Is the AFP model more pertinent ? Guidelines for equity of allocation of HCC vs non HCC patients (1)

Christophe Duvoux,
Hôpital Henri Mondor, Université Paris Est-Créteil
For the Agence de la Biomédecine HCC working group

Outline

- Background : the 2010 HCC consensus conference
- Genesis of AFP score
- AFP score : current position and perspectives
- Management of HCC burden in France

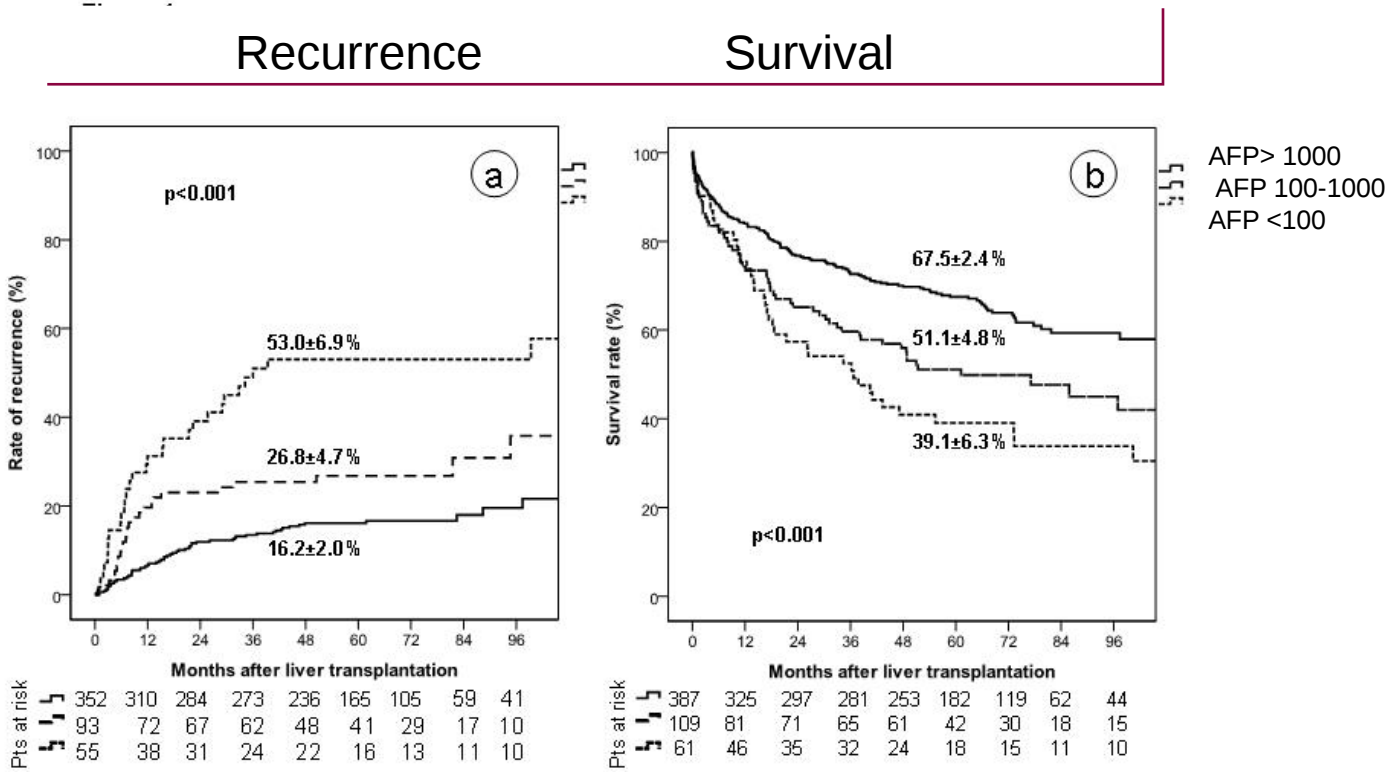
2010 Consensus conference on liver transplantation and HCC (Clavien et al. Lancet Oncol 2011)

- **Recommendation 9: the Milan criteria are currently the benchmark for selection of HCC patients for liver transplantation, and the basis for comparison with other suggested criteria.**

→ **"As evidence accumulated of good outcomes in some patients outside the Milan criteria, there was a drive to identify expanded criteria and to increase the number of eligible candidates for liver transplantation".**

- **Recommendation 10: a modest expansion of the number of potential candidates may be considered on the basis of several studies showing comparable survival for patients outside the Milan criteria**

Tumour behaviour : Predictive value of AFP at listing, on tumor recurrence and survival (training cohort)

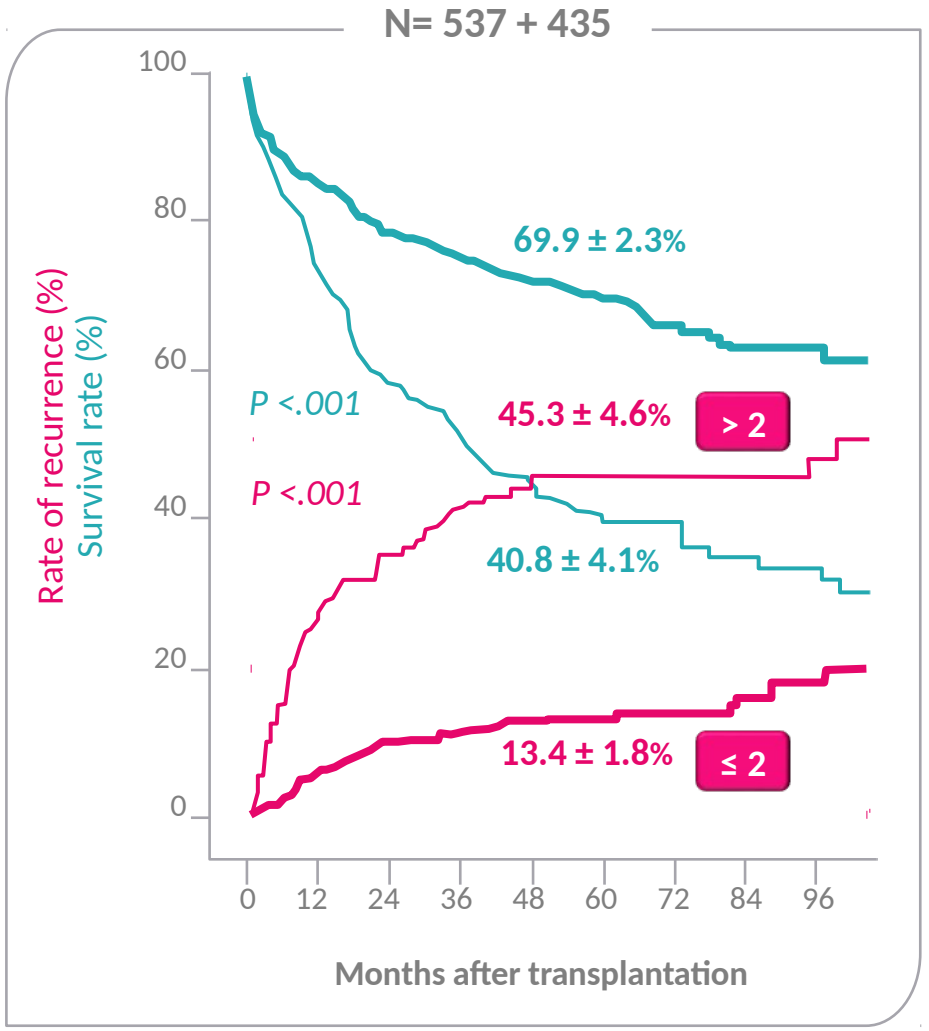


Duvoux et al. Gastroenterology 2012

Liver Transplantation for Hepatocellular Carcinoma: A model including α-Fetoprotein Improves the Performance of Milan Criteria : adopted in France by January 2013

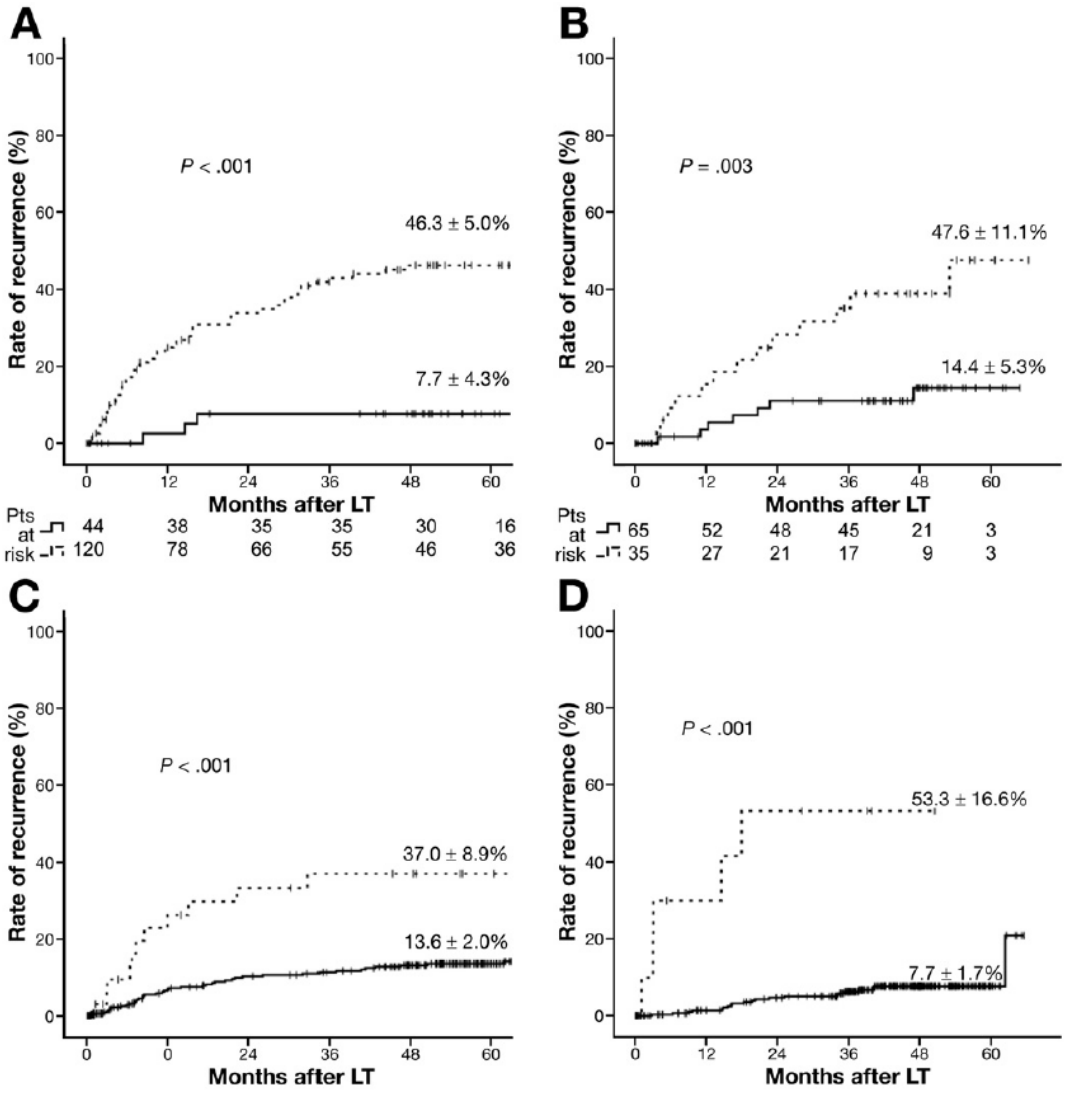
	Patients
Diametre (cm) ≤ 3 3-6 > 6	 0 1 4
Number of nodules 1-3 ≥ 4	 0 2
AFP (µg/l) ≤ 100 100-1000 > 1000	 0 2 3

→ **Risk of recurrence**
≤ 2 = LOW; > 2 = HIGH



Duvoux C et al. Gastroenterology 2012.

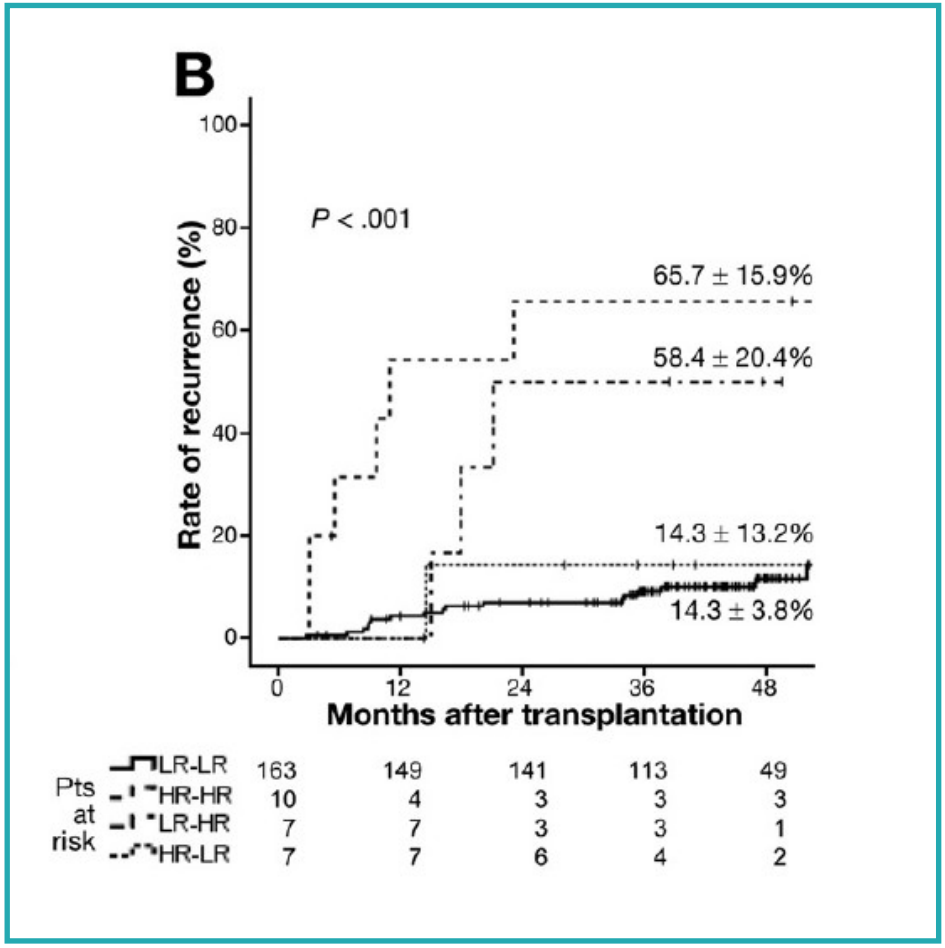
Recurrence rates in patients exceeding or within Milan criteria according to the cut off 2 in training (A) and validation (B) cohorts



Exceeding Milan

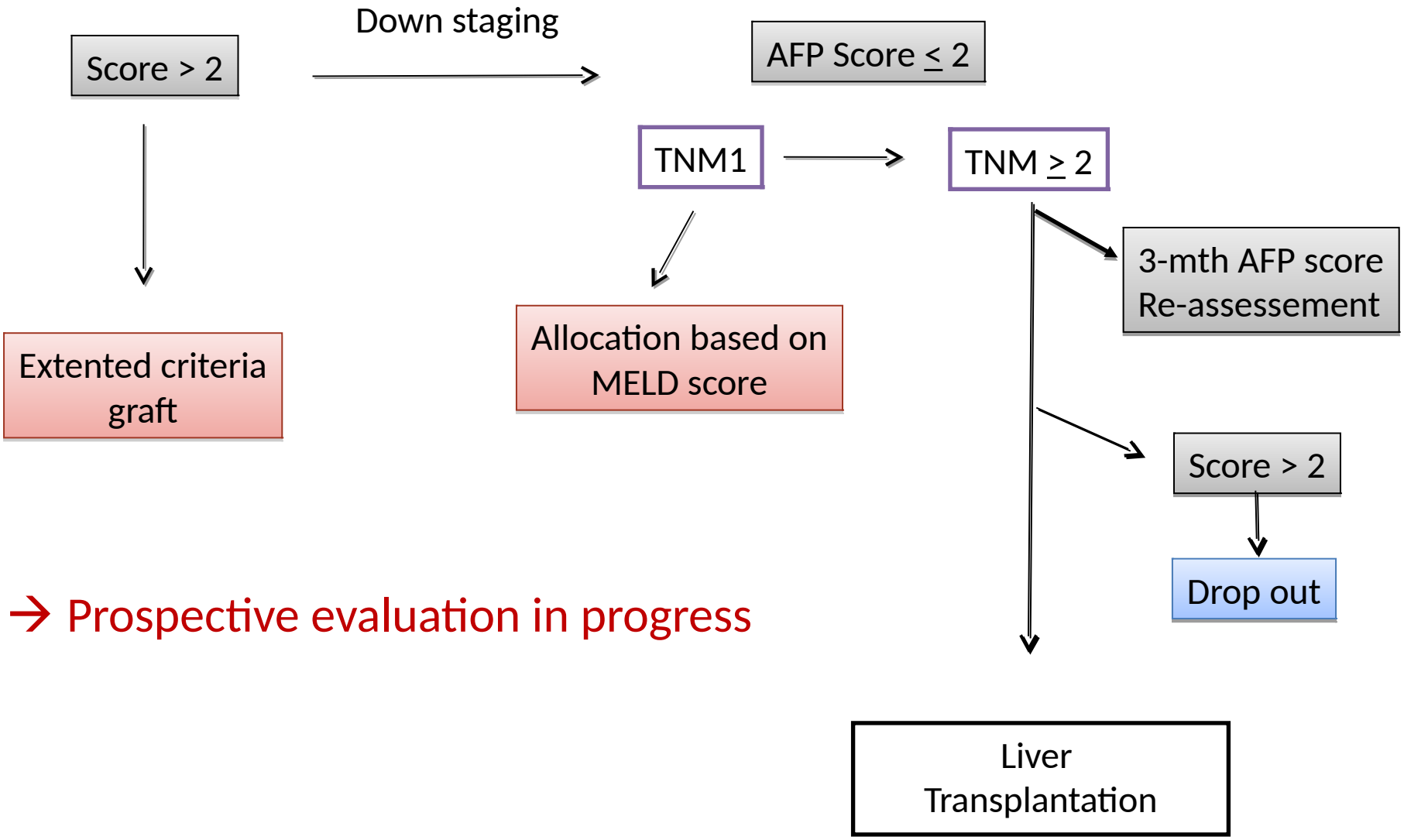
Within Milan

Impact of variations of AFP score during the waiting phase on post-LT recurrence



Duvoux C et al. Gastroenterology 2012.

French Organization for organ sharing : AFP model, adopted in July 2012 → implemented officially in January 2013



→ Prospective evaluation in progress

Is the AFP model valid in non French populations ?

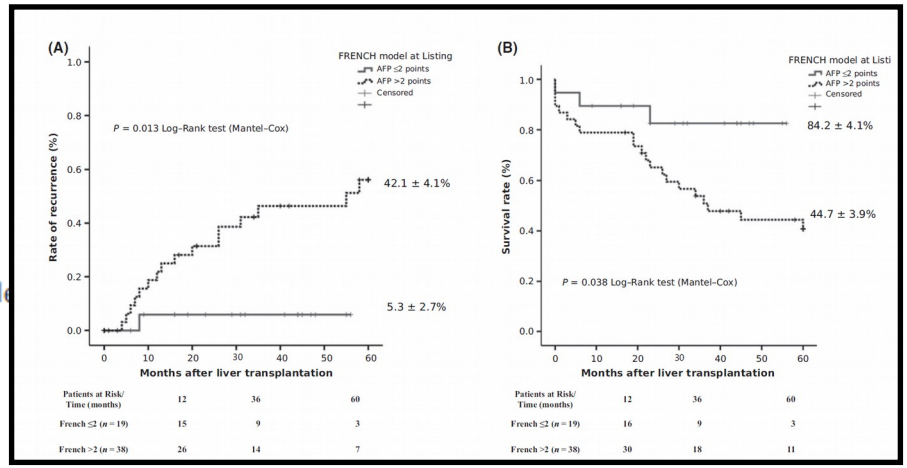
Liver International ISSN 1478-3223

ORIGINAL ARTICLE

Liver transplantation for hepatocellular carcinoma: evaluation of the alpha-fetoprotein model in a multicenter cohort from Latin America

Federico Piñero[1], Matías Tisi Baña[1], Elaine Cristina de Ataide[2], Sergio Hoyos Duque[3,4], Sebastian Marciano[5], Adriana Varón[6], Margarita Anders[7], Alina Zerega[8], Josemaría Menéndez[9], Rodrigo Zapata[10,11], Linda Muñoz[12], Martín Padilla Machaca[13], Alejandro Soza[14], Lucas McCormack[7], Jaime Poniachik[15], Luis G. Podestá[1], Adrian Gadano[5], Ilka S. F. Fatima Boin[2], Christophe Duvoux[16] and Marcelo Silva[1]On behalf of the Latin American Liver Research, Education and Awareness Network (LALREAN)

1 Hospital Universitario Austral, Pilar, Argentina
2 Hospital de Clinicas, State University of Campinas, Campinas, Brazil
3 Hospital Pablo Tobón Uribe, Medellin, Colombia
4 Universidad de Antioquía, Medellin, Colombia
5 Hospital Italiano from Buenos Aires, Buenos Aires, Argentina
6 Fundación Cardioinfantil, Instituto de Cardiología, Bogotá, Colombia
7 Hospital Alemán, Buenos Aires, Argentina
8 Sanatorio Allende from Córdoba, Córdoba, Argentina
9 Hospital Militar-Clínicas, Montevideo, Uruguay
10 Clinica Alemana de Santiago, Universidad del Desarrollo, Santiago, Chile
11 Hospital del Salvador, Universidad de Chile, Santiago, Chile
12 Hospital Universitario de Monterrey, Monterrey, Mexico
13 Hospital Guillermo Almenara, Lima, Perú
14 Hospital Universidad Católica de Chile, Santiago, Chile
15 Hospital Clínico Universidad de Chile, Santiago, Chile
16 Henri Mondor Hospital, University of Paris-Est, Creteil, France

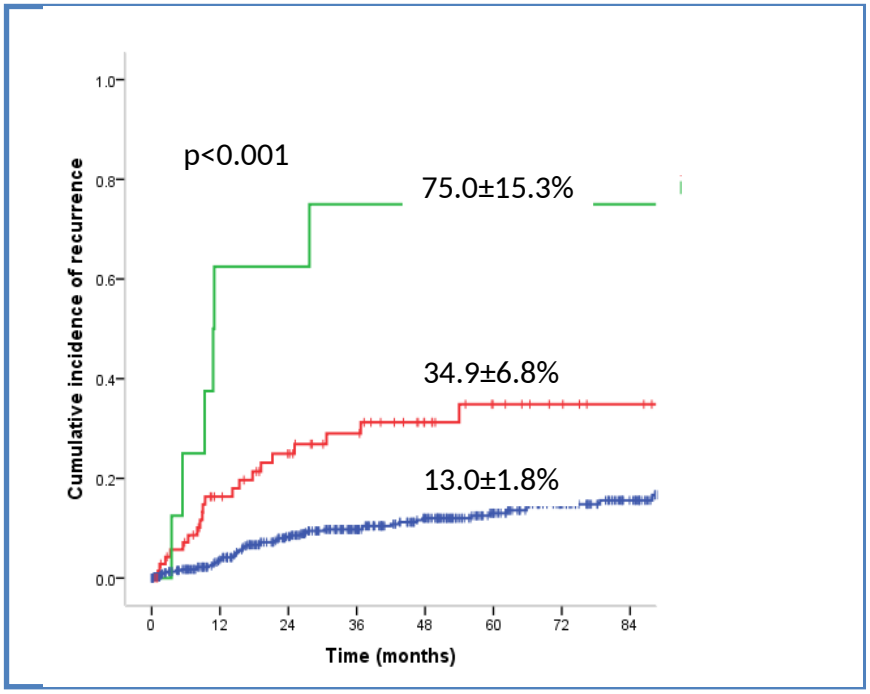


Patients beyond Milan criteria

Recurrence after liver transplantation for hepato-cellular carcinoma: validation of the AFP model in a post-hepatitic cirrhosis-based population.

Andrea Notarpaolo[1], Richard Layèse[2], Paolo Magistri[3] , Maria Gambato[4], Michele Colledan[5] , Giulia Magini[5], Lucia Miglioresi[6], Alessandro Vitale[7], Giovanni Vennarecci[8], Cecilia D Ambrosio[6], Patrizia Burra[4], Fabrizio Di Benedetto [3], Stefano Fagiuoli[5], Marco Colasanti[8], Giuseppe Maria Ettorre[8], Arnoldo Andreoli[6], Umberto Cillo[7], Alexis Laurent[9], Sandrine Katsahian[2], Etienne Audureau[2], Françoise Roudot-Thoraval[2], Christophe Duvoux[9]

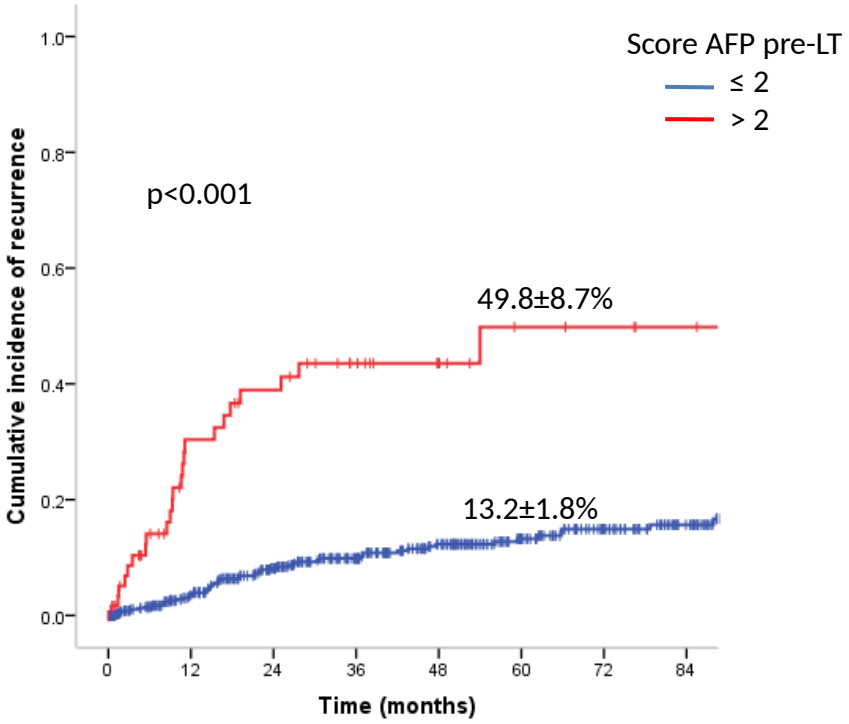
Recurrence according pre AFP cut-off



J Hep accepted for publication

Recurrence and survival in the whole population according to AFP score

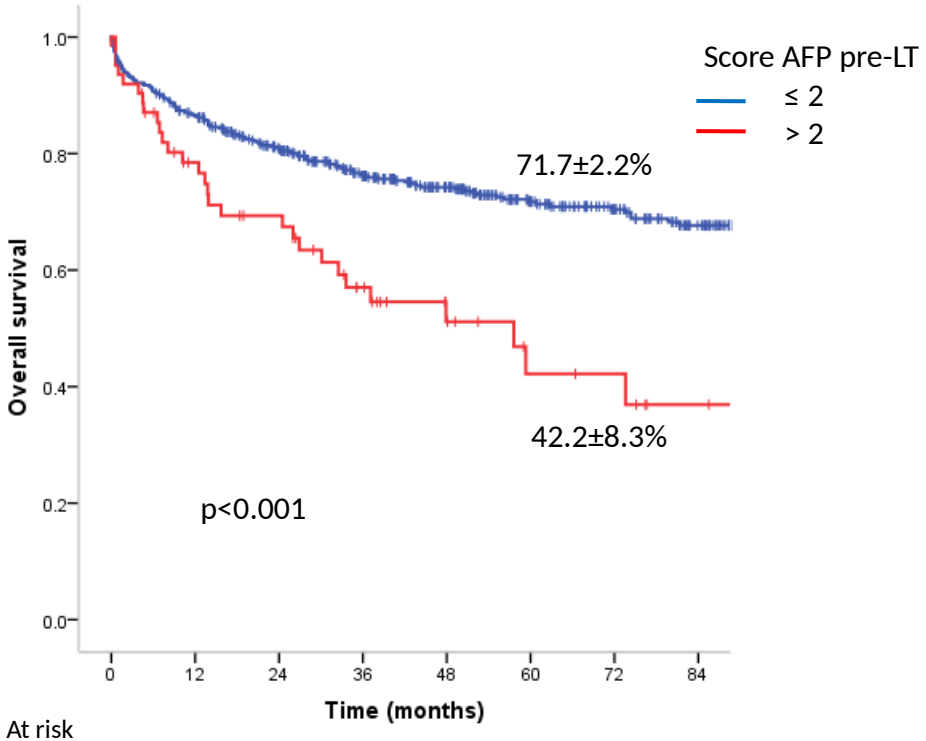
A



At risk

score≤2	512	420	345	284	228	172	132	98
Score ≥3	62	33	27	19	12	7	6	4

B

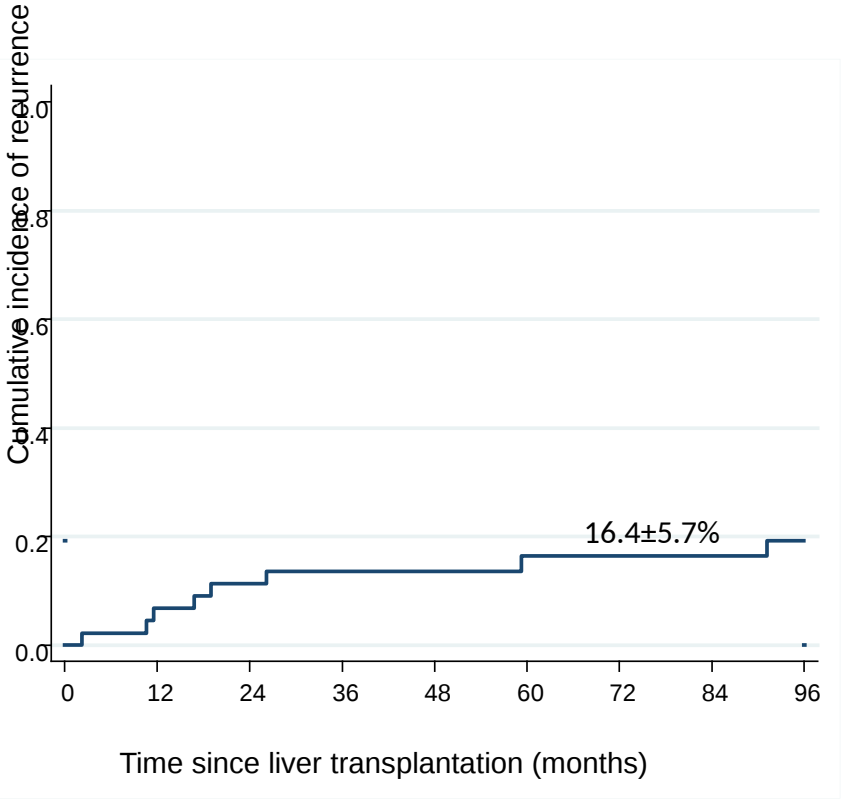


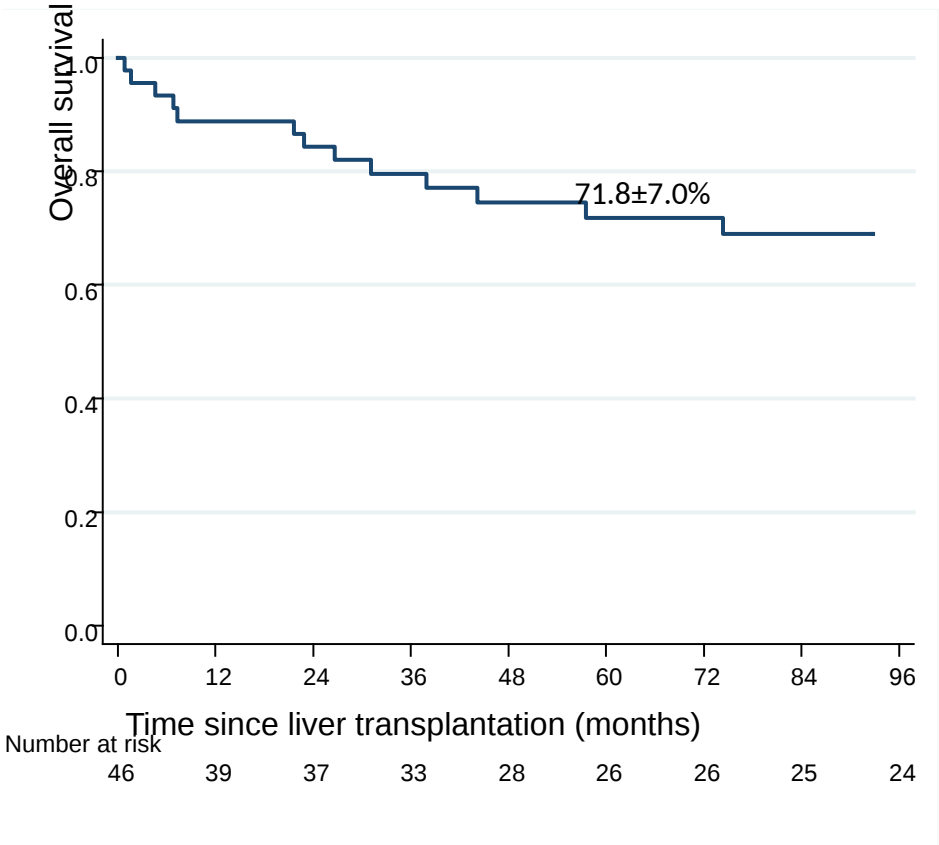
At risk

Score≤2	512	431	365	298	239	179	141	105
Score≥3	62	43	36	24	15	9	7	4

Notarpaolo et al. J Hep Accepted for publication

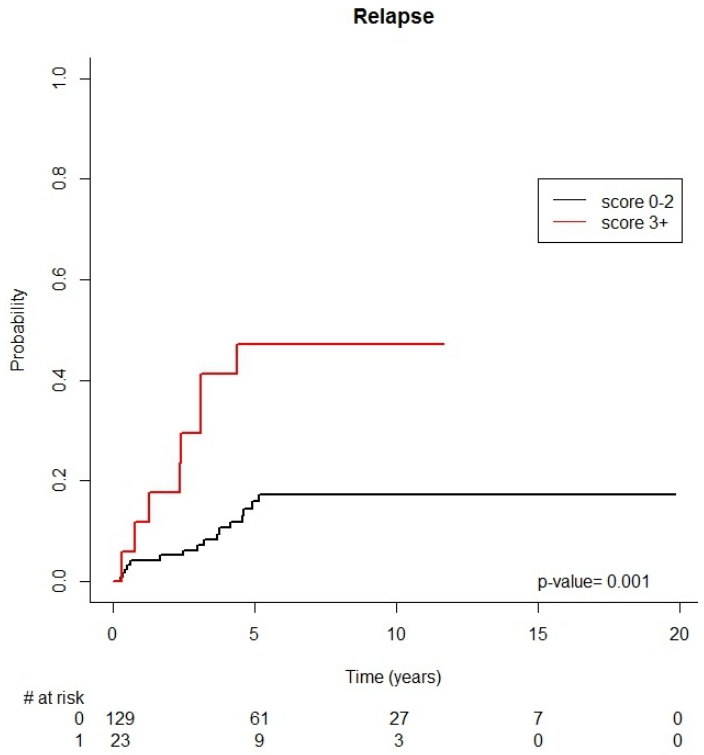
Recurrence and survival in 46 patients undergoing successful Down staging from AFP score > 2 (3) to ≤ 2 (0)

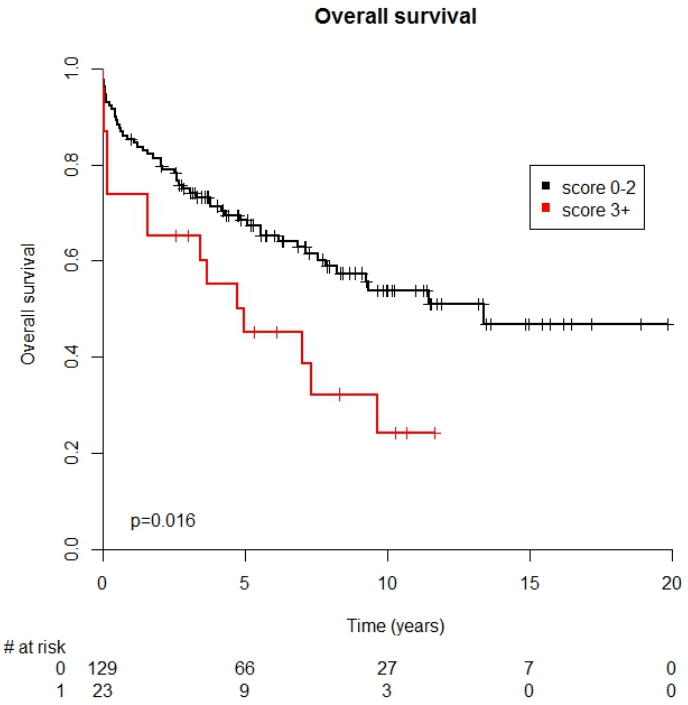




Notarpaolo et al. J Hep
accepted for publication

Validation of the AFP model in an English series of 152 pts (Royal Free Hospital)





Unpublished/Confidential; on cortesy of Andy Burroughs, RFH,
G Bizouard, S Katsahian & F Roudot-Thoraval, Department of Biostatistics, Paris-Est University

AFP model/score

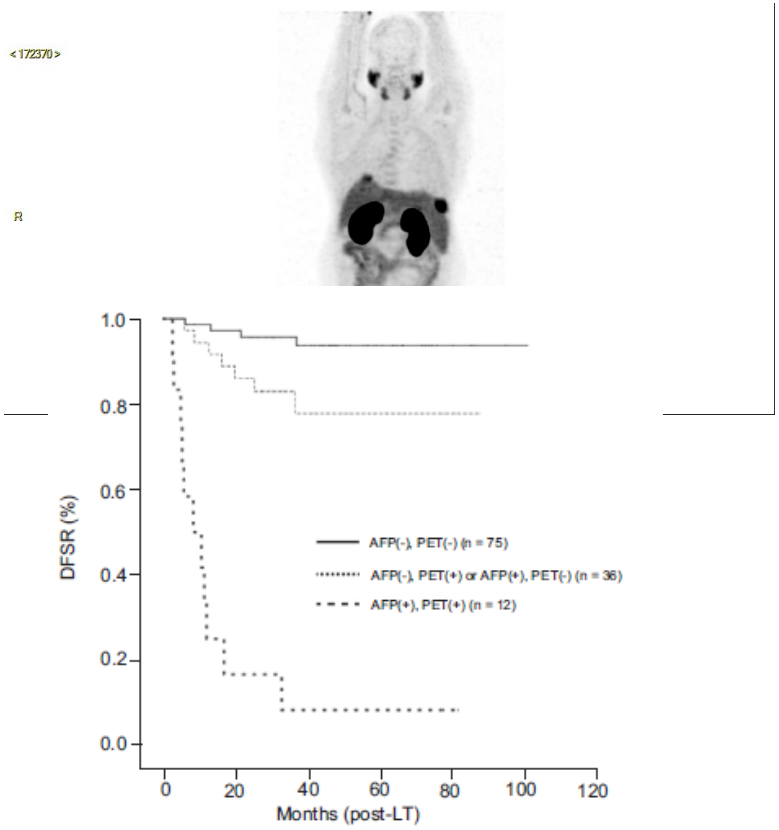
- Reproducible/robust
- Fulfill the EASL guidelines for introducing a biomarker in a decision-making algorithm
- Improve the predictive value of Milan criteria
- Easy to implement :
  - baseline AFP and imaging: non invasive
  - 3-month reassessment
- In programs restricted to Milan criteria
  - allows a reasonable evidence-based expansion of HCC criteria
- In programs with no restriction,
  - allows an evidence-based control of HCC indications

Room for an improvement ?

Better characterization of tumour behaviour to better identify patients who will not recur.

- Analysis of larger data set of patients with AFP score >2
- New biomarkers
- Functional imaging
- Molecular tools

- AFP+18 fdg PET scan



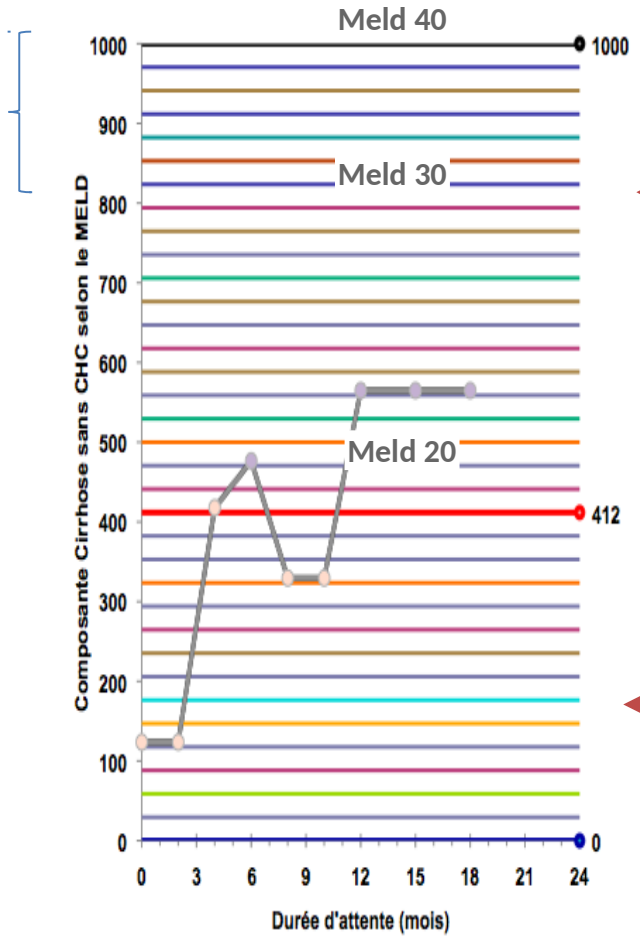
Hong et al. J Hep 2016

MANAGING HCC BURDEN

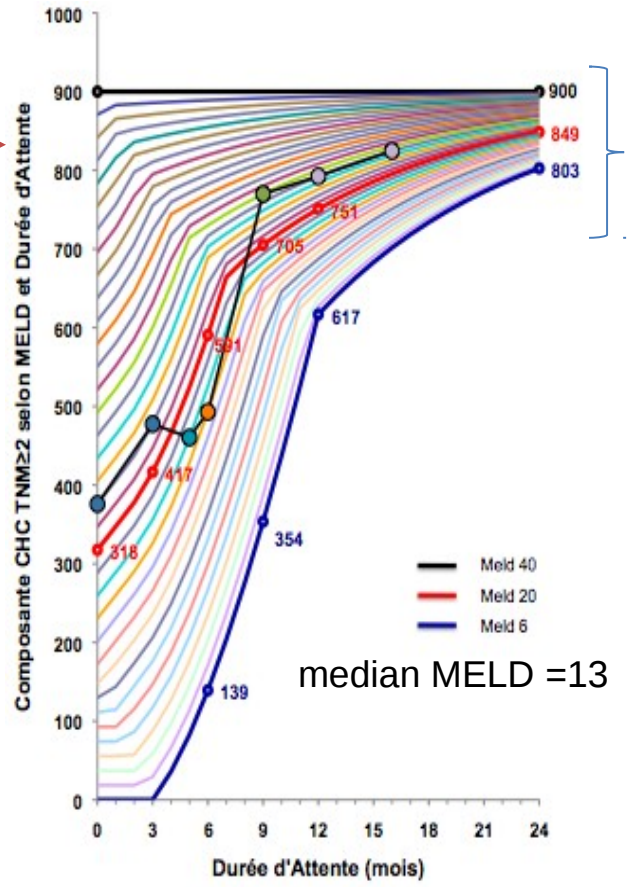
Competition between decompensated cirrhosis and HCC in France

30% indications

De-compensated cirrhosis: depending on severity and based on utility, time-independant

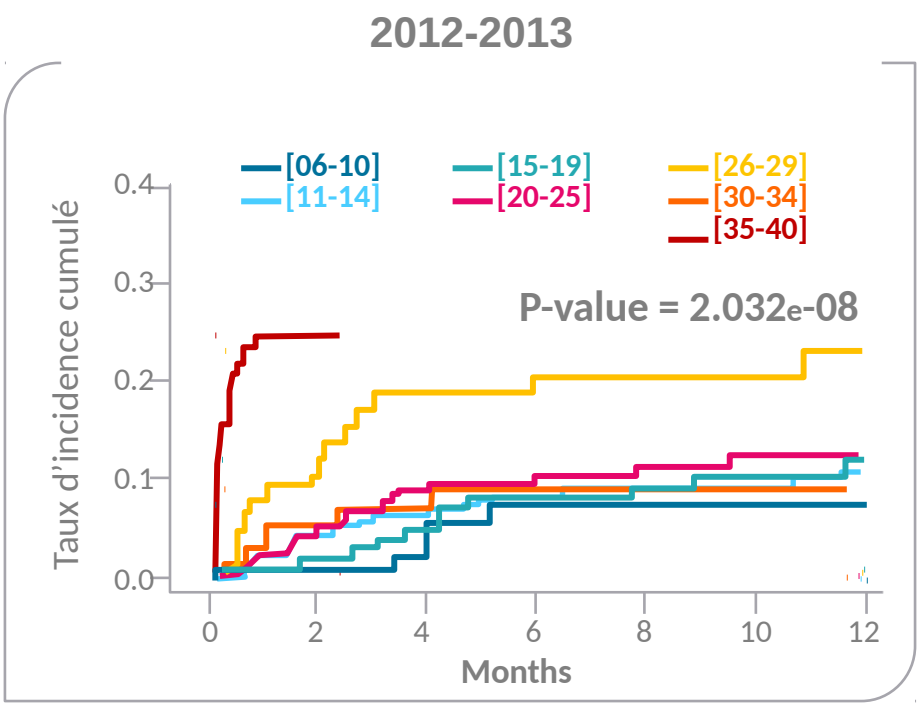


HCC: based on Equity
Time-dependant, quite independant of HCC staging or treatment



35% indications

Impact of competition between end-stage cirrhosis and HCC on the risk of death and drop out in de-compensated cirrhotics



Agence de la Biomédecine 2014

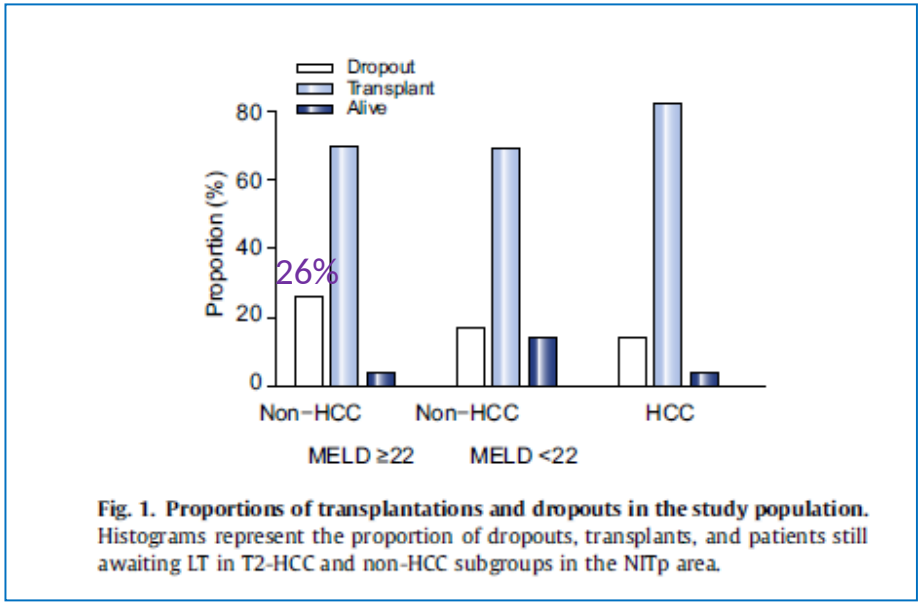


Fig. 1. Proportions of transplantations and dropouts in the study population. Histograms represent the proportion of dropouts, transplants, and patients still awaiting LT in T2-HCC and non-HCC subgroups in the NITp area.

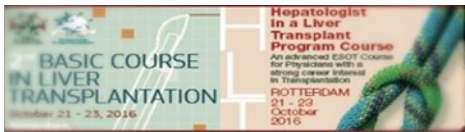
Vitale et al. J Hepatol 2014

How to improve the system ?

Refining allocation for HCC

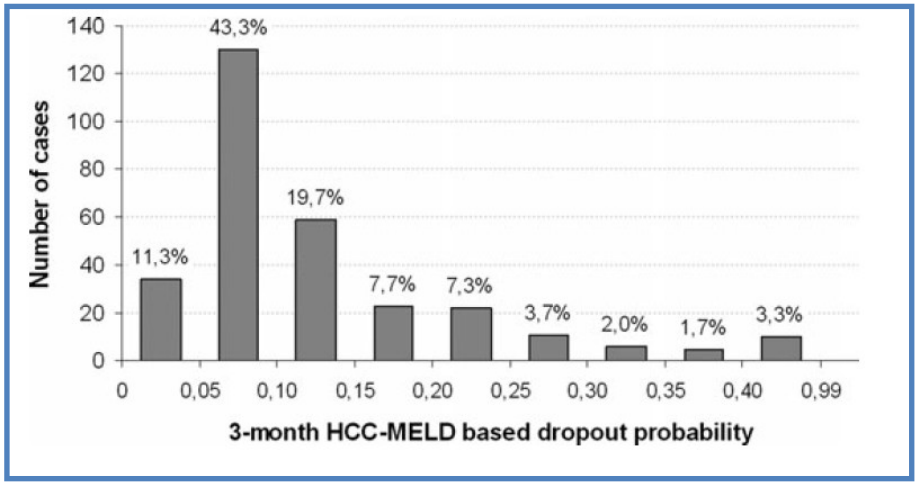
Attempts to modelize the risk of drop out in HCC patients

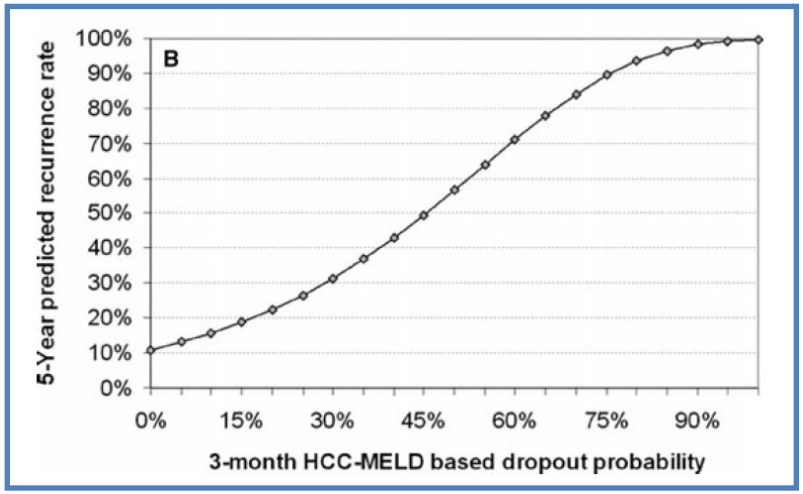
Vs practical policy



An attempt to equate drop out between HCC and de-compensated cirrhosis using HCC Meld

HCC MELD : $1–0.920 \exp [0.09369 \times (MELD - 12.48) + 0.00193 \times (AFP - 97.4) + 0.1505 (\text{maximum tumor size} - 2.59)$ (Freeman et al. AJT 2006)

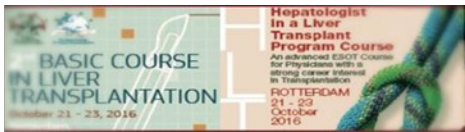




Cuchetti et al. Am J Transplant 2011

Drawbacks of mathematical models

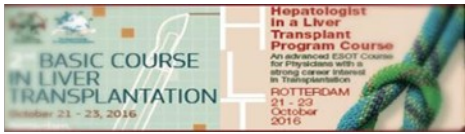
- Drop-out probability for HCC correlates with a higher risk of recurrence post-LT.
- The models have been designed in Milan-based programs.
- The models are not validated in external cohorts
- Do not take into account tumour behaviour and response to treatment on the waiting list.
- Limited applicability in daily practice.



Initial French allocation system for HCC patients

Factors not taken into account for allocation:

- Tumor stage
- Treatment options
- Response to treatment



Introducing utility in the HCC allocation system

Apply to HCC the principle of the « sickest first policy » which drives allocation for de-compensated cirrhosis:
TIPS-like strategy

Allocate liver grafts to HCC patients according to

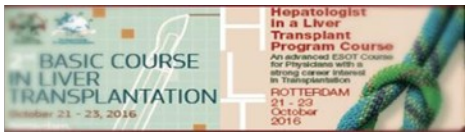
Staging/severity

Possibility of Curative treatments

Response to treatment

Ablate/resect and wait strategy

Redistribution of liver grafts to non HCC patients at high risk of death/drop out



PREDICTORS OF DROPOUT

Criteria for low dropout risk

1 lesion 2-3 cm

Complete response to 1st treatment

AFP after 1st treatment < 20 ng/mL

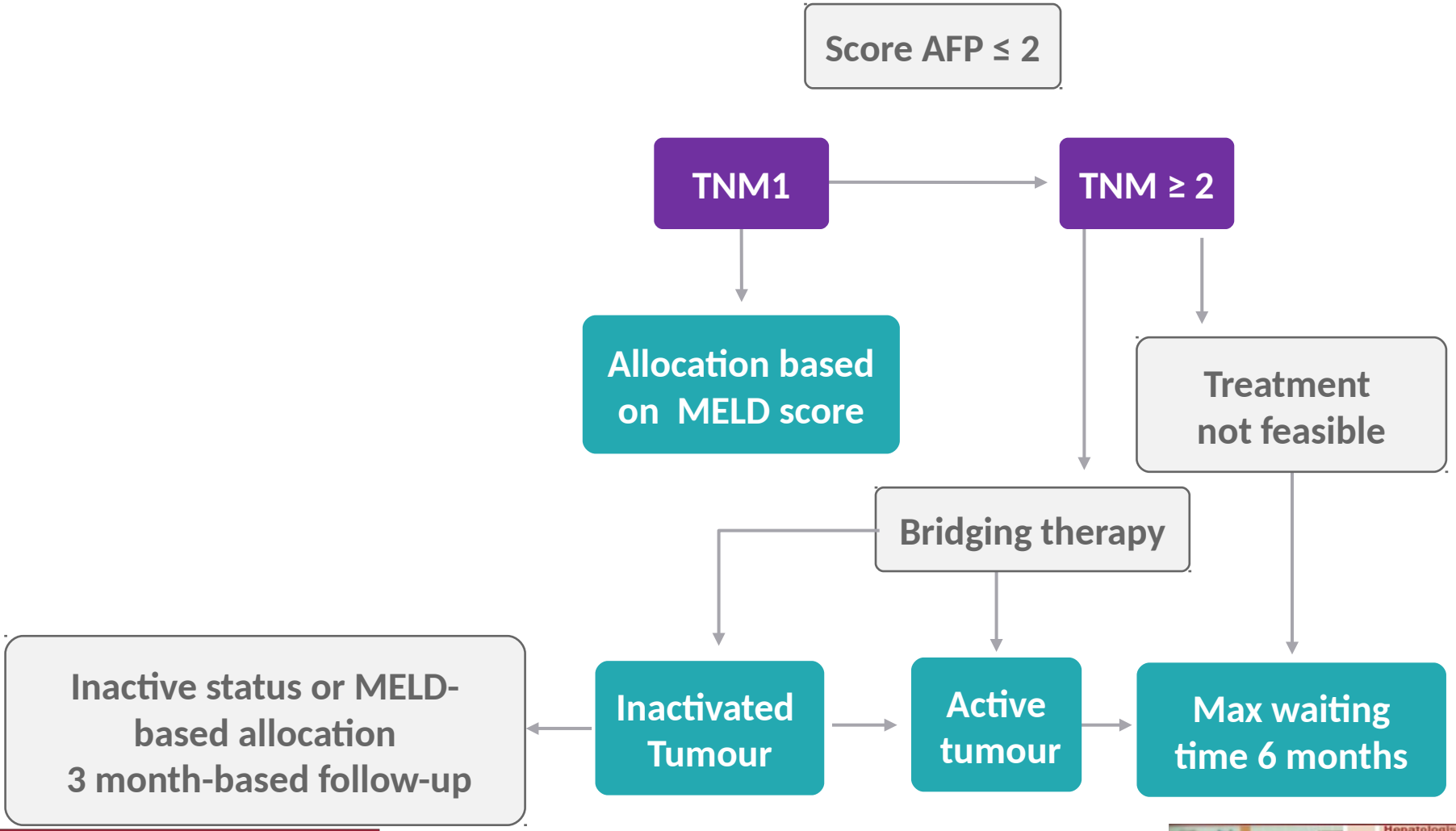
→ Cumulative dropout risks of 1.3% at 1 year, and 1.6% at 2 years.

→ Accounts for 20% of entire cohort

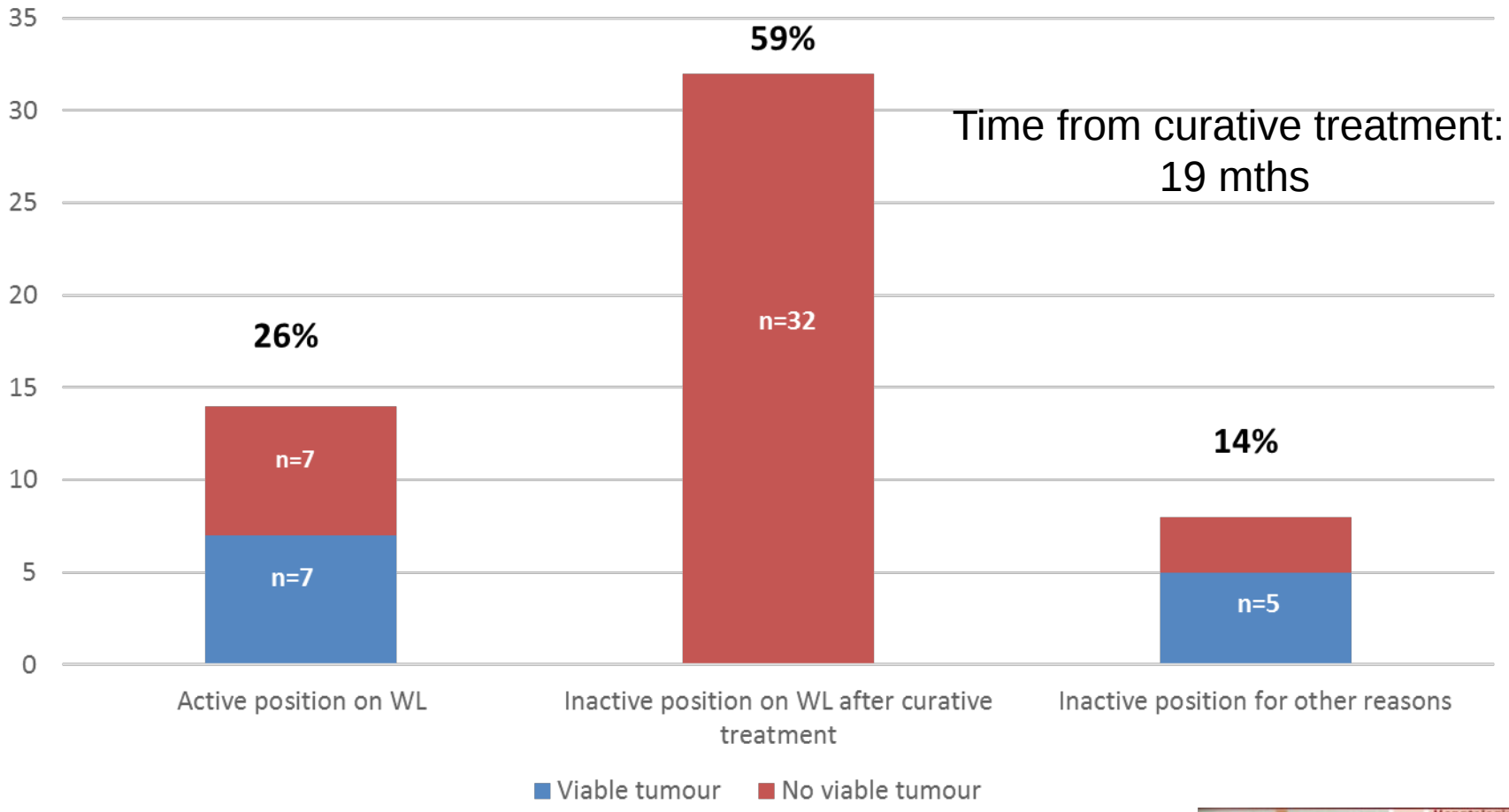
UCSF Transplant

Mehta N, et al. Liver Transpl 2013;19:1343-1353

ABM HCC working group: general principles
New rules adopted nationally by July 2015



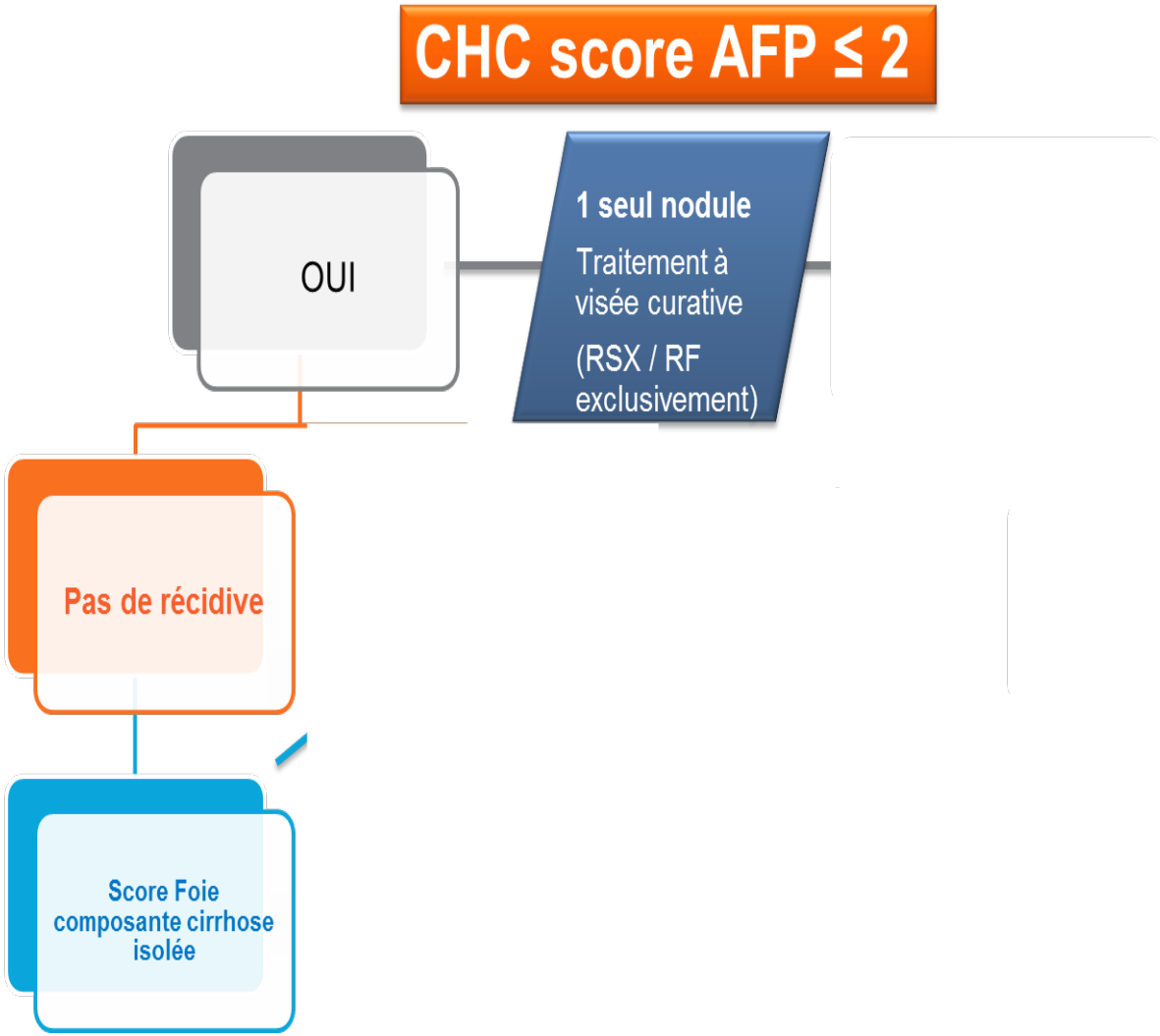
Features of 54 HCC patients listed at Henri Mondor Hospital on 09/27/2016



Take home messages

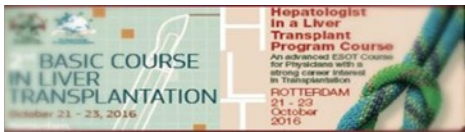
- A reasonable, controlled expansion of HCC criteria is feasible by taking into account biological behavior of the tumour together with size and number
- The increasing HCC burden impacts the risk of death of de-compensated patients with medium MELD score and deserves refinement of current allocation rules.
- Mathematical models are imperfect to refine allocation
- Pragmatic ablate/resect and wait strategy and increasing utility in HCC allocation may be an option which deserves prospective evaluation and is currently implemented in France.

METHODE : algorithme de priorisation d'accès à la greffe des nouveaux inscrits pour CHC en fonction la réponse au traitement d'attente



Additional rules

- **Standardization of contra-indications to resection, TA, TACE**
  - ➔ **HCC/ABM + SIAD working groups**
- **Standardization of HCC imaging evaluation**
  - ➔ **SIAD working group** (réunions du 9 07 2013 et 28 01 2014)
- **Mandatory 3-month report of imaging features** (specific file) transfered to OSO
- **Information on bridging therapies during the waiting phase** (specific file)
- **Prospective evaluation of the performance of the system**
  - ➔ **Applicability**
  - ➔ **Drop out for progression to AFP score >2**



Les zones grisées doivent être renseignées pour compléter le formulaire CHC CRISTAL

Nom : H. | Prénom : Jacques | Date de Naissance / Age : 22/05/56 60,3 | Sexe : M

Cause(s) de l'hépatopathie : Alcool | si autre, préciser : | Fibrose : F4 | Groupe : A

Caractéristiques tumorales avant tout traitement

Centre de Référence | Date Diagnostic : 10/09/15

- Nombre de nodules typiques
- Localisation (segment)
- Diamètre (cm)
- Preuve histologique
- α Fproteine (ng/ml-Date)
- Score aFP
- Nombre de nodulor atypiquor
- Localisation (segment)
- Diamètre (cm)

Envahissement biliaire
Envahissement vasculaire
Métastases
MELD
CHILD

Traitement (1) | Segment | Date Tt:
Traitement (2) | Segment | DateTt :

Caractéristiques tumorales et autres traitements avant inscription

Date :

- Nombre de nodules typiques actifs
- Localisation (segment)
- Diamètre RECIST (cm)
- Diamètre mRECIST (cm)
- Alpha Foeto Proteine
- Score aFP
- Nombre de nodulor atypiquor
- Localisation (segment)
- Diamètre (cm)

Envahissement biliaire
Envahissement vasculaire
Métastases
MELD
CHILD

Traitement (3) | Segment | Date Tt :
Traitement (4) | Segment | Date Tt:

Caractéristiques tumorales et autres traitements avant inscription

Date :

- Nombre de nodules typiques actifs
- Localisation (segment)
- Diamètre RECIST (cm)
- Diamètre mRECIST (cm)
- Alpha Foeto Proteine
- Score aFP
- Nombre de nodulor atypiquor
- Localisation (segment)
- Diamètre (cm)

Envahissement biliaire
Envahissement vasculaire
Métastases
MELD
CHILD

Traitement (5) | Segment | Date Tt :
Traitement (6) | Segment | Date Tt:

Caracteristiques tumorales à l'inscription

Date Inscription :

- Nombre de nodules typiques actifs
- Localisation (segment)
- Diamètre RECIST (cm)
- Diamètre mRECIST (cm)
- α Fproteine (ng/ml-Date)
- Score aFP
- Nombre de nodulor atypiquor
- Ø du plus gros nodulo atypiquor (cm)

Envahissement biliaire
Envahissement vasculaire
Métastases
MELD
CHILD
NEFG

Traitements d'attente / Down staging

Traitement (1) | Segment :
Date Tt :
Traitement (2) | Segment :
Date Tt :

Transplantation dans score aFP

Indication de transplantation
Projet thérapeutique
Date récidive
Délai récidive/ Tt curatif (mois)
Date RCP :

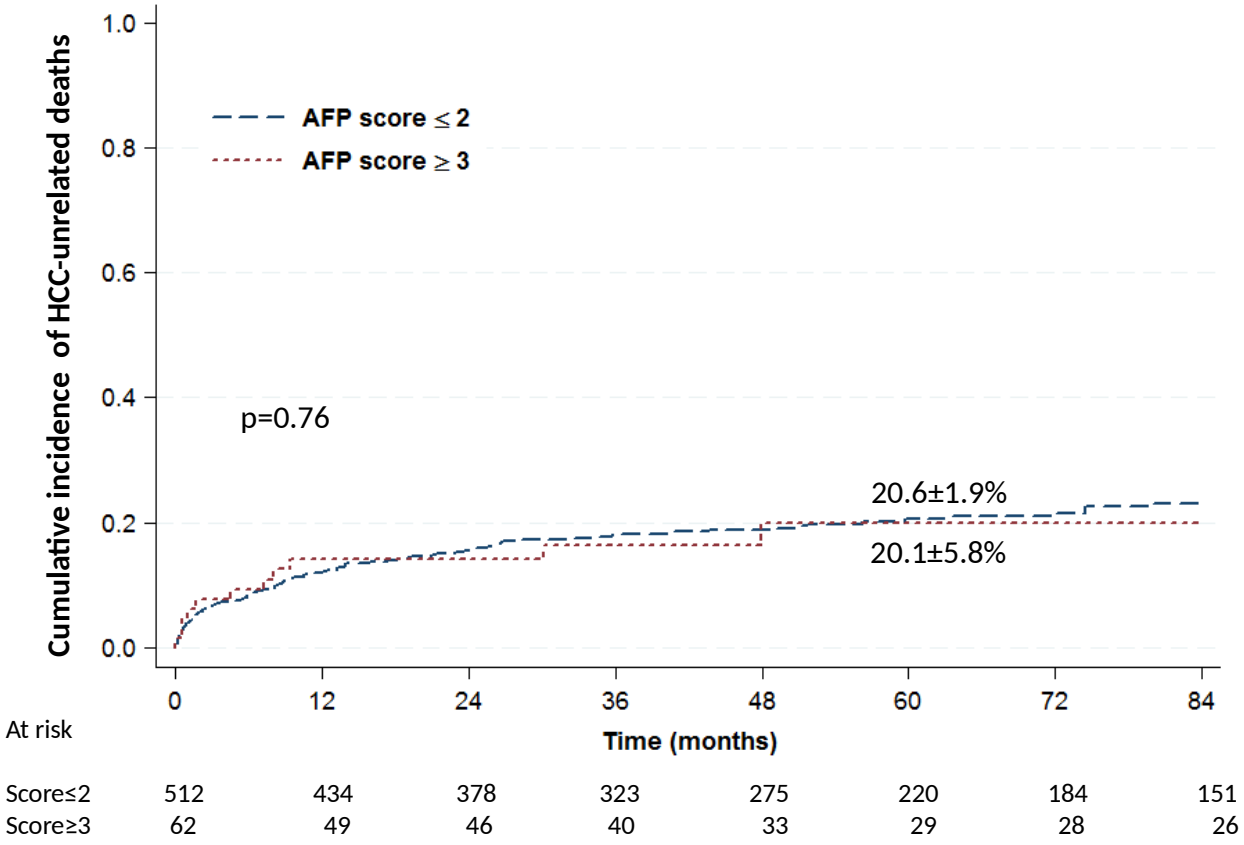
Transplantation hors score aFP

Indication de transplantation
Projet thérapeutique
Date RCP :

Composante expert CHC non traitable | Date :
Composante Récidive CHC | Date :

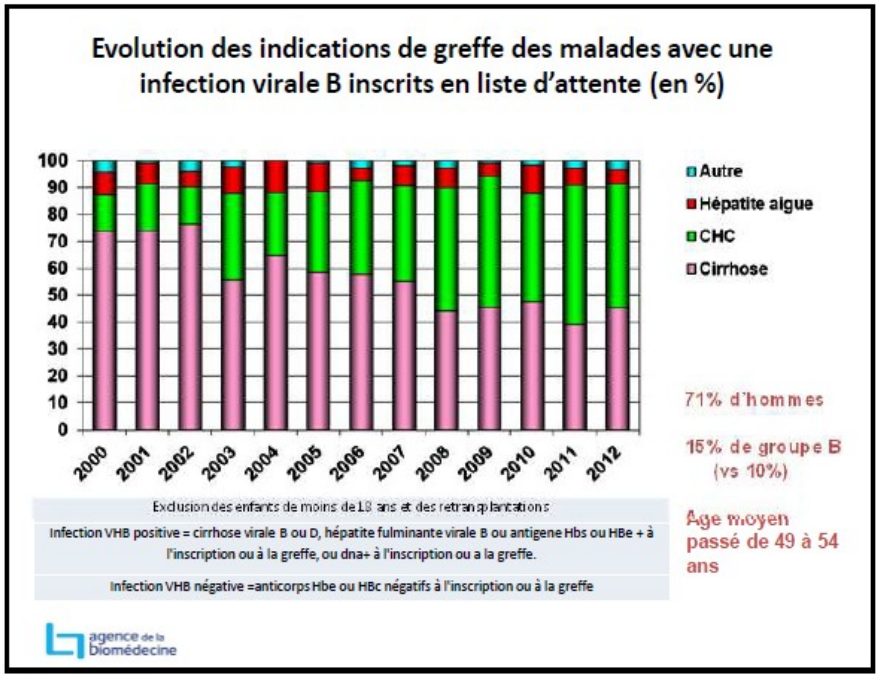
Statut sur liste

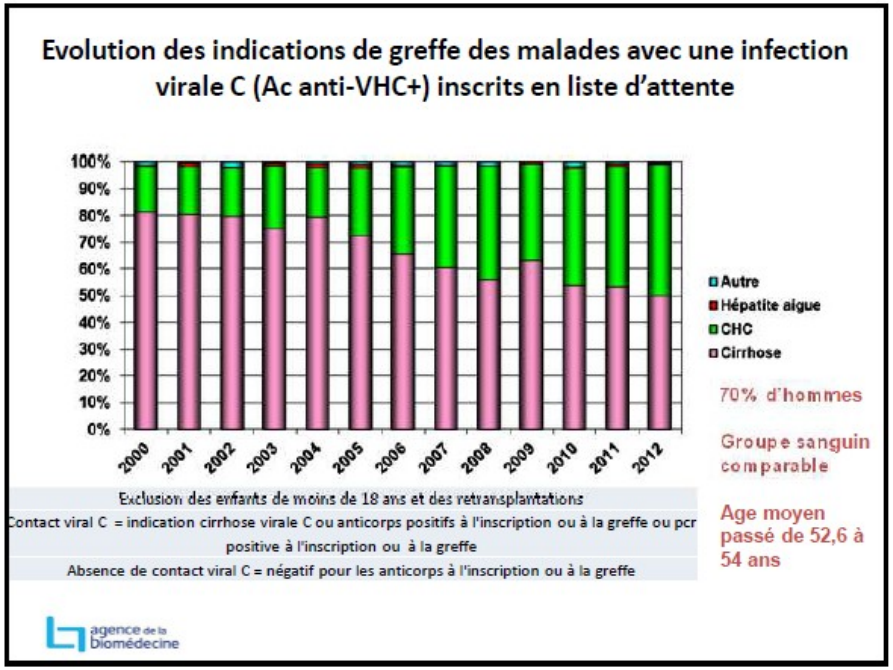
Non HCC related deaths by competing analysis



Notarpaolo et al. J Hep Accepted for publication

Proportion of HBV and HCV candidates listed for ESLD vs HCC in France over time

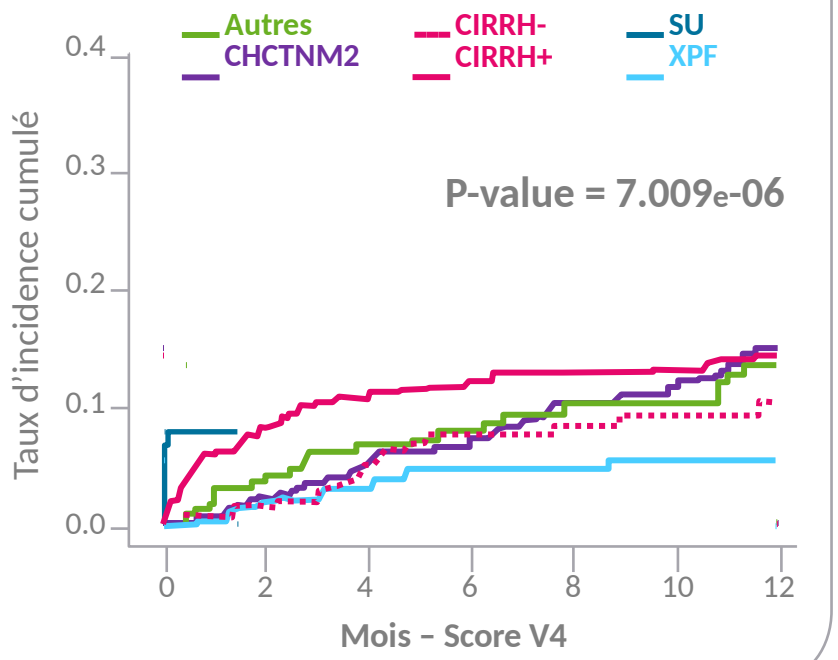




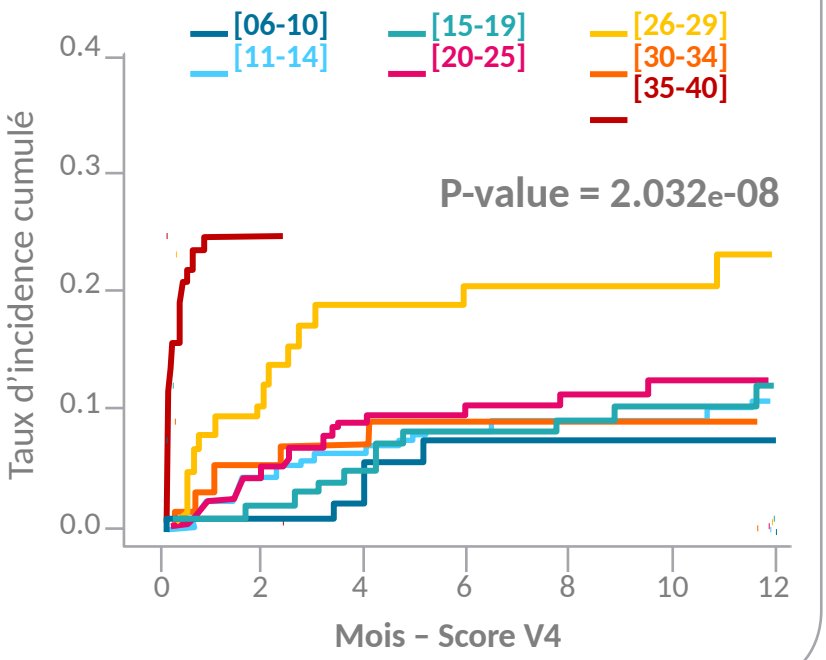
Limites du système

La compétition CHC / cirrhose et le risque de sortie de liste pour aggravation

Décès et retrait de liste pour aggravation selon la maladie initiale



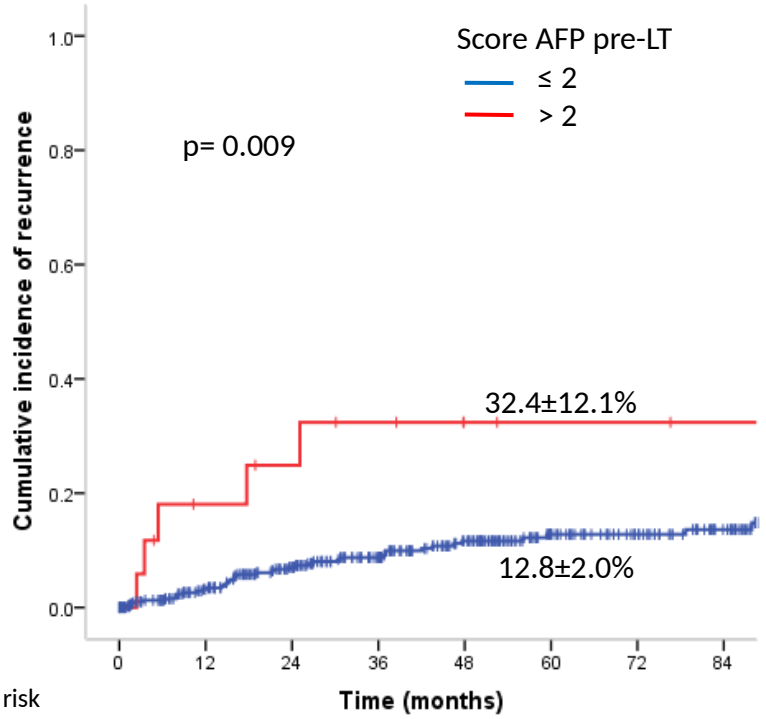
Décès et retrait de liste pour aggravation selon le MELD (inscription) : CIRRH



→ **Probabilité de sortie de liste pour décès ou aggravation des cirrhoses décompensées**

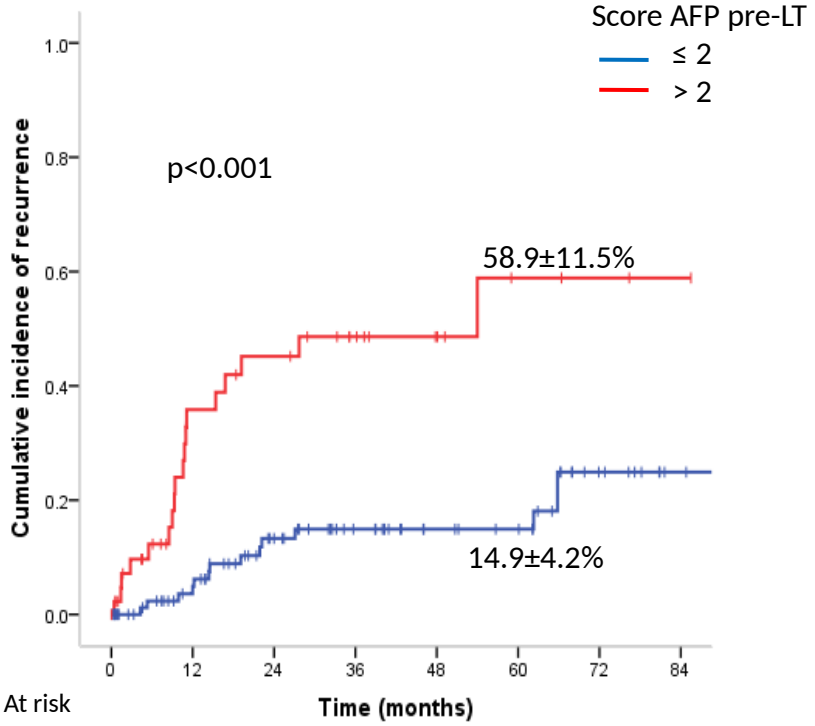
AFP model in a HCV/HBV based population

A. Patients within Milan criteria



At risk								
Score≤2	415	345	289	241	195	142	116	89
Score≥3	17	12	10	8	5	4	4	3

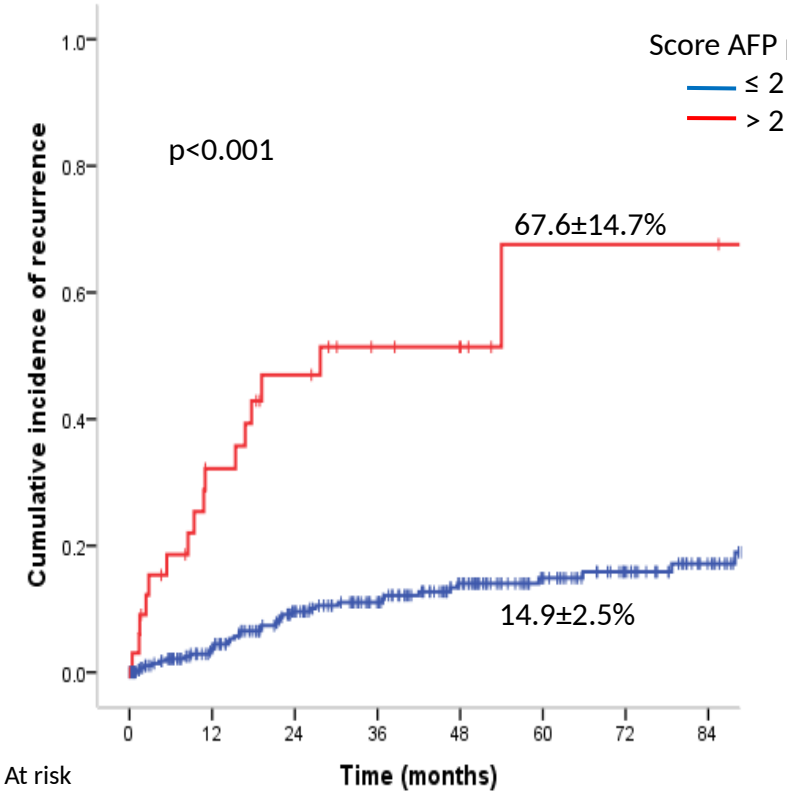
B. Patients beyond Milan criteria



At risk									At risk
Score≤2	97	75	56	43	33	30	16	9	Score≤2
Score≥3	45	21	17	11	7	3	2	1	Score≥3

HCV population

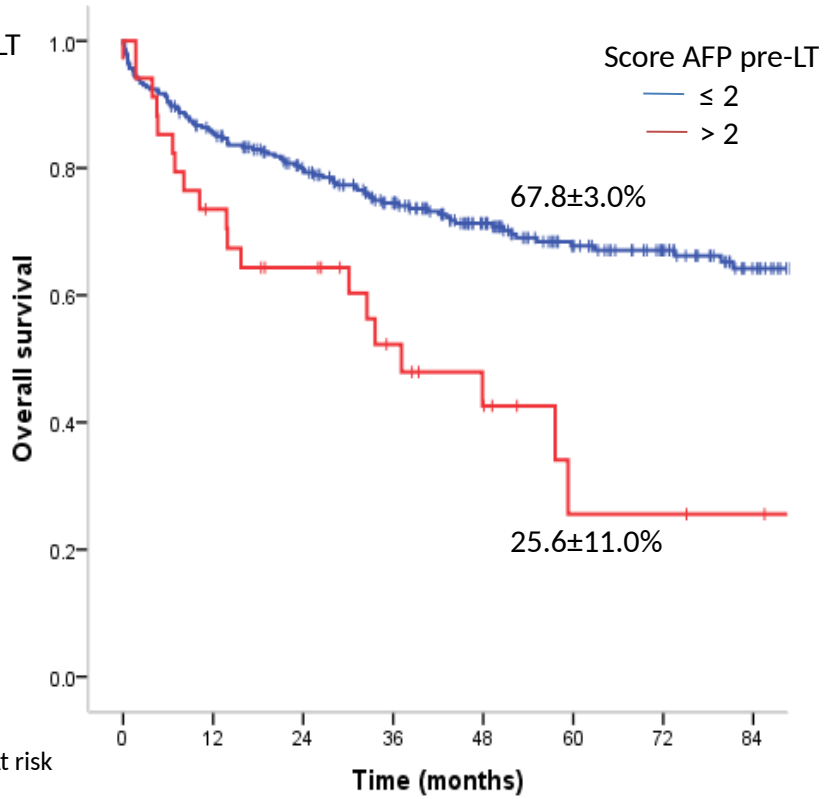
A- recurrence



At risk

Score≤2	303	245	198	166	130	97	77	54
Score≥3	34	19	13	8	6	2	2	2

B-Overall survival



At risk

Score≤2	302	252	215	176	137	102	83	58
Score≥3	34	24	19	12	8	3	4	2

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