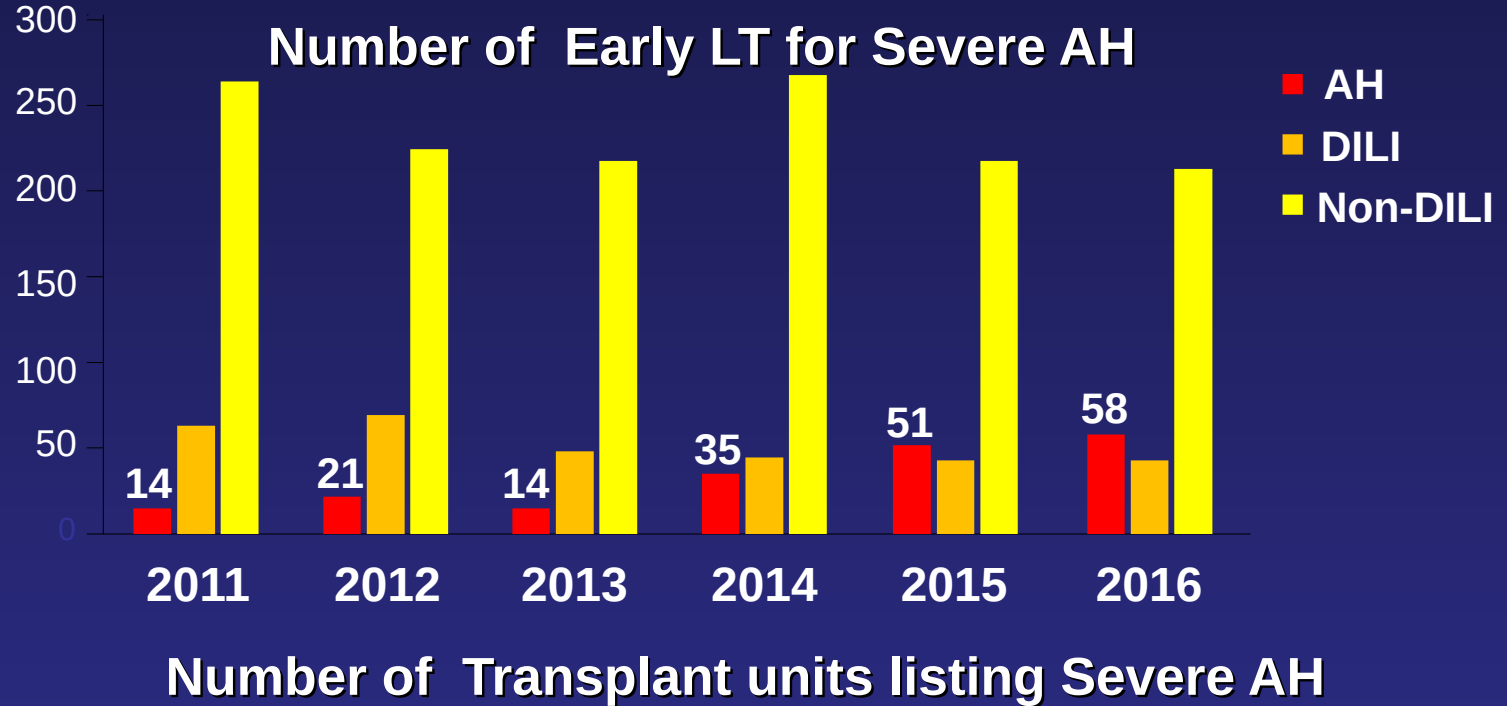
KEY MESSAGES

- Among the seven Canadian liver transplant programs, there is overall strong concordance in transplant policies toward patients with ALD with respect to adherence to the 'six-month rule' and no transplantation for severe acute alcoholic hepatitis.
- Canadian transplant policies regarding ALD are consistent with current American and European practices, but there is broad interest, particularly in Europe, toward further evaluation of LT in severe, medically refractory, acute alcoholic hepatitis in light of growing evidence of a survival benefit.

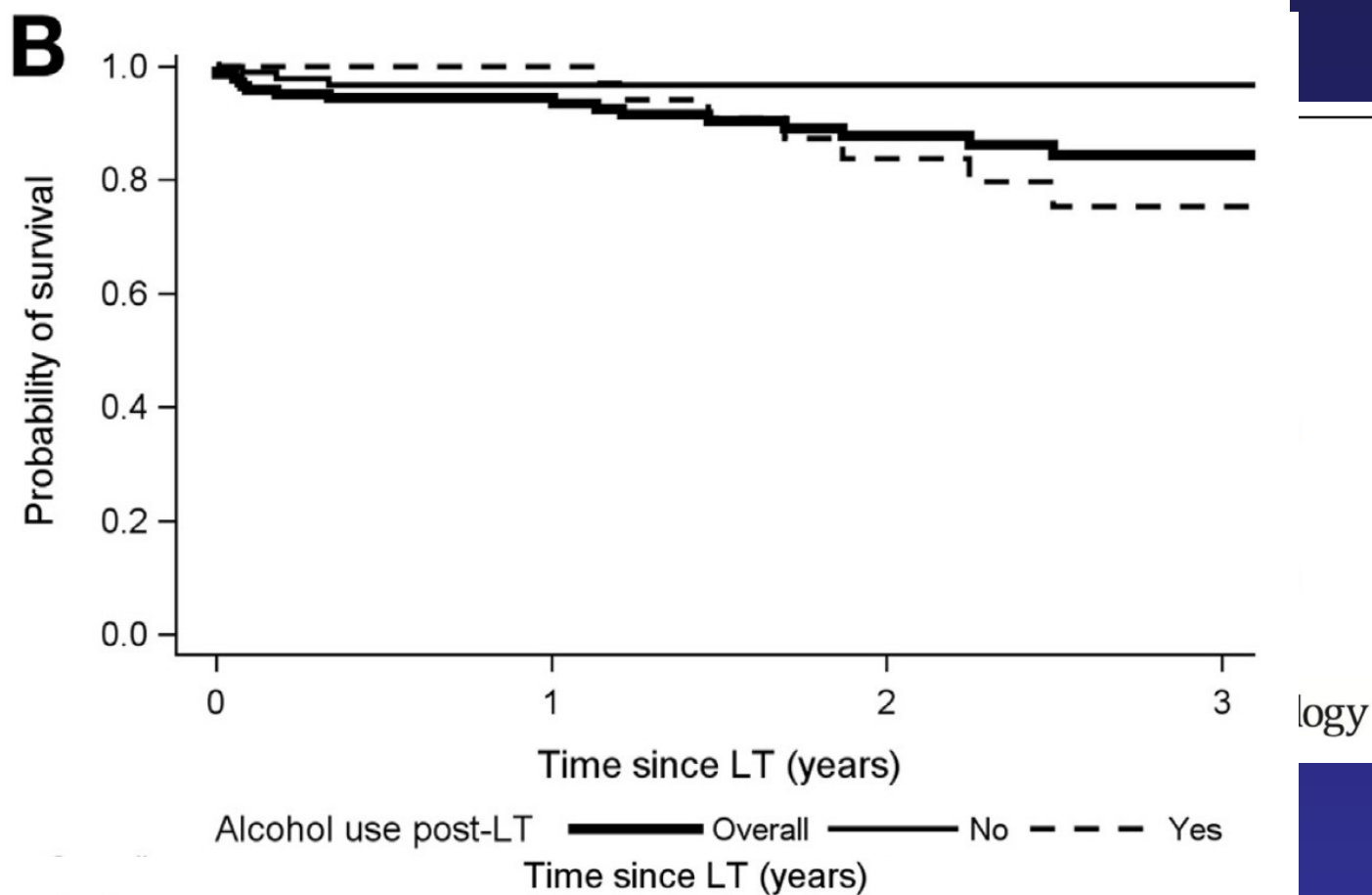
Experts have to work at a homogenization of rules: USA example



USA is evaluating Early Transplantation In Severe Alcoholic Hepatitis



American Evaluation of Early TH in severe AH



American Evaluation of Early TH in severe AH

Table 3. Univariate Risk of Overall Post-Liver Transplantation Death

Characteristic	HR (95% CI)	<i>P</i> value
More than 10 drinks/d at presentation	3.17 (1.04–9.67)	.04
Post-LT alcohol use		
Any alcohol use post-LT	3.54 (1.06–11.85)	.04
Sustained alcohol use post-LT ^a	4.59 (1.45–14.54)	.01

**Improvement in selection of
candidates for early LT**

Null responders are the candidates for early LT?

Complete responders

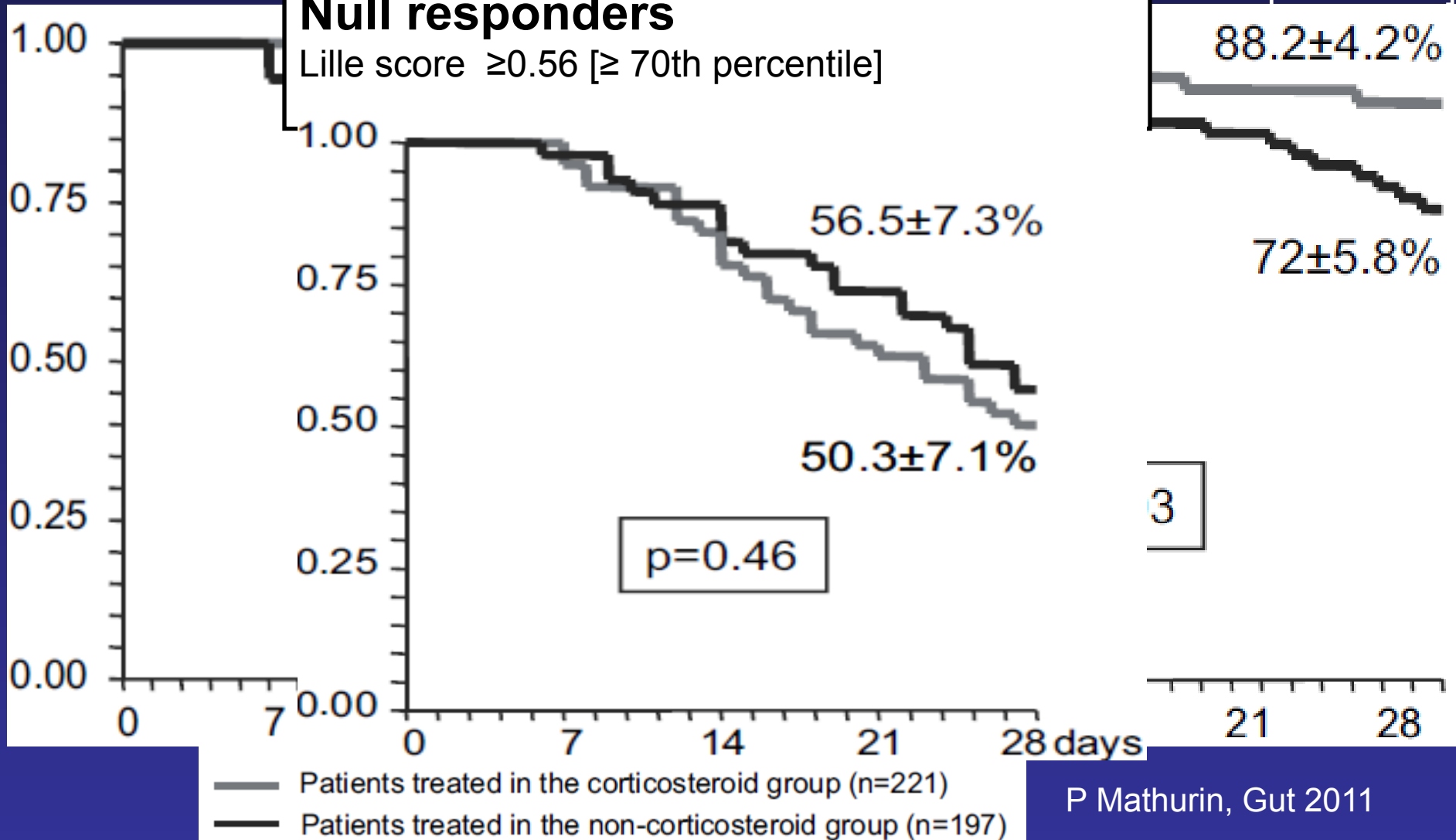
Lille score ≤ 0.16 [$\leq 35^{\text{th}}$ percentile]

Partial responders

Lille score $0.16 < \text{Lille score} \leq 0.56$ [$35^{\text{th}} - 70^{\text{th}}$ percentile]

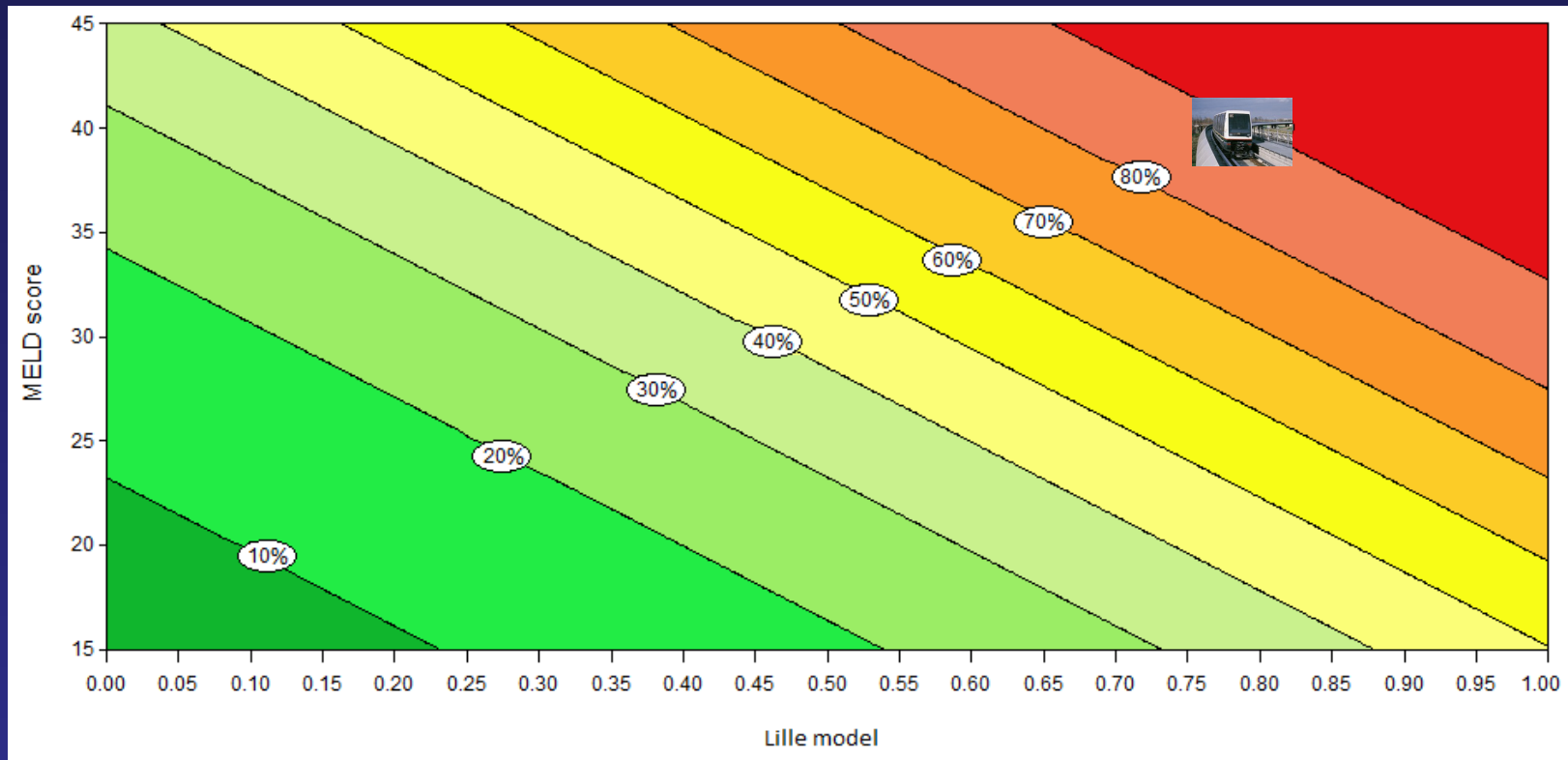
Null responders

Lille score ≥ 0.56 [$\geq 70^{\text{th}}$ percentile]



Combining Data from Liver Disease Scoring Systems

outcome as a continuum in probabilities of death



PHRC QuickTrans-HAA

Control group
Alcoholic candidates
for liver transplantation

AH not responding to medical therapy
Algorithm based on objective criteria
Range of Score from 0 to 250

Algorithm score ≥ 220

Algorithm score < 220

Classical selection
6-month criteria

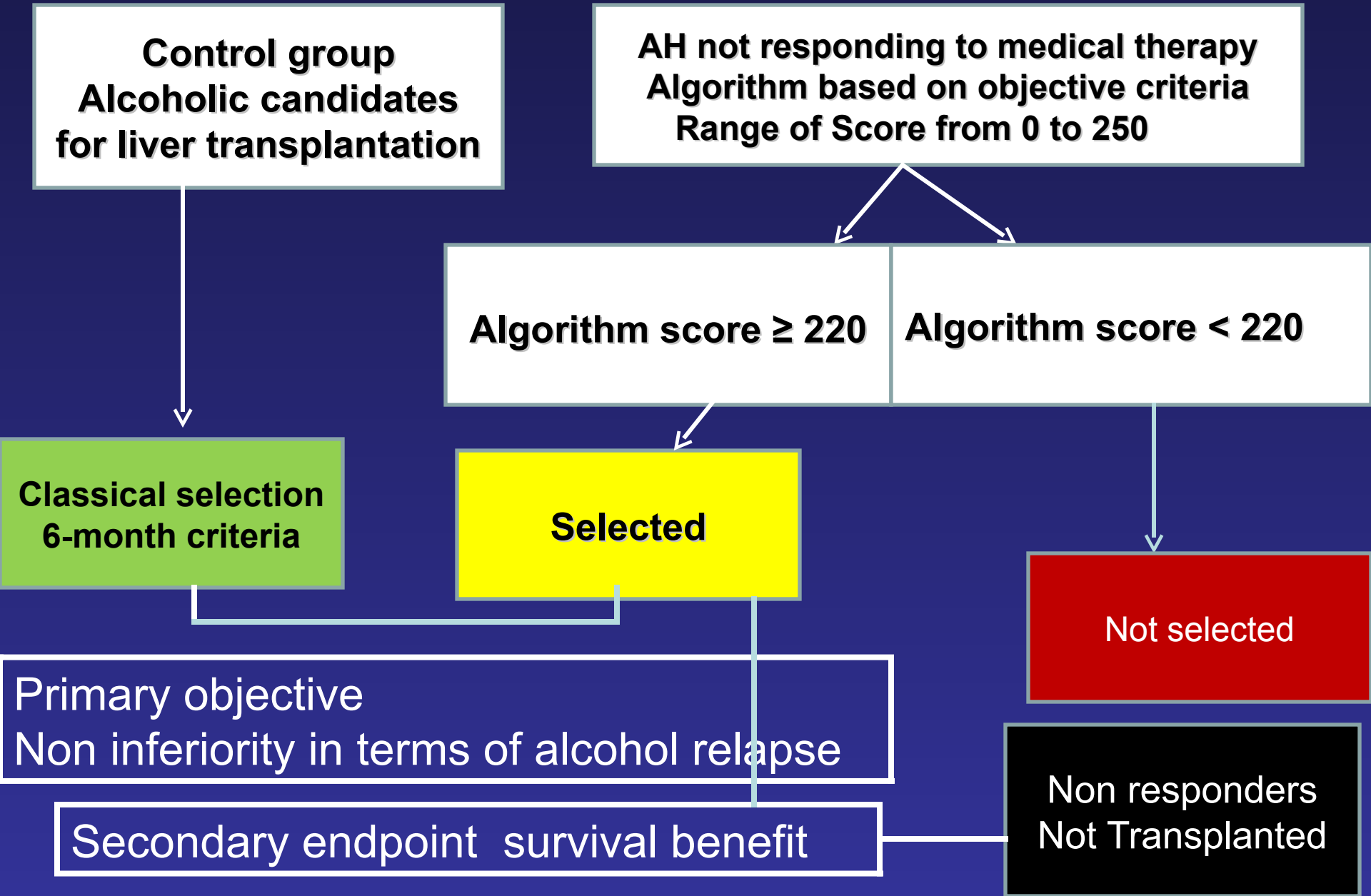
Selected

Not selected

Primary objective
Non inferiority in terms of alcohol relapse

Secondary endpoint survival benefit

Non responders
Not Transplanted



Algorithm Of the PHRC QuickTrans-HAA

➤ Consultation meeting

- Evaluation of addiction specialist separately (note already assigned)
- Collegiate award points with need for a global consensus
- Notify date of this meeting and present.

➤ Evaluation summary:

- If score ≤ 200 : Patient not considered as a candidate, will not be registered in transplant list
- If $200 < \text{score} \leq 220$: A second assessment by addiction specialist and the team need to be done before final decision
- If score > 220 : Patient candidate for transplant in accelerated procedure



Specific algorithm for encephalopathy patients

Algorithm Of the PHRC QuickTransHAA

Evaluation of Family (Alcohol problem in relatives, relationship with patient)

Psychiatric Evaluation

Comorbidities

Addiction Evaluation

Conclusions

- After a first episode of alcoholic hepatitis, early liver transplantation may be proposed in non-responders as most deaths occur within 2 months in the watch-and-wait strategy
- These encouraging results seem to be confirmed by other groups including american centers
- International database collecting information on survival and addiction is warranted in order to provide more facts and less conjecture in future discussions of the role of early LT in treatment of severe alcoholic hepatitis
- For this objective, French and Belgian centers devote themselves to to test the algorithm for selection of candidates to early LT in alcoholic hepatitis (PHRC QuickTransHAA)

Research is rigorous learning, teaching and Friendship

