Liver Transplantation for Hepatocellular Carcinoma: which model ?

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For the Agence de la Biomédecine HCC working group

Outline

- Background : the issue of Milan criteria and the 2010 HCC consensus conference
- HCC and expanded criteria
- Genesis of the AFP score
- AFP score : current position
- Perspectives

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.**

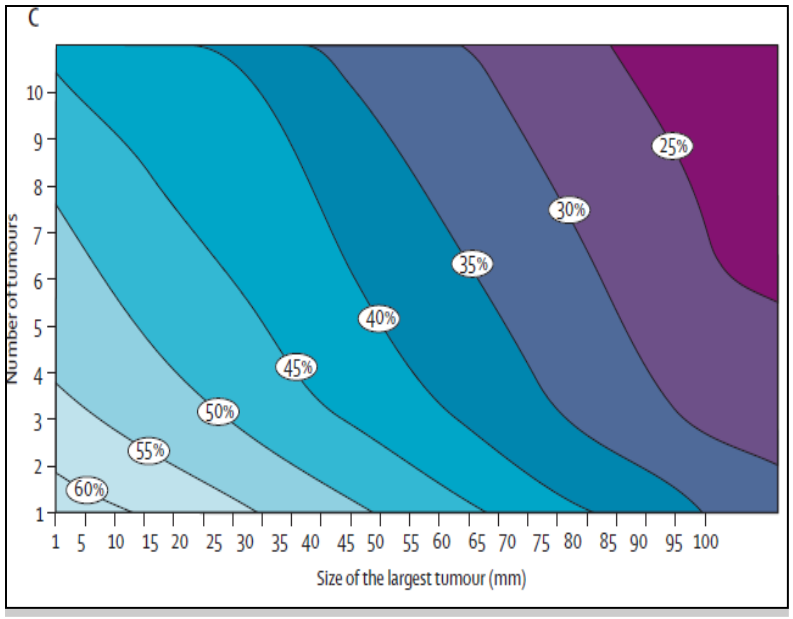
→ **"As evidence accumulated of good outcomes in some patients outside the Milan criteria, there was a drive to identify expanded criteria and to increase the number of eligible candidates for liver transplantation".**

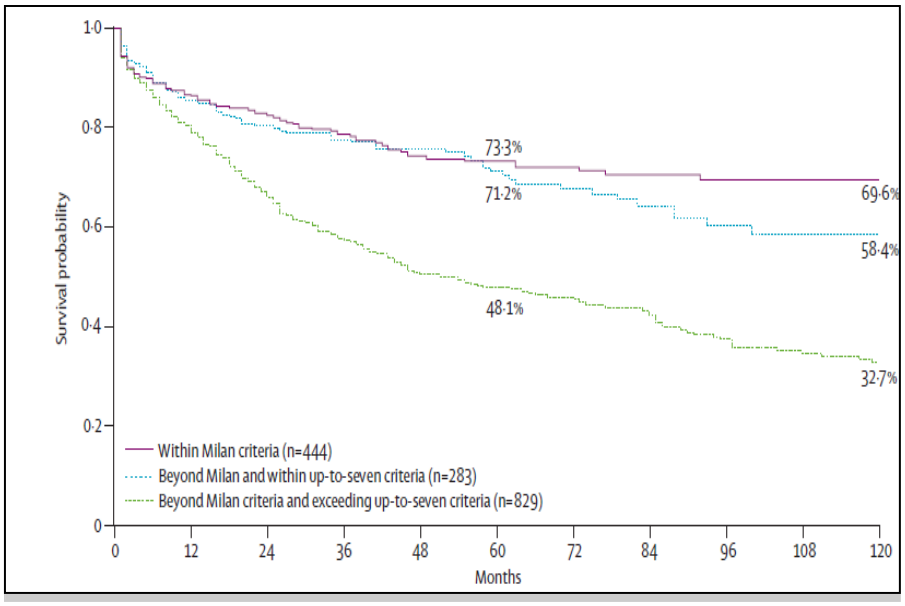
- **Recommendation 10: a modest expansion of the number of potential candidates may be considered on the basis of several studies showing comparable survival for patients outside the Milan criteria**

Expanded criteria in the litterature

Criteria	Ref	LT period	Median follow-up (mnths)	N pts with extended criteria (%)	5-yr recurrence Milan+ / Milan- extended +	5-yr survival Milan+ / Milan- extended +
UCSF : 1 lesion ≤ 6,5 cm ou 2-3 tumours ≤ 4,5 cm et sum of diam ≤ 8 cm	Yao et al.	88-00	24	ND	11,4%	75%
	Yao et al.	01-06	26	38 (22%)	9,1/ 6,4%	80%/82%
Canada : 1 tumour ≤ 7,5 cm ou multiple ≤ 5 cm	Kneteman et al.	96-04	ND	21 (52%)	5% / nd (à 4 ans)	85 / 83% (à 4 ans)
Kyoto : ≤ 10 tumours, ≤ 5 cm et PIVKA-II ≤ 400mAU/ml	Ito et al.	99-06	29	30 (30%)	9,7 / 7,3%	86,7% / ND
CUN : 1 tumour ≤ 6 cm ou 2-3 tumours ≤ 5 cm	Herrero et al.	91-05	ND	26 (35%)	4 / 0%	70 / 73% (68% ITT)
Dallas : 1 tumour ≤ 6 cm ou 2-4 tumours ≤ 5 cm	Onaca et al.	92-05	74	138 (18%)	NA/NA	61% / NA
5-5 : ≤ 5 tumours ≤ 5 cm	Duvoux et al.	88-98	55	62 (18%)	20 / 24%	60 / 55,1%
	Badran et al.	99-01	53	35 (20%)	8,9 / 11,6%	80 / 79,5%

The issue of the expanded criteria…





Up to 7 : Number of tumors + diameter in cm ≤ 7

→ From the the explant pathology in 1566 patients

Mazzaferro et al. Lancet Oncol 2009

However

- Those criteria had been derived from explant pathology
- Primary end-point: survival
- Applicability/translation to pre LT imaging was rarely studied nor validated prospectively
- Non consensus had been achieved on which criteria should be used

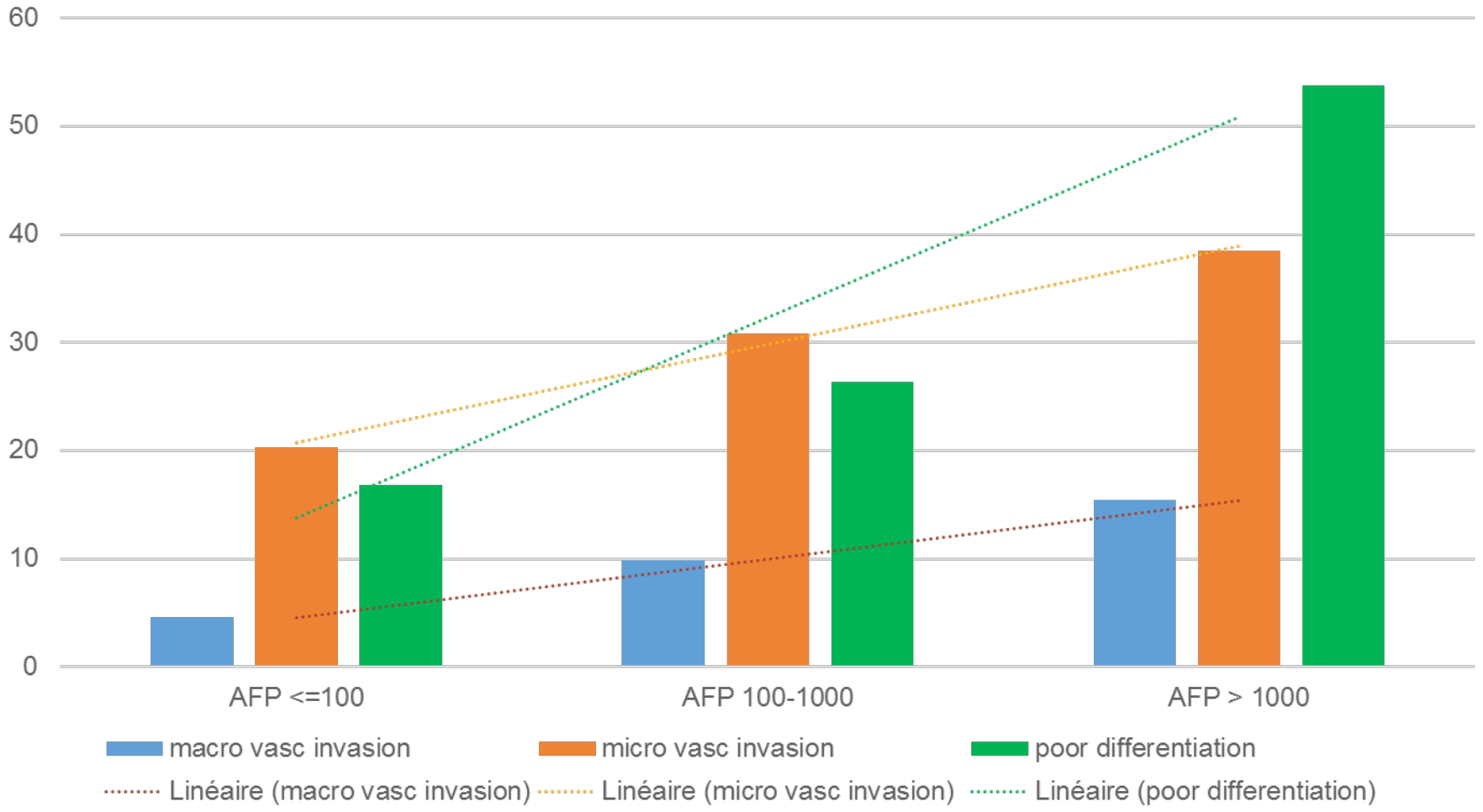
The issue of Alfa Foeto Protein…

Decaens et al. Liver International 2011

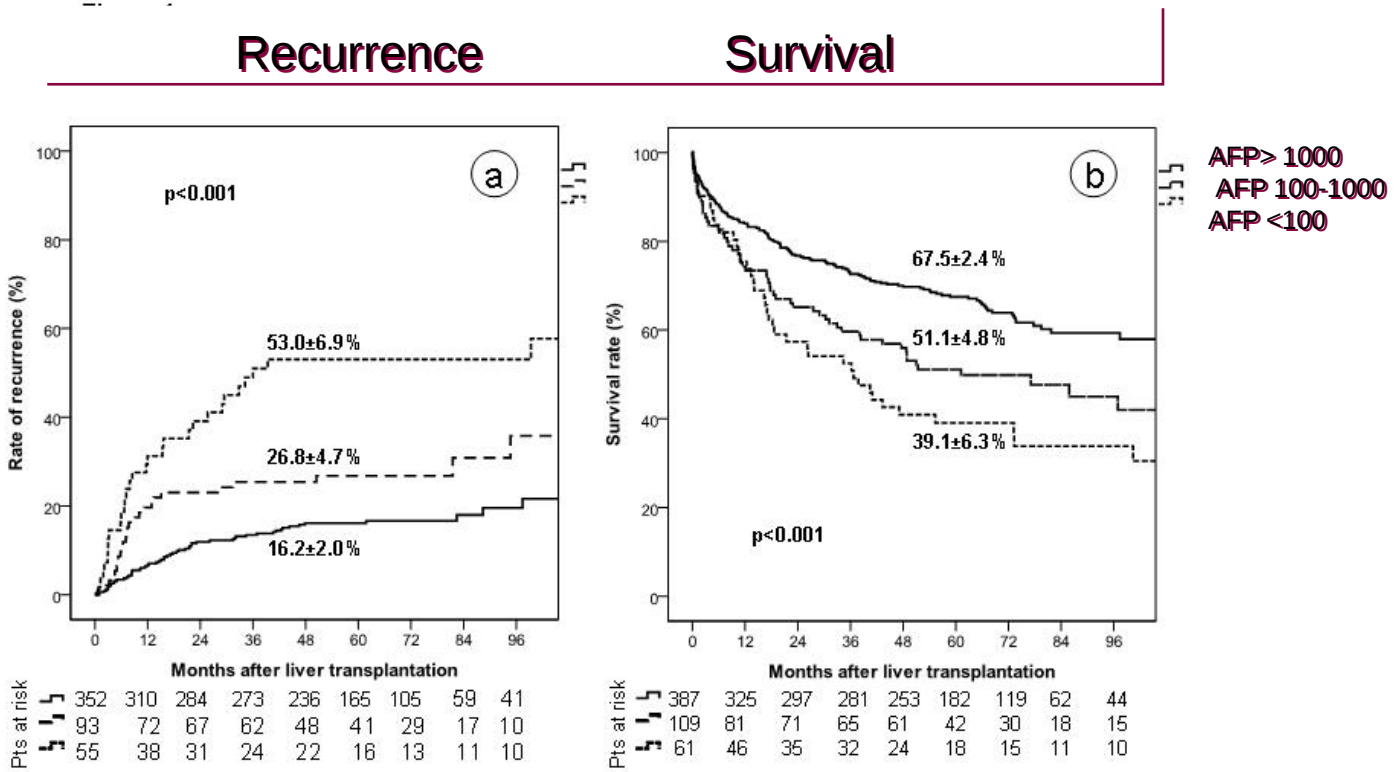
Facteurs associated with recurrence in uni variate analysis

α-FP (ng/ml)		
≤ 200	65.7	
200–2000	52.7	0.0002
> 2000	31.4	
Prothrombin time		
< 60%	39.3	
≥ 60%	57.4	0.04
Alkalin phosphatase		
Normal (157)	61.7	
1–2 N (129)	65.6	0.05
> 2N (51)	44.7	
Pre- or post-LT treatment for HCC		
No (117)	52.0	
Yes (251)	64.2	0.005
Number of nodules		
1 (213)	60.7	
2 or 3 (127)	61.1	0.025
4 or more (29)	51.7	
Maximal diameter of the largest nodule		
≤ 2 cm (86)	75.5	
2–3 cm (97)	68.2	
3–5 cm (114)	59.1	< 0.0001
> 5 cm (68)	35.3	

Relationship between AFP and pathological features of the explant



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



Duvoux et al. Gastroenterology 2012

GASTROENTEROLOGY 2012;143:986–994

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

- **Retrospective cohort of 597 pts transplanted for HCC between 1988 and 2001 in 16 French Centres (> Milan : 32%)**

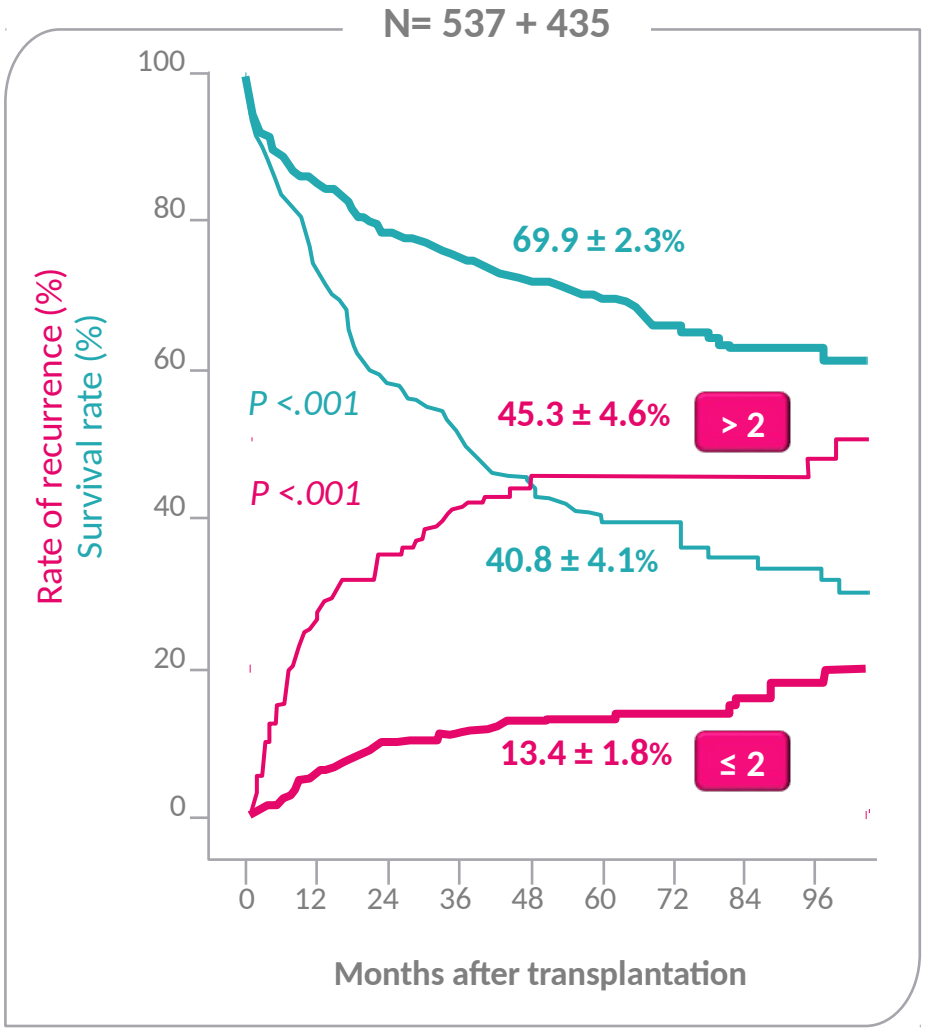
→ **Uni- and multivariate analysis for predictors of recurrence**
→ **Design of predictive model of recurrence**
→ **Design of a simplified, user-friendly version of the model**
→ **Comparison against Milan criteria**

→ **Validation in a cohort of 435 pts transplanted in 20 French centres between 2003 and 2005 and followed prospectively for 5 yrs under the control of the French OSO, Agence de la Biomédecine**

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.

The AFP model improves performances of Milan criteria

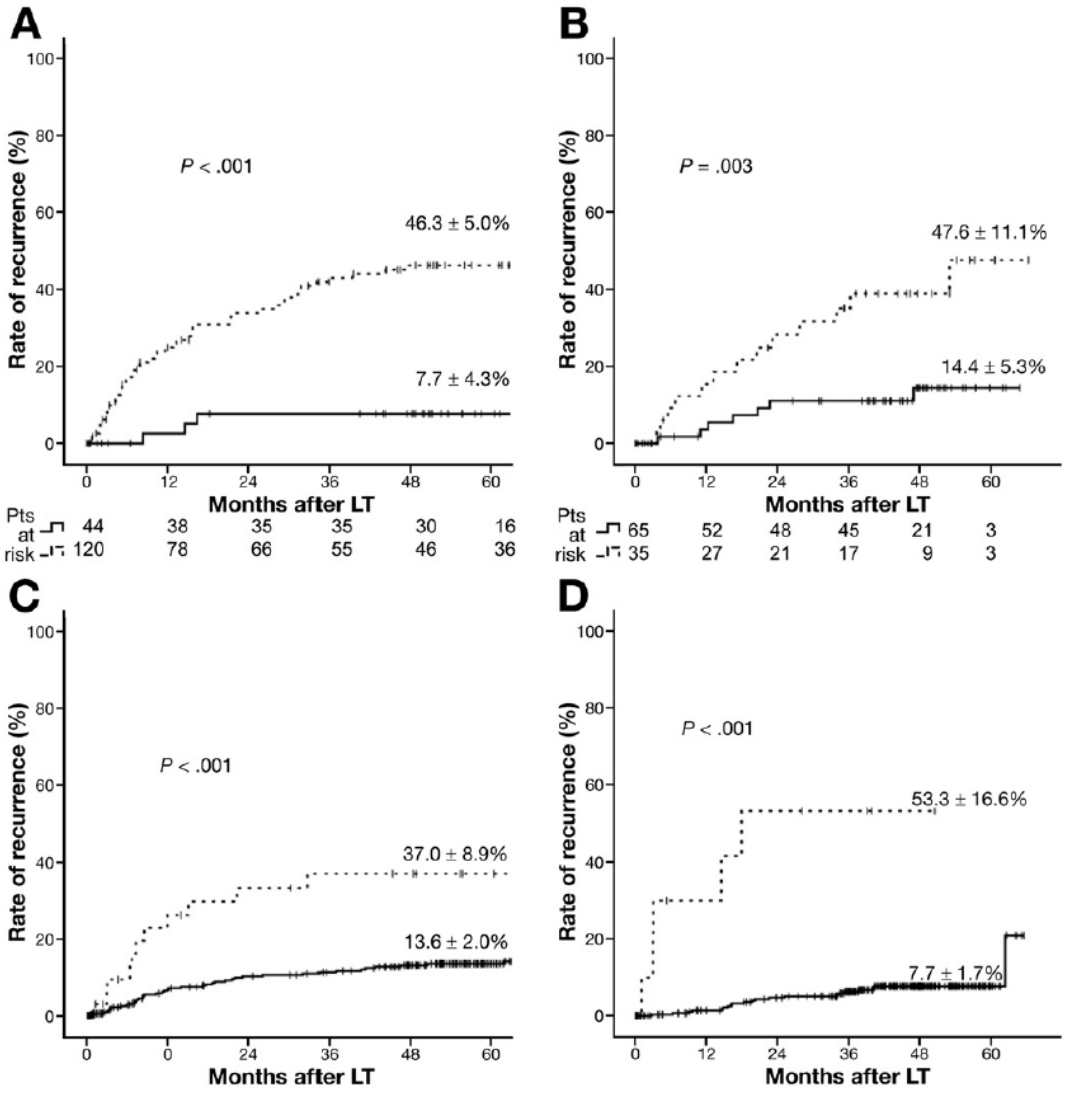
Score : 0 to 9 points
Cut-off value : 2

→Two different prognostic groups

Score ≤ 2 : low risk patients → Beyond Milan criteria
2 to 3 nod, ≤ 6 cm, AFP ≤ 100
≥ 4 nod, ≤ 3 cm, AFP ≤ 100

Score ≥ 3 : high risk patients → Within Milan criteria
3 nod, ≤ 3 cm, AFP > 1000
1 nod 3-5 cm , AFP 100-1000

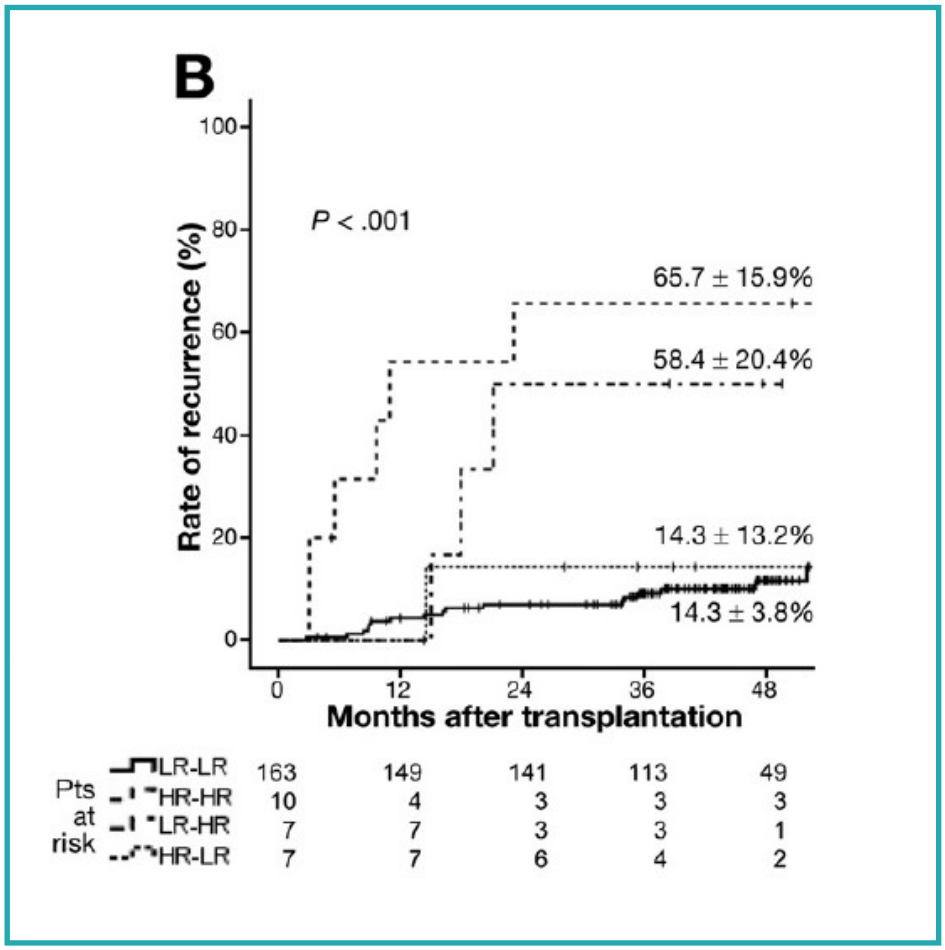
Recurrence rates in patients exceeding or within Milan criteria according to the cut off 2 in training (A) and validation (B) cohorts



Exceeding Milan

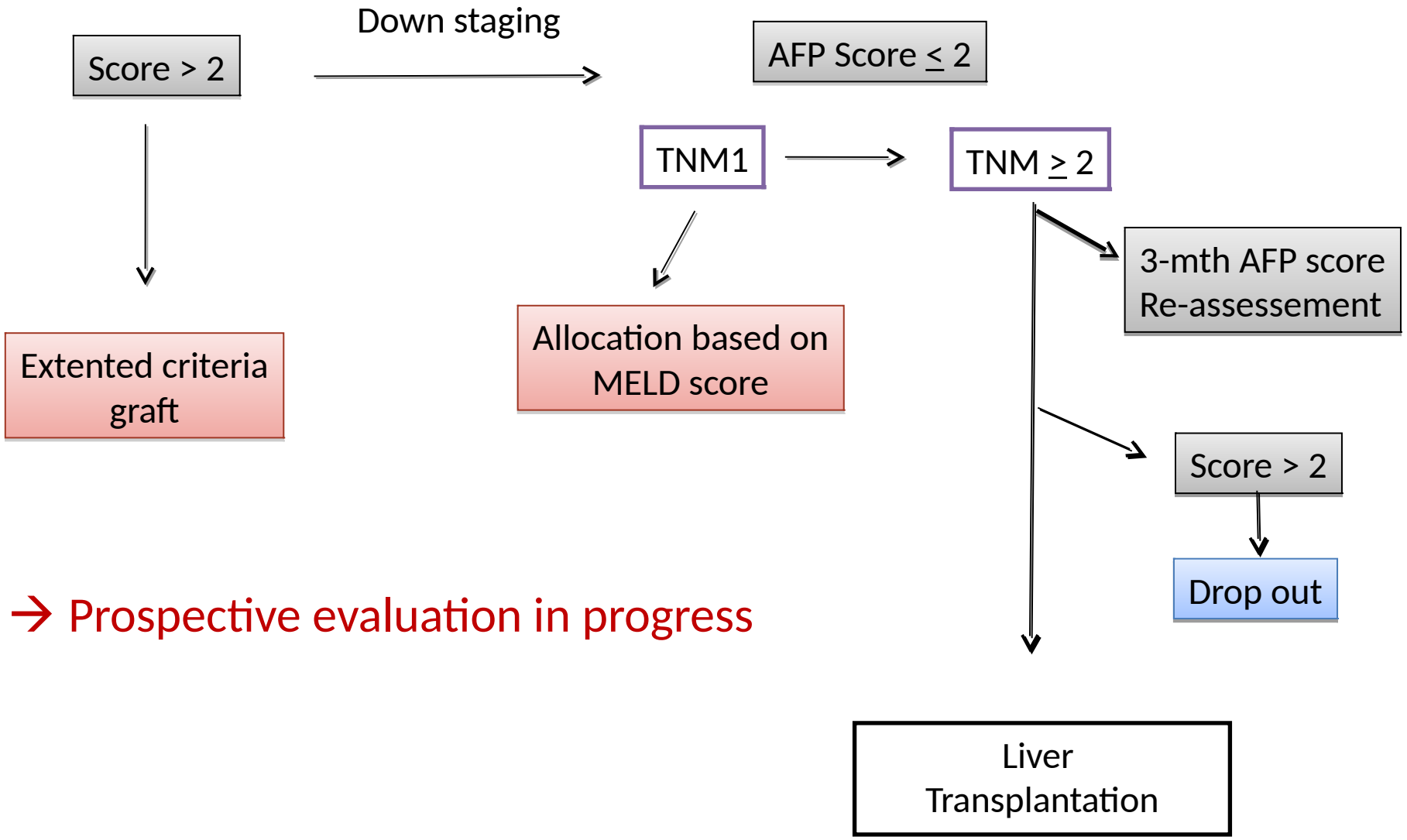
Within Milan

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)

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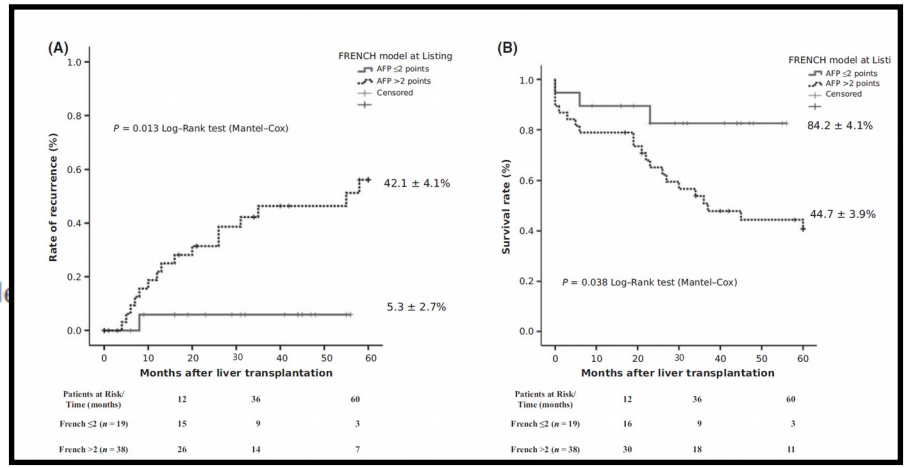
2 Hospital de Clinicas, State University of Campinas, Campinas, Brazil
3 Hospital Pablo Tobón Uribe, Medellin, Colombia
4 Universidad de Antioquía, Medellin, Colombia
5 Hospital Italiano from Buenos Aires, Buenos Aires, Argentina
6 Fundación Cardioinfantil, Instituto de Cardiología, Bogotá, Colombia
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

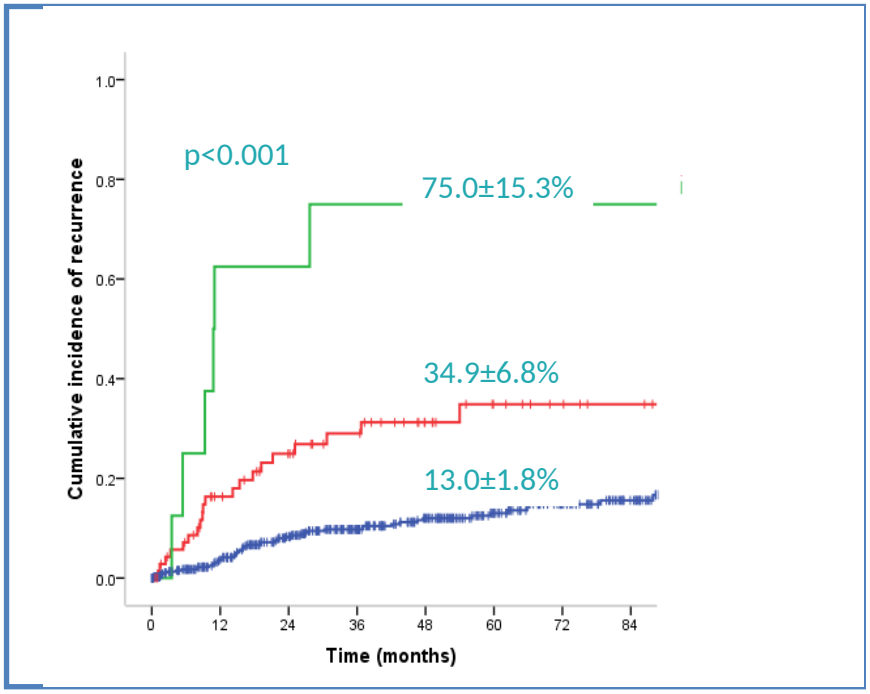


Patients beyond Milan criteria

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]

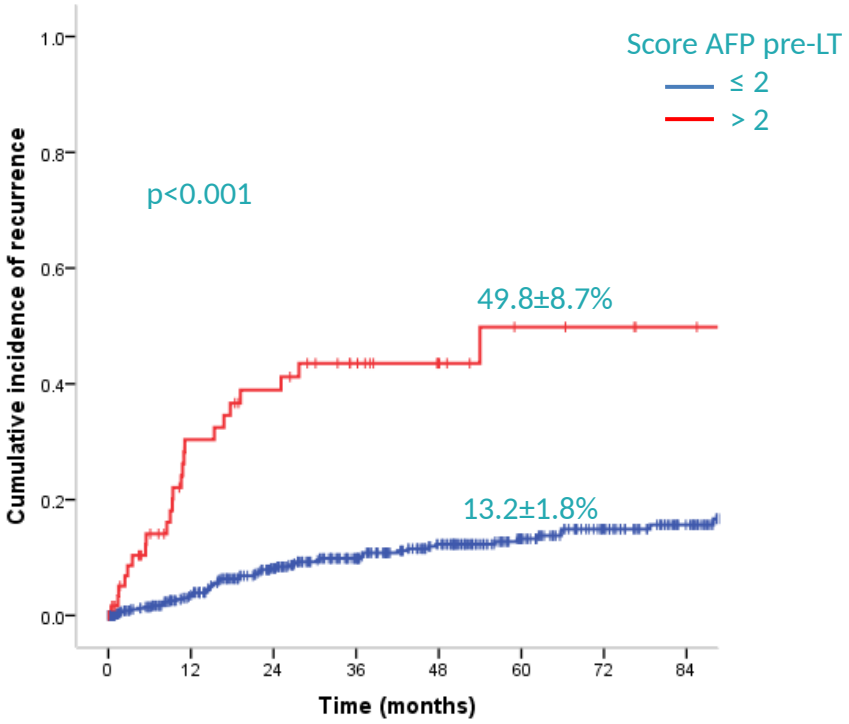
Recurrence according pre AFP cut-off



J Hep accepted for publication

Recurrence and survival in the whole population according to AFP score

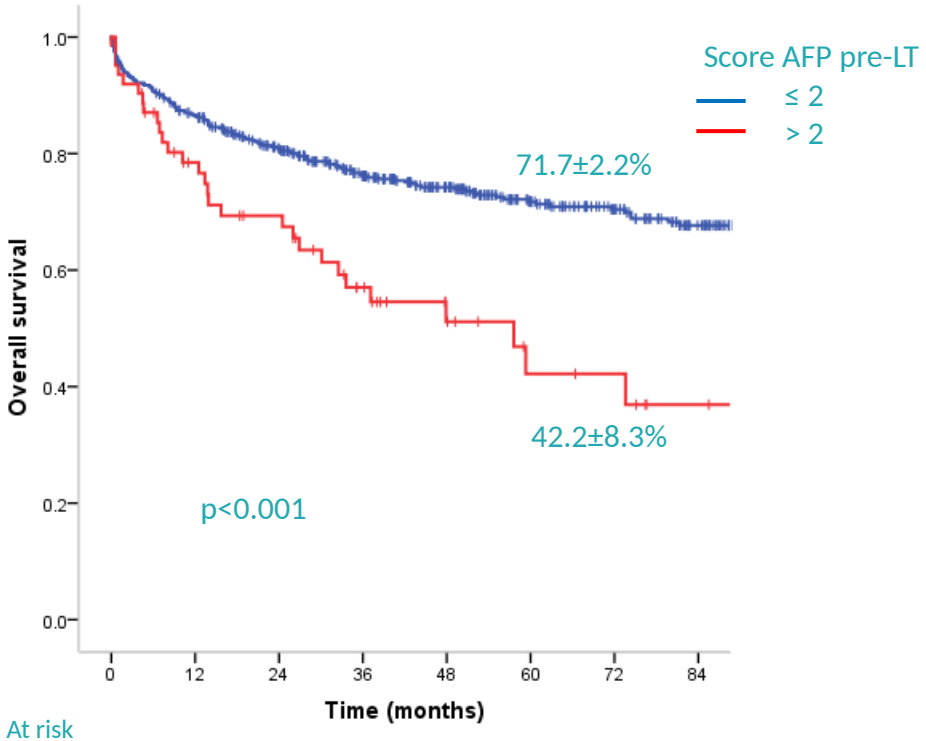
A



At risk

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

B

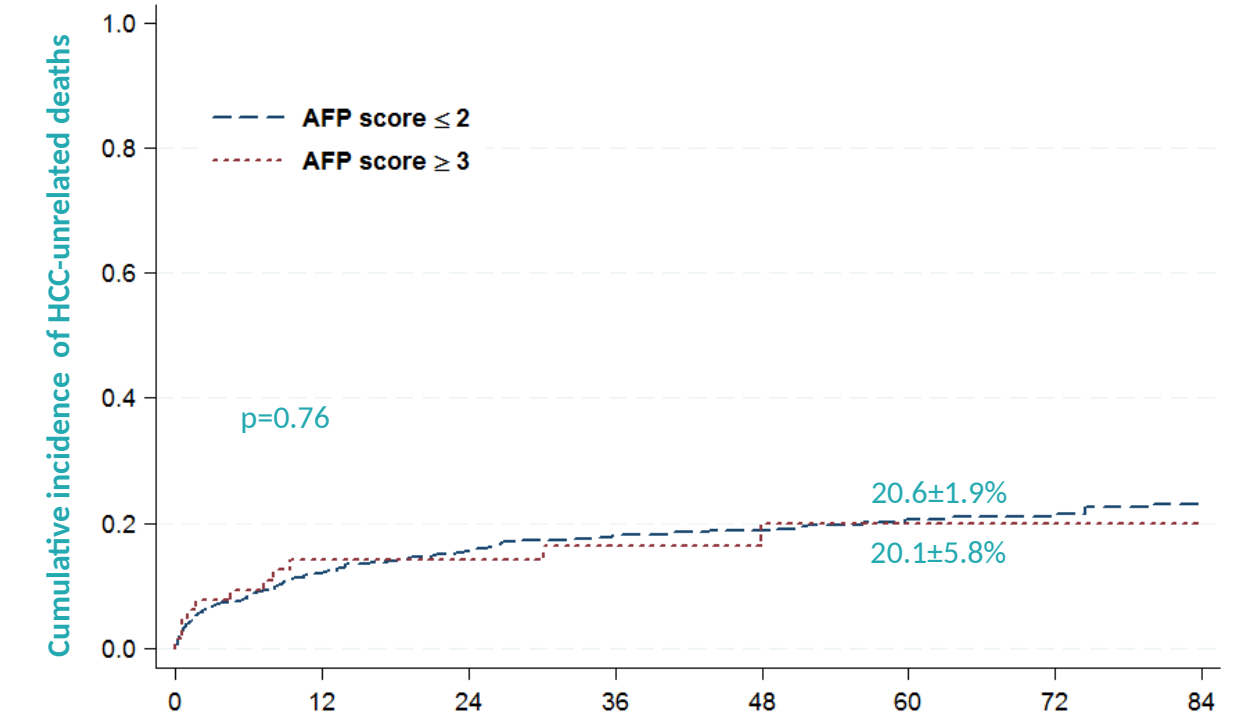


At risk

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

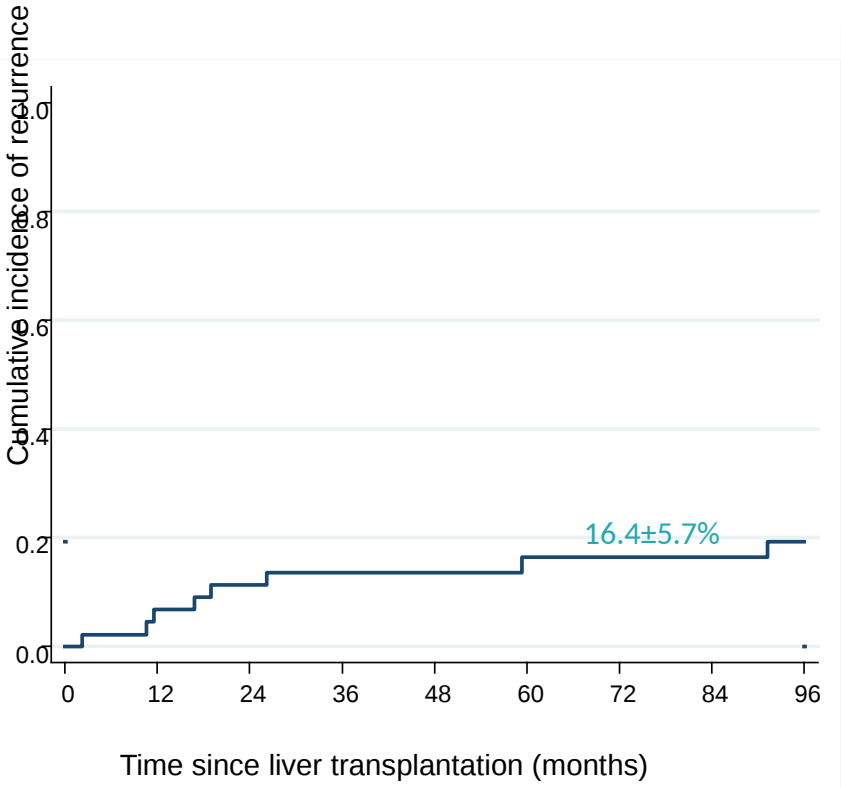
Notarpaolo et al. J Hep Accepted for publication

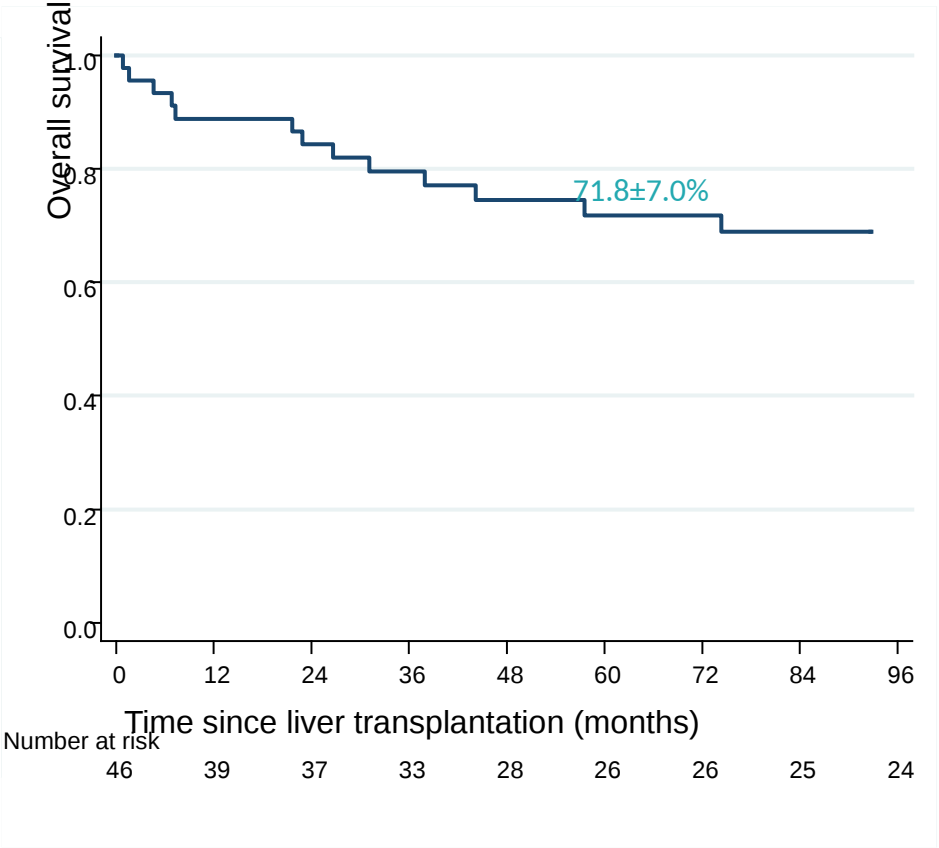
Non HCC related deaths: Competing risk analysis



Notarpaolo et al. J Hep Accepted for publication

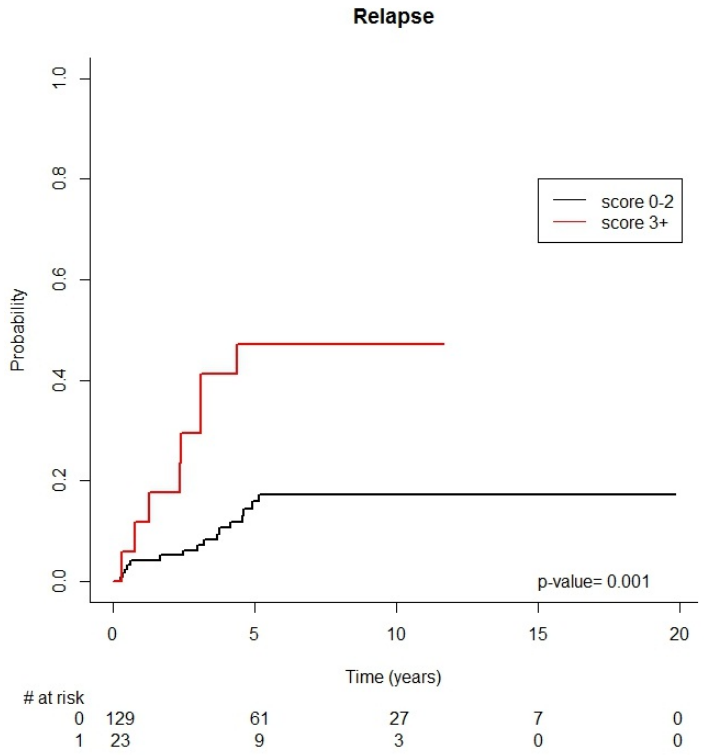
Recurrence and survival in 46 patients undergoing successful Down staging from AFP score > 2 (3) to ≤ 2 (0)

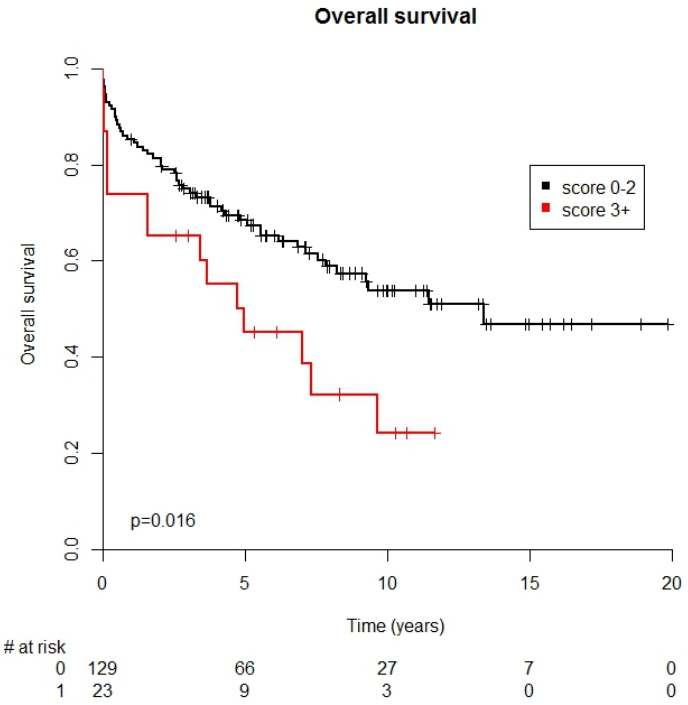




Notarpaolo et al. J Hep accepted for publication

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

JUST TRY IT ☺

Perspectives

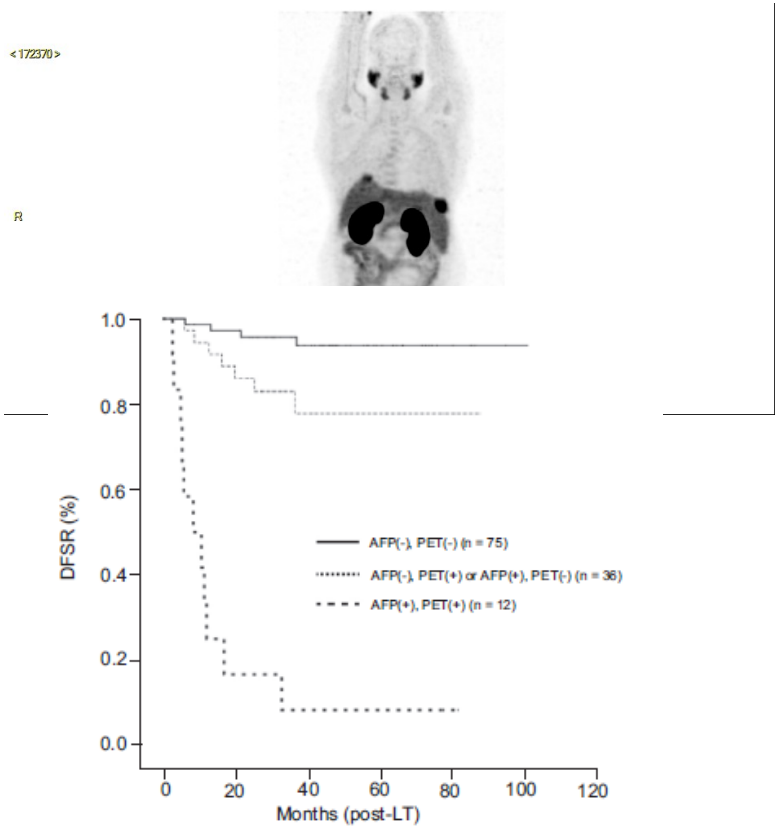
- Website → AFP model on line
- Promotion of AFP model throughout Europe : Euro-transplant 2017
- Better identification of patients who not recur although with AFP score > 2
  - Toward AFP score 2.0 : pooled data from the French and Italian cohort and refinement of tumour size, number and AFP threshold
  - Functional imaging ?
  - Molecular signatures ?

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

Limitations of Milan criteria

Milan criteria are comfortable
for the transplantation team
But not for the liver transplantation candidate !

Duvoux et al; SFT 2006. ILTS 2007