

MÁSTER EN HEPATOLOGÍA

UAM
Universidad Autónoma
de Madrid

 Universidad
de Alcalá

Asignatura: Cirrosis Hepática III

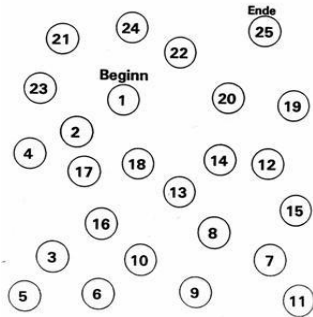
RELEVANCIA DE LA ENCEFALOPATÍA HEPÁTICA MÍNIMA. IMPACTO EN LA PROGRESIÓN DE LA CIRROSIS

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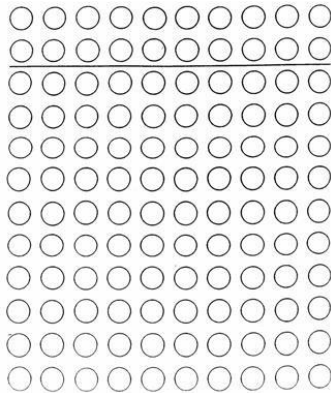
Useful tools in the management of Minimal Hepatic Encephalopathy

1. Psychometric Hepatic Encephalopathy Score (PHES)
2. Critical Flicker Frequency
3. Inhibitory Control Test
4. Stroop Test
5. Sickness Impact Profile
6. GLS mutations
7. Oral Glutamine Challenge

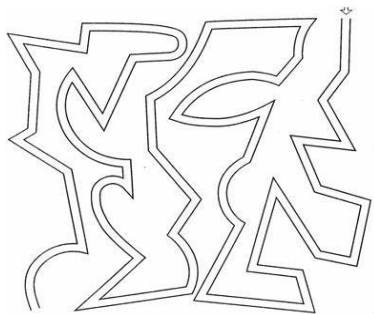
NCT A



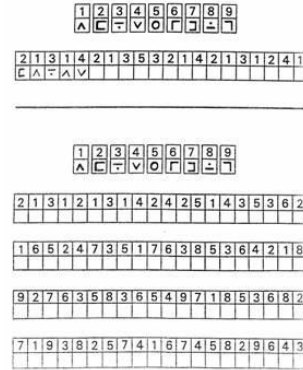
SERIAL DOTTING



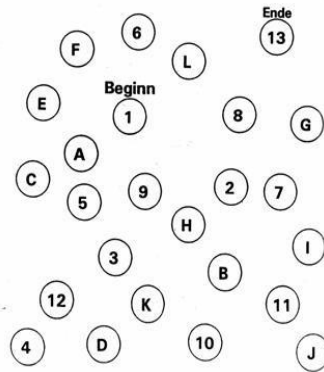
LINE TRACING TEST



DST



NCT B



Psychometric Hepatic Encephalopathy Score (PHES)

<http://www.redeh.org/>

DIAGNOSIS OF MINIMAL HEPATIC ENCEPHALOPATHY BY PSYCHOMETRIC TEST (PHES)

PSYCHOMETRIC HEPATIC ENCEPHALOPATHY SCORE

Patient Data		Psychometric Test	
Age	49	Digit symbol test (2)	53
Studies (1)	18	Number connection test-A (3)	32
		Number connection test-B (3)	65
		Serial dotting test (3)	19
		Line drawing test (4)	49

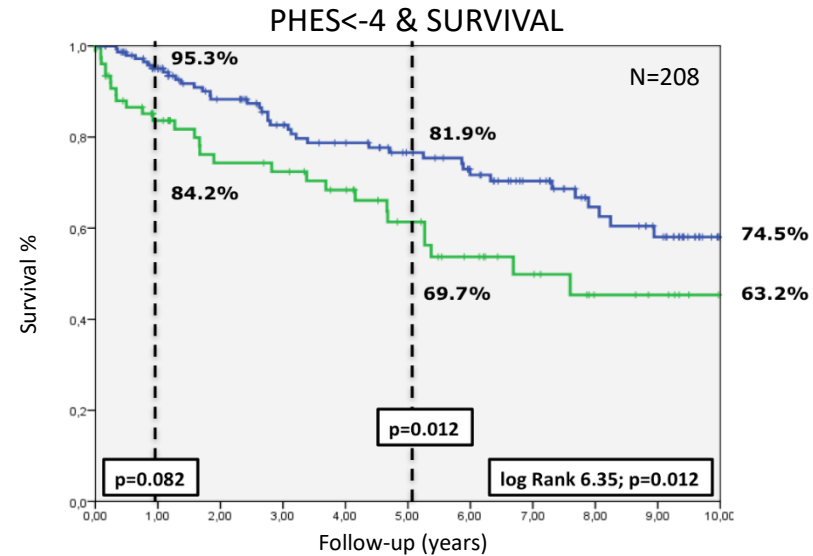
calculate

DIAGNOSIS OF MINIMAL HEPATIC ENCEPHALOPATHY BY PSICOMETRIC TEST (PHES)

	Expected result	Observed result	Parcial Puntuacion
Digit symbol test	50.42	53	0
Number connection test-A	28.634	32	0
Number connection test-B	72.02	65	0
Serial dotting test	49.888	19	1
Line drawing test	84.59	49	1

The resulting PHES puntuacion is 2 points, so the conclusion is "Patient WITHOUT MHE data" [New Score](#)

Romero-Gómez et al. Hepatology 2007



Ampuero et al. Gastroenterology 2015

Critical Flicker Frequency deciphering the spectrum of HE

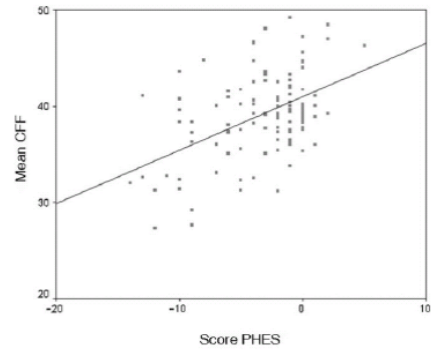
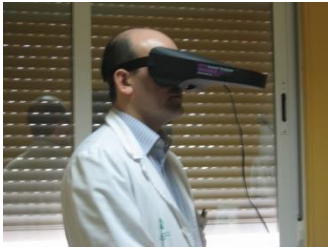


Fig. 1. Correlation between PHEs and mean CFF in patients with cirrhosis ($r = 0.54$; $P < 0.001$).

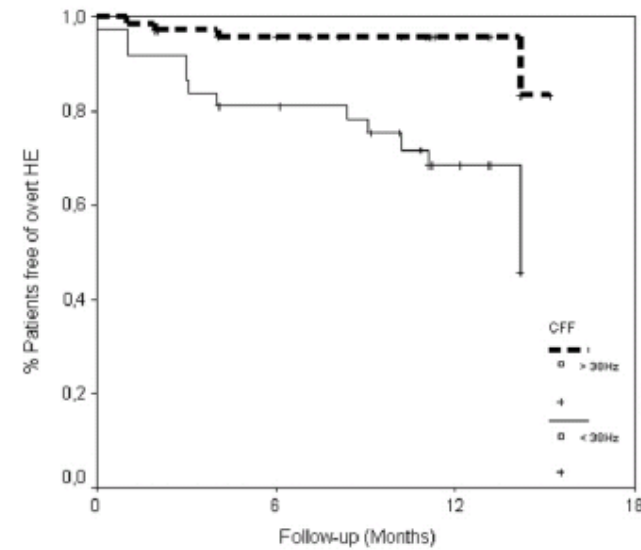
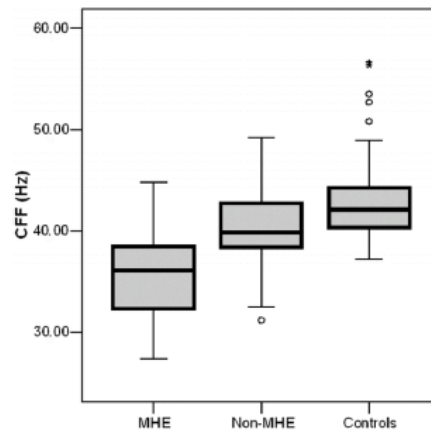
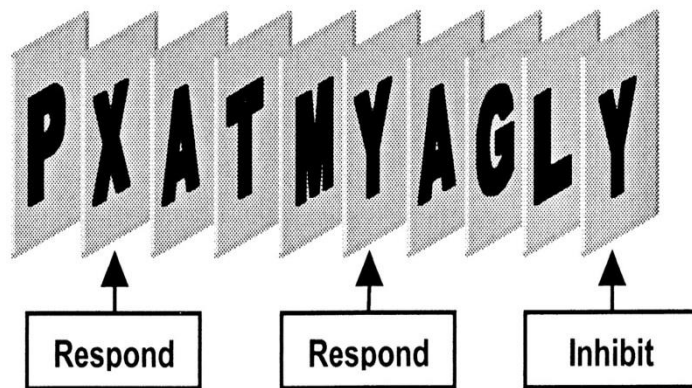
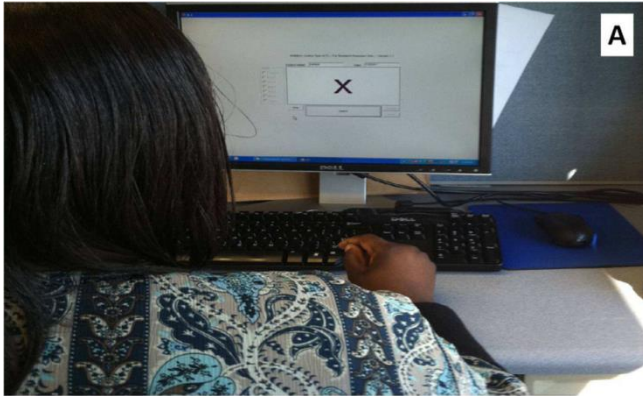


Fig. 4. Prediction of overt HE by CFF in patients with cirrhosis (log-rank 15.08; $P < 0.0001$).

Domains tested by ICT
Response inhibition
Sustained attention
Vigilance
Psychomotor speed



Inhibitory Control Test

Subject views computer screen on which one letter is flashed per 500 milliseconds.

“**Target**” : When X and Y are observed in an alternating fashion.

“**Lure**” : When X or Y are seen in a non-alternating fashion.

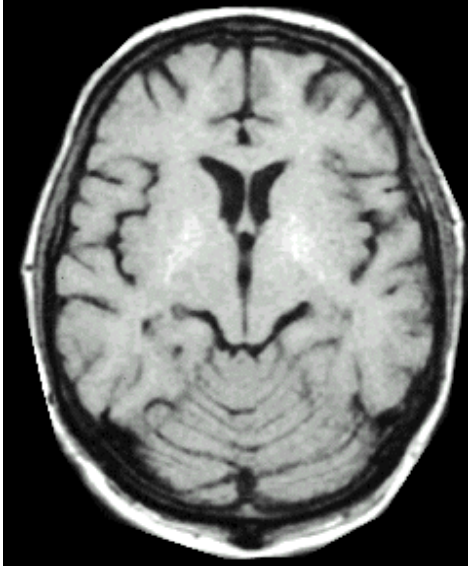
“**Inhibition**” : When subject can successfully stop from responding to lures.

ICT & HE	MHE negative (n=48)	MHE positive (n=87)
% response to LURES	9% (n=3)	28% (n=11)*
% response to TARGETS	97%	92%#
Lure reaction time (msec)	525±68	553±87#
Target reaction time (msec)	487±29	438±55#
	*P<0.0001	P<0.001#



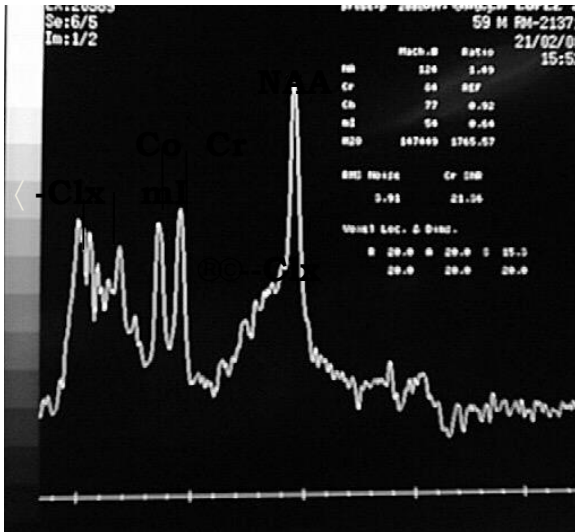
Magnetic Resonance: T1 hyperintensity

MR&HE



- Prevalence: 52-100%
- Related to liver dysfunction and porto-systemic shunts.
- Manganese deposits
- Parkinson's signs.

Magnetic Resonance spectroscopy



- Raised glutamine concentration and decreased myoinositol and choline peak.

Rose C. Gastro 1999;117:640-644; Spahr L. Gastro 2000;119:774-781; Inoue E. Radiology 1991;179:551-555; Taylor Robinson SD. Metab Brain Dis 1995;10:175-188; Córdoba J et al. Metab Brain Dis 2002;17:415-29

Do we need to study all cirrhotic patients? How to screen MHE?

SICKNESS IMPACT PROFILE

- 18. I am confused and start several actions at a time.
- 21. I forget a lot; for example, things that happened recently, where I put things, appointments.
- 28. I spend much of the day lying down in order to rest.
- 31. I have difficulty doing handwork; for example, turning faucets, using kitchen gadgets, sewing, carpentry.
- 36. I am not working at all.

$$\text{MHE risk} = \text{SIP (0 - 9.3)} + \text{Gender (0 - 1.2)} + \text{Child (0 - 1.6)} + \text{varices (0 - 2.1)}$$

MHE risk > 3.3 (n=73)

5 (6.8%)

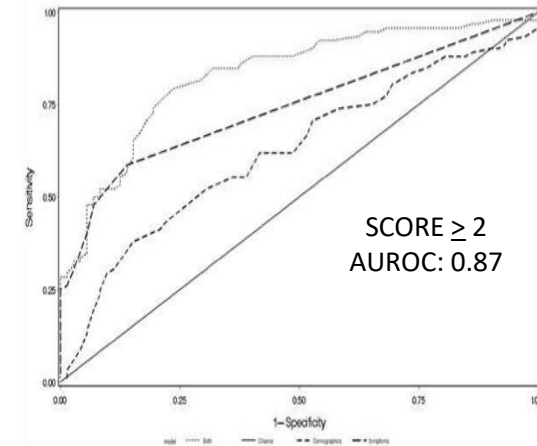
MHE risk < 3.3 (n=100)

43 (43%)

[Groeneweg et al. J Hepatol 2000;32:748]

Clinical selection (Five questions to select patients):

1. I do not maintain balance
2. I act irritable or impatient with myself
3. I'm not doing any of my physical activity
4. I'm eating much less than usual
5. Age & Gender





Do we need to study all cirrhotic patients? How to screen MHE?

The patient is shown the name of a colour written in a different colour from the colour name and asked to say the name of the colour in which the word is written.

Trial time >> reaction time >> errors >> corrects >> no response >> interference score

Table 3. EncephalApp performance in subjects with MHE diagnosed using ICT and PHES using adjusted norms; results displayed in median (IQR)

	MHE	No MHE	P value
<i>PHES as gold standard</i>			
OffTime (s)	95.07 (86.07, 110.69)	79.29 (68.86, 89.92)	<0.0001
OnTime (s)	110.92 (98.83, 130.62)	92.36 (80.02, 103.45)	<0.0001
OffTime+OnTime (s)	208.39 (185.73, 239.23)	173.65 (148.86, 191.77)	<0.0001
OnTime-OffTime (s)	16.01 (7.55, 29.07)	12.79 (6.22, 19.60)	0.001
No. of off runs	6.00 (5.00, 7.00)	5.00 (5.00, 6.00)	0.006
No. of on runs	6.00 (5.00, 8.00)	6.00 (5.00, 7.00)	0.002

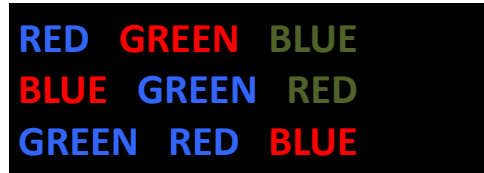
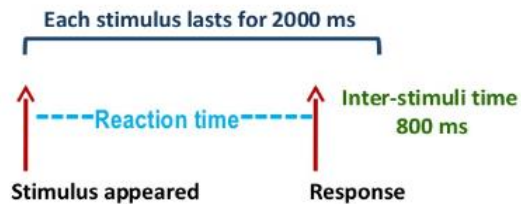
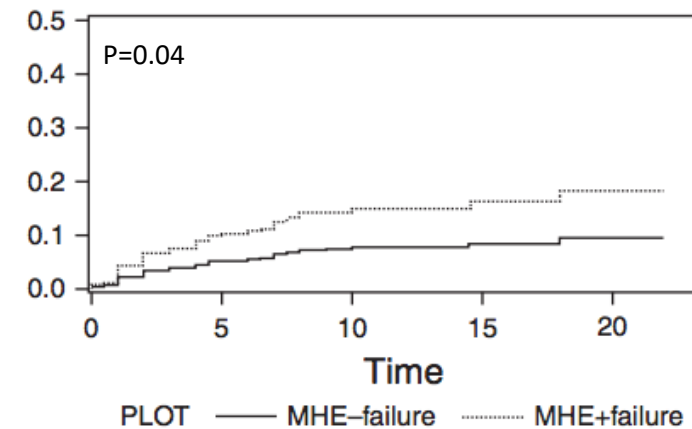


Table 4. Concordance of adjusted norm-based diagnosis of MHE according to EncephalApp with that diagnosed using PHES and ICT lures

	AR	OH	VA	Combined
<i>PHES vs. EncephalApp</i>				
Sensitivity	0.63	0.84	0.83	0.80
Specificity	0.48	0.63	0.67	0.61

a Based on STROOP regression
All patients



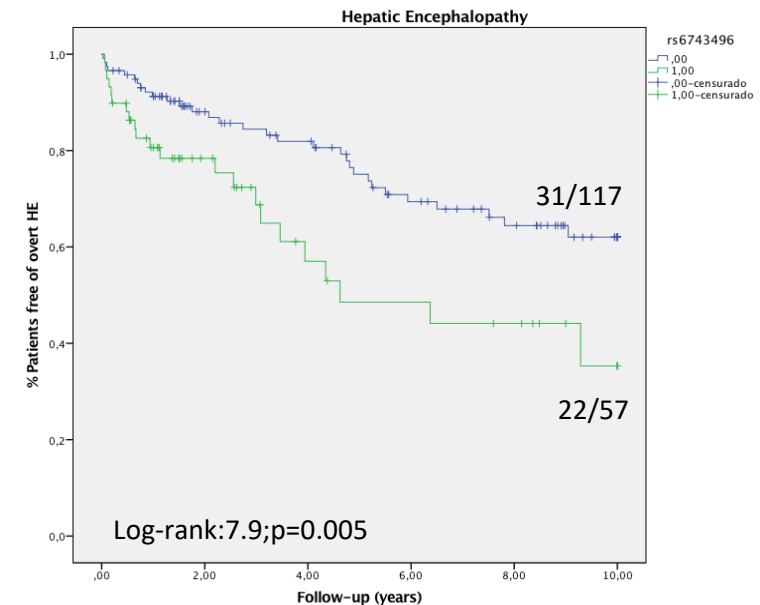
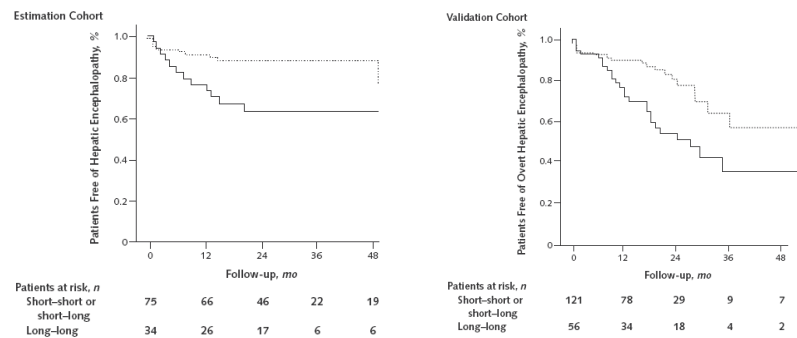
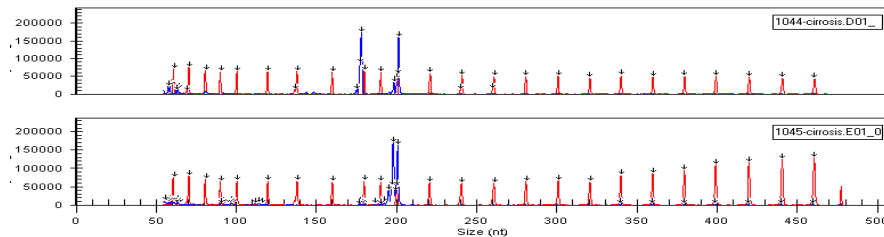
Bajaj et al. Hepatology 2013; Allampati et al AJG 2016

Do we need to study all cirrhotic patients? How to screen MHE?

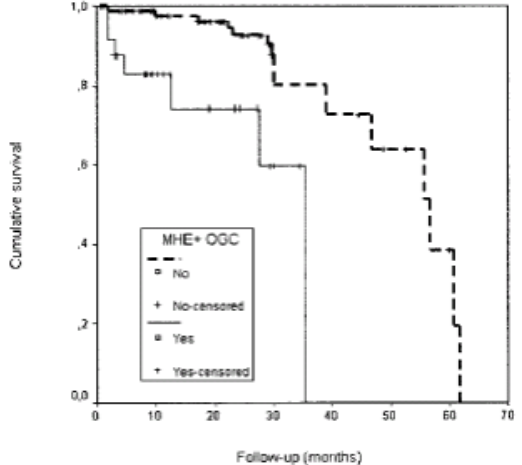
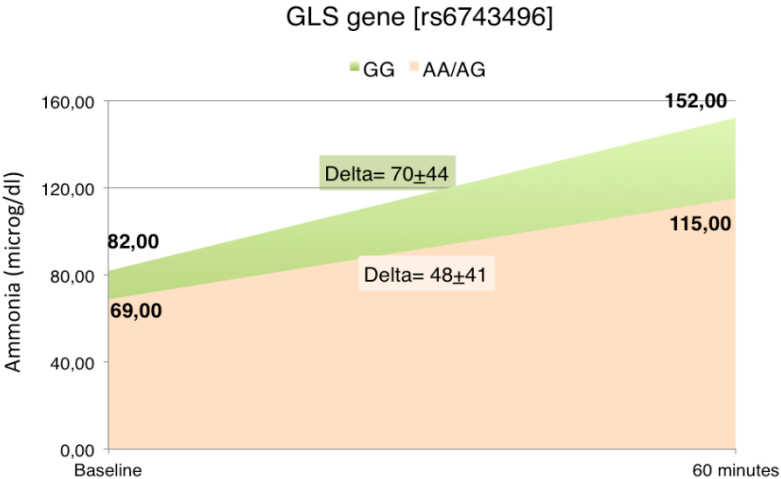
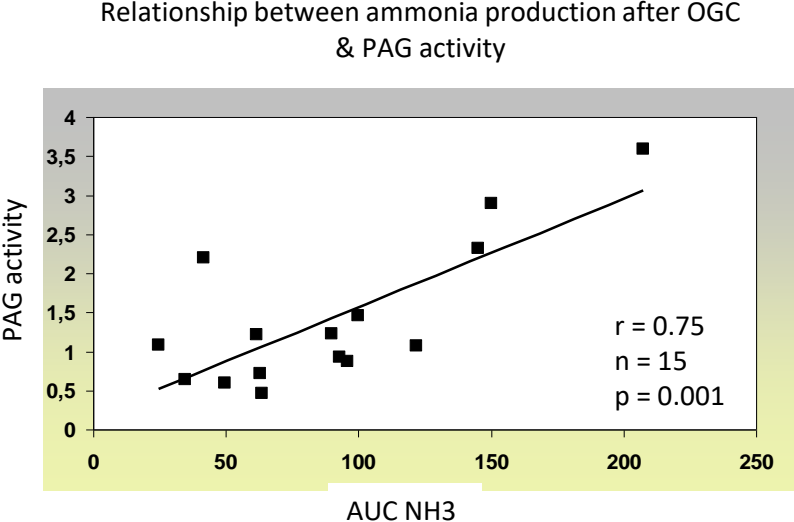
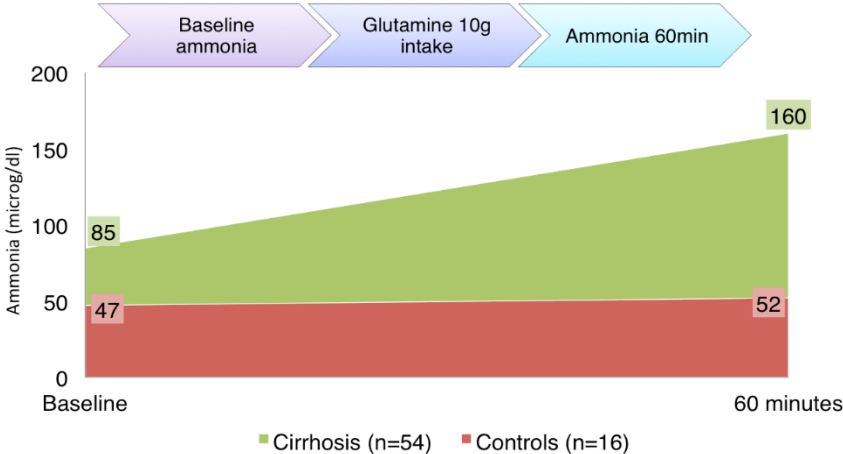
Glutaminase gene & HE

EC 3.5.1.2 - L-GLUTAMINE AMIDOHYDROLASE

GenBank*	Nucleotide change	Localization in gene <i>GLS</i>	Allelic frequency in Caucasians (%)*	Heterozygosity in Caucasians (%)**
rs3771310	C→T	Intron 6	22.5	47.8
rs6743496	A→G	Intron 7	35.8	57.8
rs2883713	C→T	Intron 9	38.3	63.3
rs3088307	C→G	3'UTR	45.8	51.1
5'UTR ms	8>>24	5'UTR	bimodal	31.5%



Oral Glutamine Challenge and Hepatic Encephalopathy

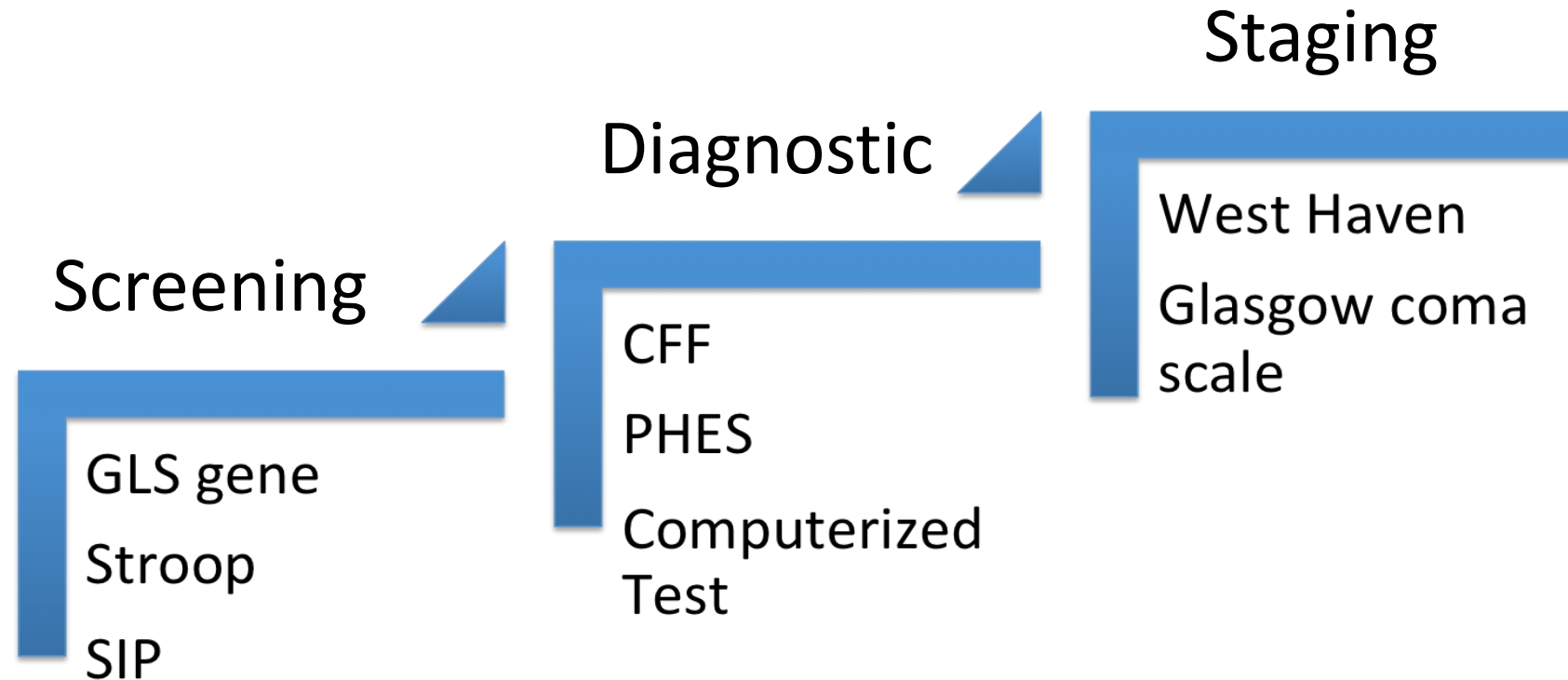


	↑	↑	↑	↑	↑	↑
MHE+ OGC: Yes; N=	25	13	8	3		
No; N=	93	74	63	19	10	6



Oppong et al Hepatology 1997; James LA. Br J Nutr 1998; Romero-Gómez M, et al. J Hepatol 2004; Romero Gómez. Hepatology 2004; Irima J Gastrointestin Liver Dis 2013; Ampuero AASLD 2016

Deciphering the Spectrum of Hepatic Encephalopathy



What's in a name?

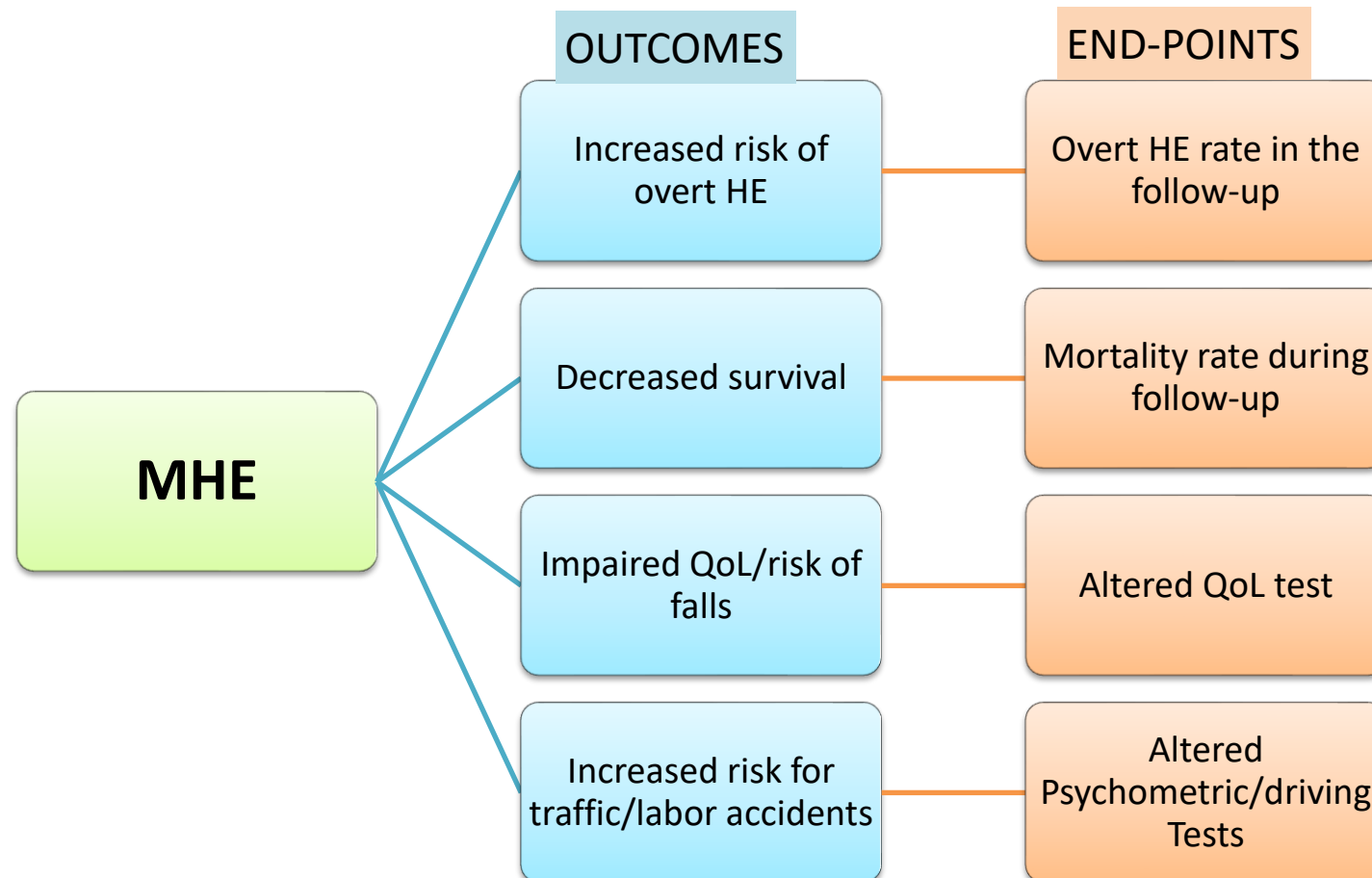
Subclinical: pertaining to an early stage of a disease; having no noticeable clinical symptoms.

Minimal: barely adequate or the least possible: minimal care.

Covert: Concealed, secret, disguised.

Low-grade: of an inferior quality, worth, value.

Overt: open to view or knowledge; not concealed or secret



MHE predicts Overt HE

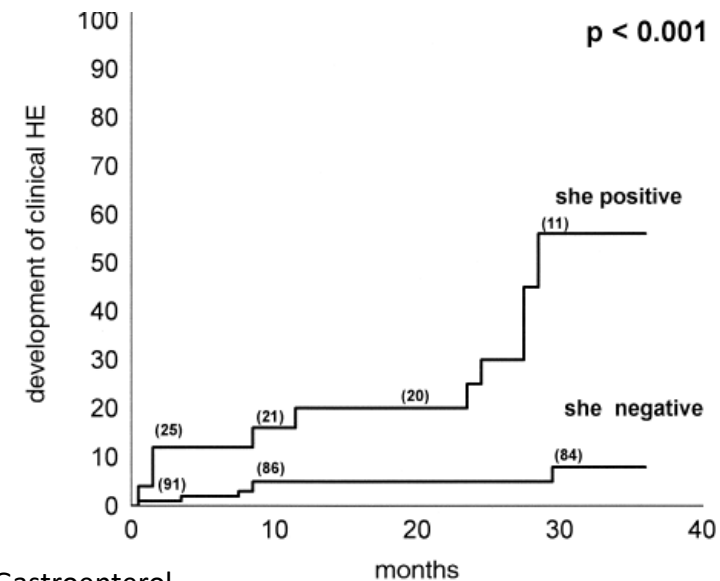
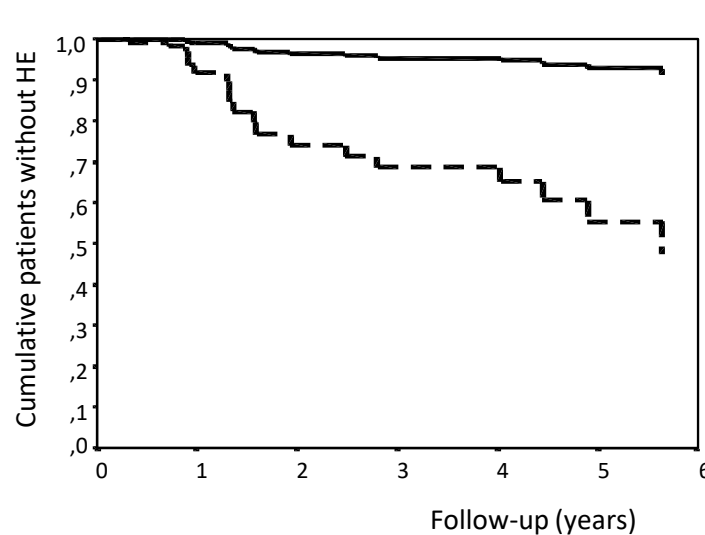
Table 2. Mean Follow-Up, Number of Decompensating Events During Follow-Up, Liver-Related Death, and Total Death

	SHE+ (n = 25)	SHE- (n = 91)	p Value
Follow-up, mean (range)	25.6 (2–39)	28.8 (1–49)	0.21
Decompensating events, number (%)			
Encephalopathy	10 (40)	6 (7)	<0.001
Variceal bleeding	3 (12)	10 (11)	1.0
Jaundice	2 (8)	8 (9)	1.0
Ascites	5 (25)	15 (16)	0.09
Liver-related death, number (%)	4 (16)	5 (6)	0.43
Total death, number (%)	6 (24)	12 (13)	0.22

SHE = subclinical hepatic encephalopathy.

Clinical Hepatic Encephalopathy During Follow-Up

Entry Feature	Relative Risk	95% CI	p Value
SHE (positive vs negative)	3.7	1.2–11	0.02
Child-Pugh (B/C vs A)	19.3	4.1–90.8	<0.001
Clinical HE in history (present vs absent)	0.67	0.2–2.2	0.5



CFF & ICT predicted overt HE

CFF

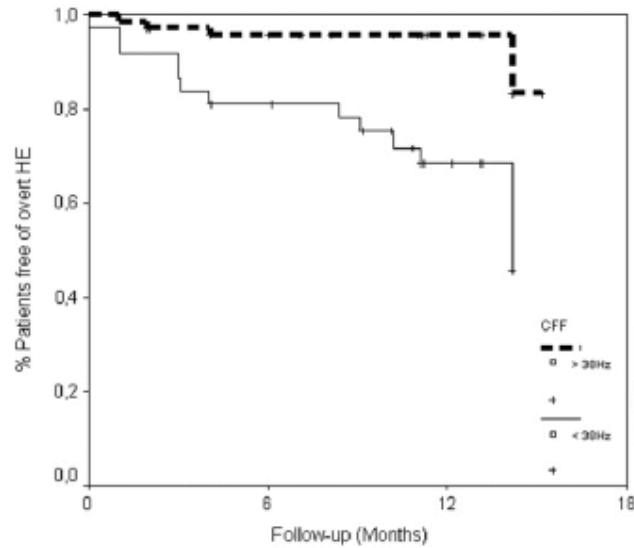
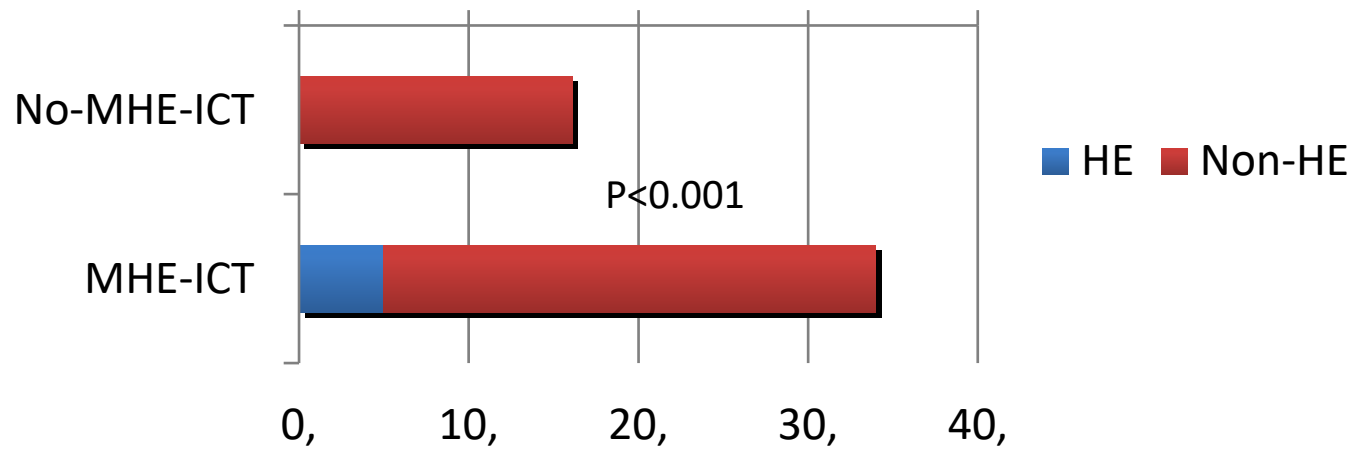
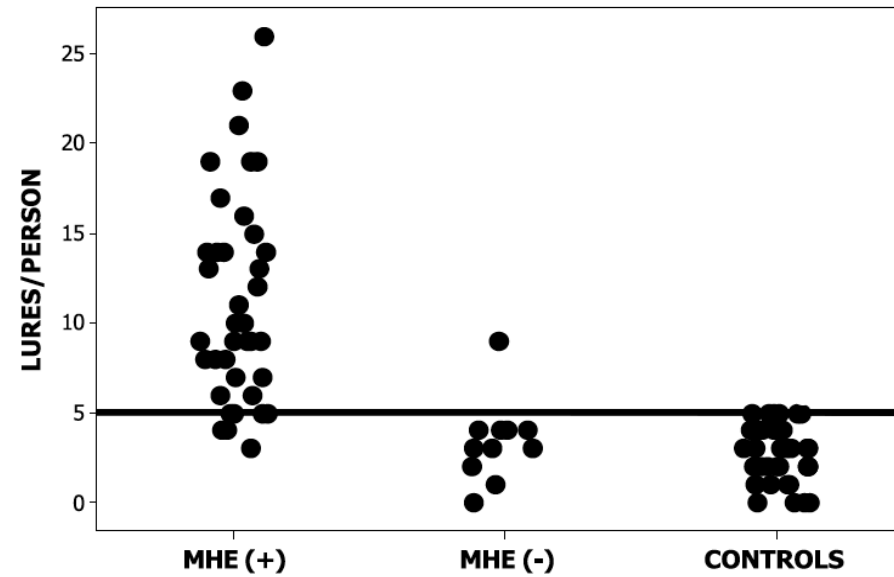


Fig. 4. Prediction of overt HE by CFF in patients with cirrhosis (log-rank 15.08; $P < 0.0001$).



Romero Gómez et al. Hepatology 2007;45:879

Bajaj et al. Am J Gastro 2007

MHE: Quality of life and risk of falls

Falls:

Medical care: 54%

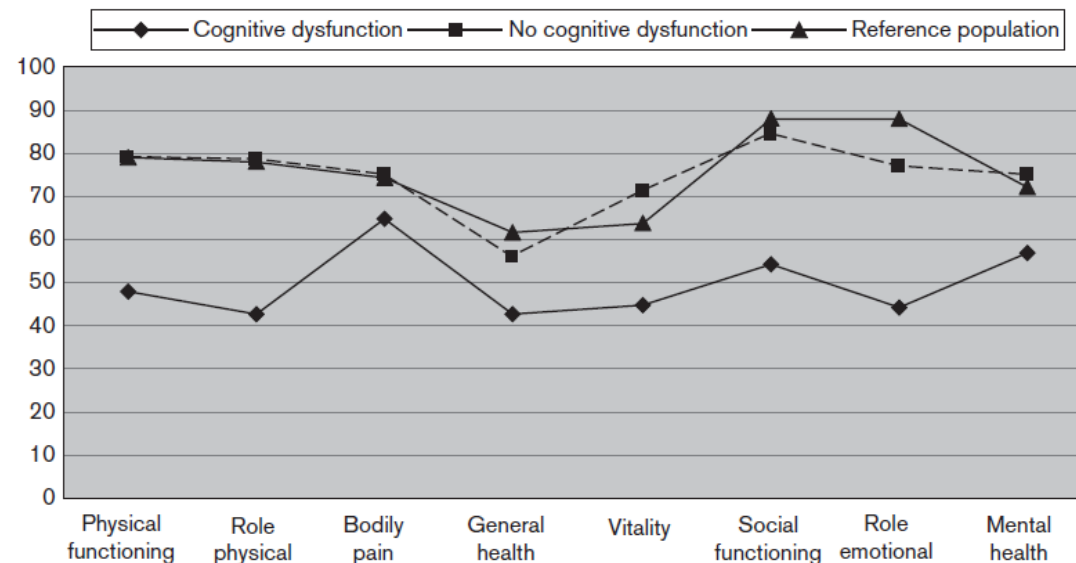
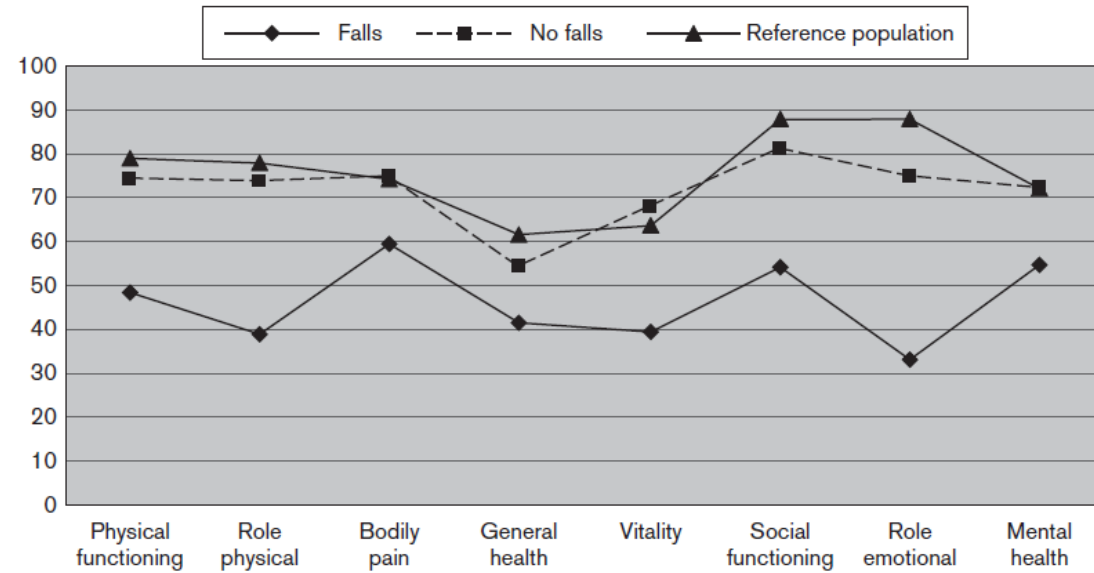
Fractures 18%

HR QoL

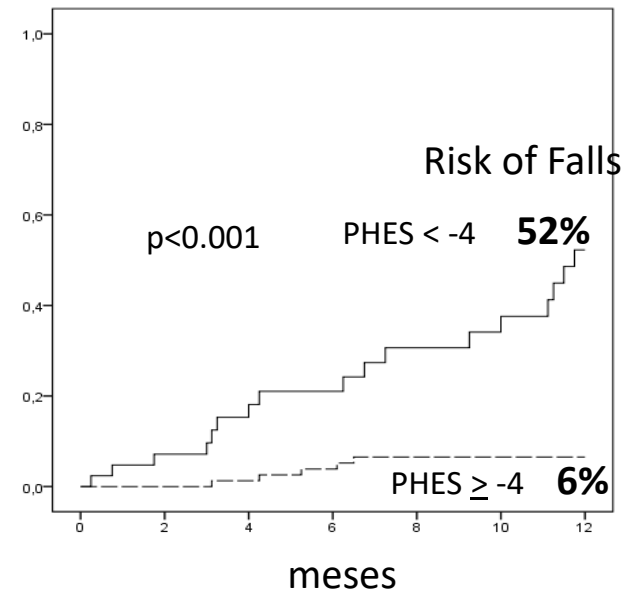
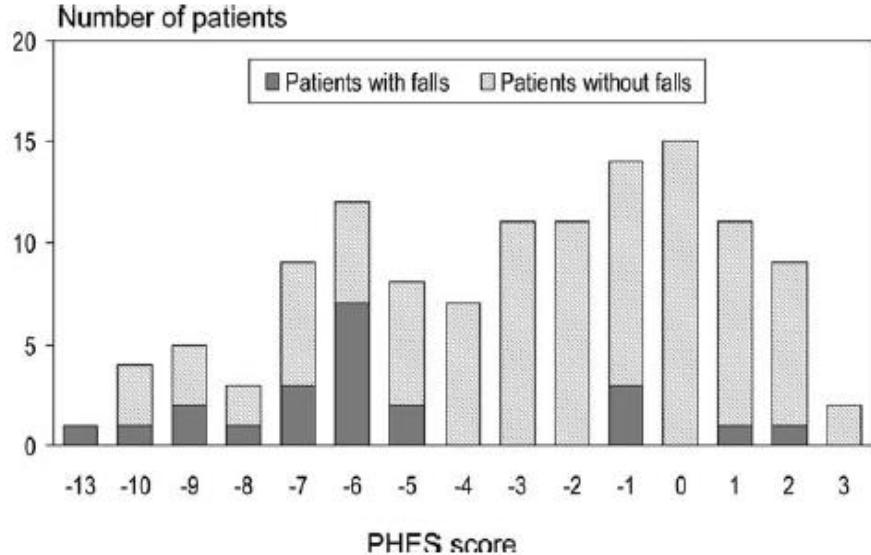
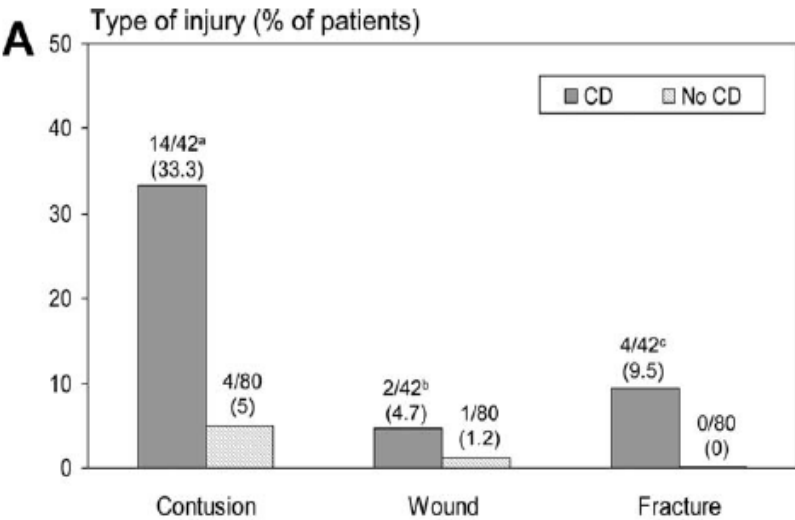
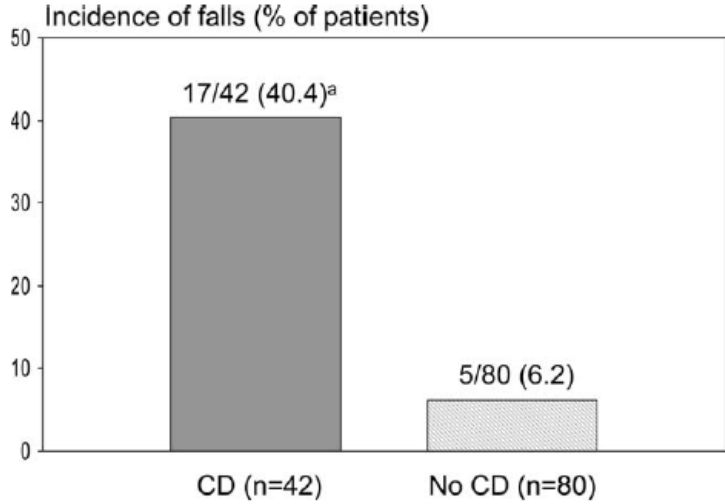
SF-36:

Physical component score

Mental component score



MHE and risk of falls



Impact of MHE on driving fitness

The Effect of Fatigue on Driving Skills in Patients With Hepatic Encephalopathy

Jasmohan S. Bajaj, MBBS, MD, MS¹, Muhammad Hafeezullah, MBBS⁴, Yelena Zadvornova, MD⁴, Eric Martin, MD⁴, Christine M. Schubert, PhD², Douglas P. Gibson, Psy D, MPH³, Raymond G. Hoffmann, MD⁵, Arun J. Sanyal, MBBS, MD¹, Douglas M. Heuman, MD¹, Thomas A. Hammeke, PhD⁶ and Kia Saeian, MD, MS⁴



Table 3. Complete driving simulator performance

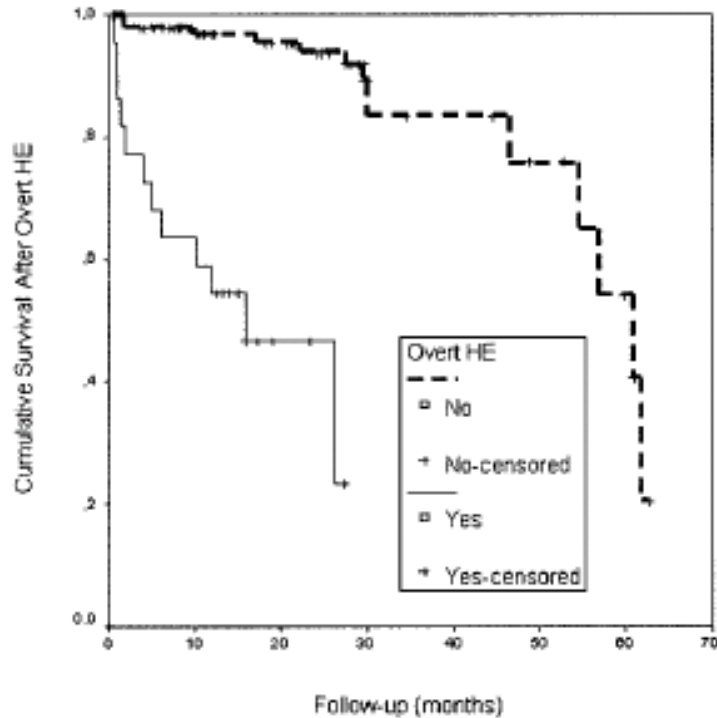
	Controls (n=67)	Patients with cirrhosis (n=100)		
		NMHE (n=27)	MHE (n=51)	OHE (n=22)
Mean speed (mph)	29.8±5.7	31.7±4.8	30.7±6.4	31.4±6.1
Length of run (s)	2018±441	1866±315	1899±400	2014±630
Vehicular collisions (median)	1.0±0.1 (1)	0.7±1.2 (1)	2.0±2.1*** (3)	1.4±2.2*** (2)
Speeding citations (median)	0.9±0.1 (1)	1.5±1.4 (1)	1.8±2.1 (1)	4.7±6.6 (2)
Road-edge excursions (median)	4.3±5.5 (2)	3.4±2.8 (2)	8.2±7.8*** (6)	5.8±4.5*** (5)
Center crossings (median)	7.9±6.9 (6)	6.7±2.7 (6)	13.1±12.5*** (9)	11.9±9.1*** (8.5)

MHE, minimal hepatic encephalopathy; mph, miles per hour; NMHE, cirrhotics without minimal or overt hepatic encephalopathy; OHE, patients with recent overt hepatic encephalopathy on treatment with lactulose.

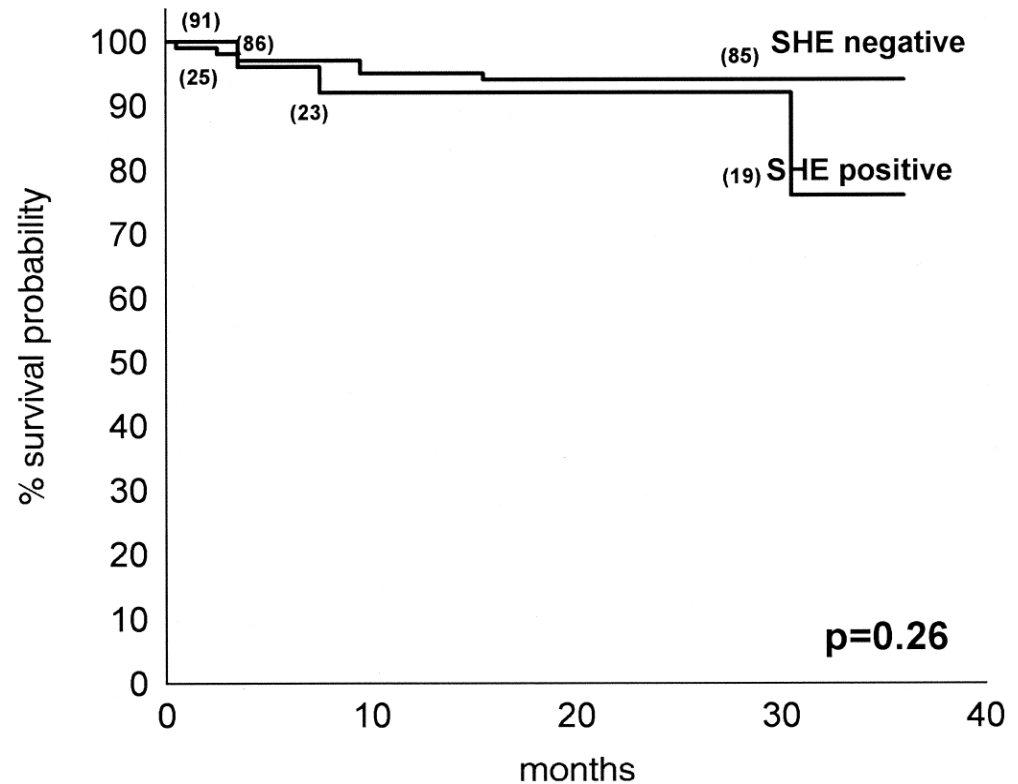
* $P < 0.01$ compared with controls. ** $P < 0.01$ compared with NMHE patients.

MHE and OHE patients were significantly impaired compared with controls and NMHE patients on simulation. There were no significant differences between the OHE and MHE group with respect to all aspects of the simulator performance. The controls and NMHE patients were similar on all simulator outcomes.

Overt HE predicts survival but MHE ...



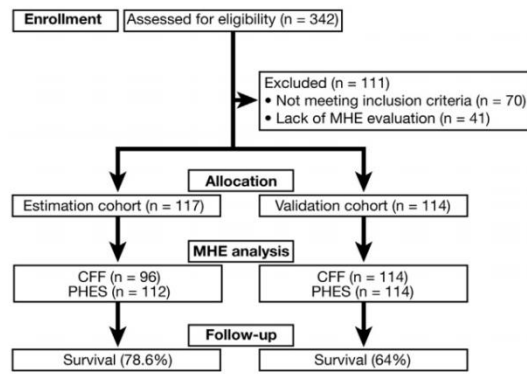
	↑	↑	↑	↑	↑	↑	↑
Overt HE: Yes; N=	22	14	3				
No; N=	104	80	67	23	13	8	4



Short-term follow-up?
Small size cohorts?

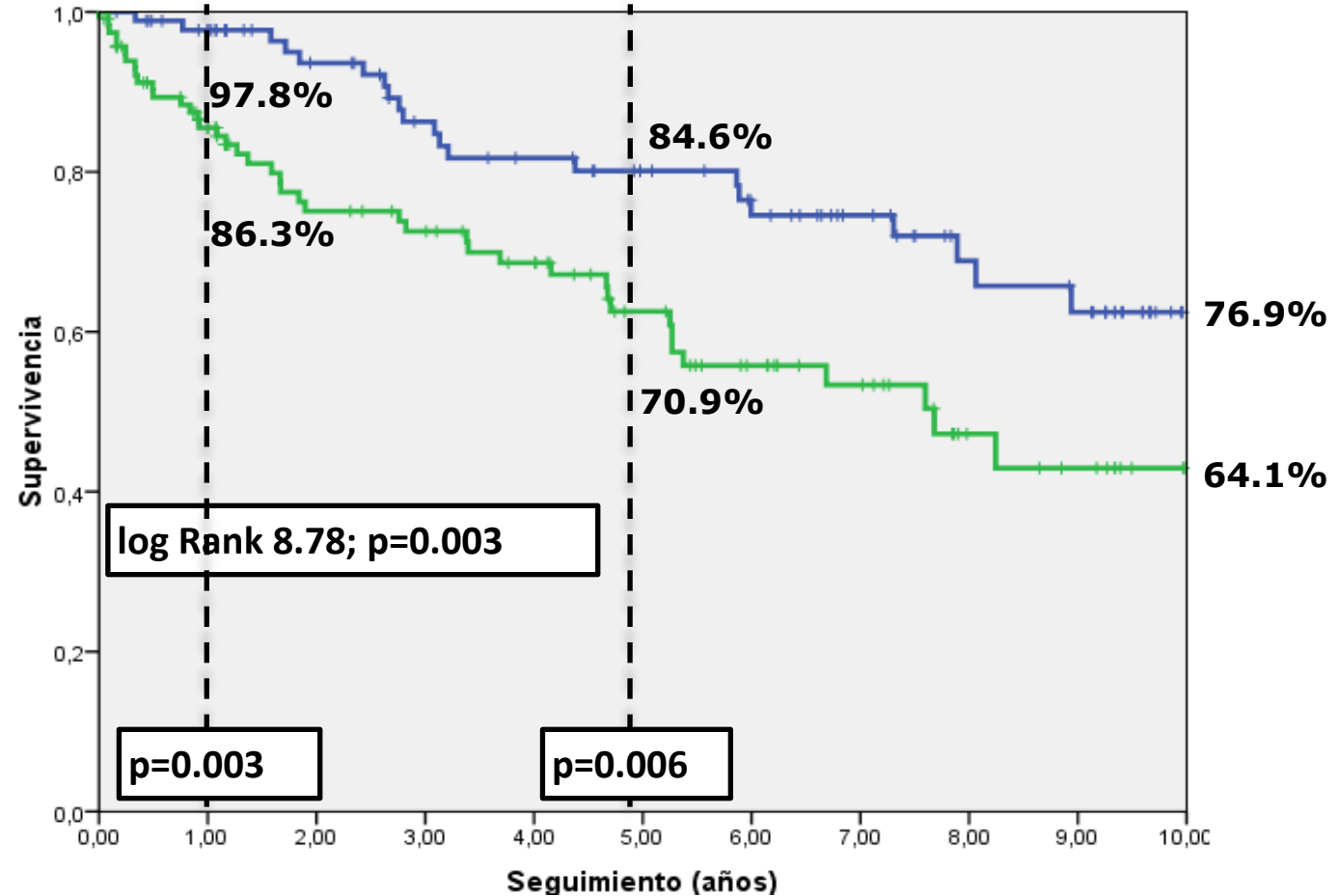
Hartmann et al. Am J Gastro 2000
Romero-Gómez et al. Hepatology 2004

MHE & SURVIVAL

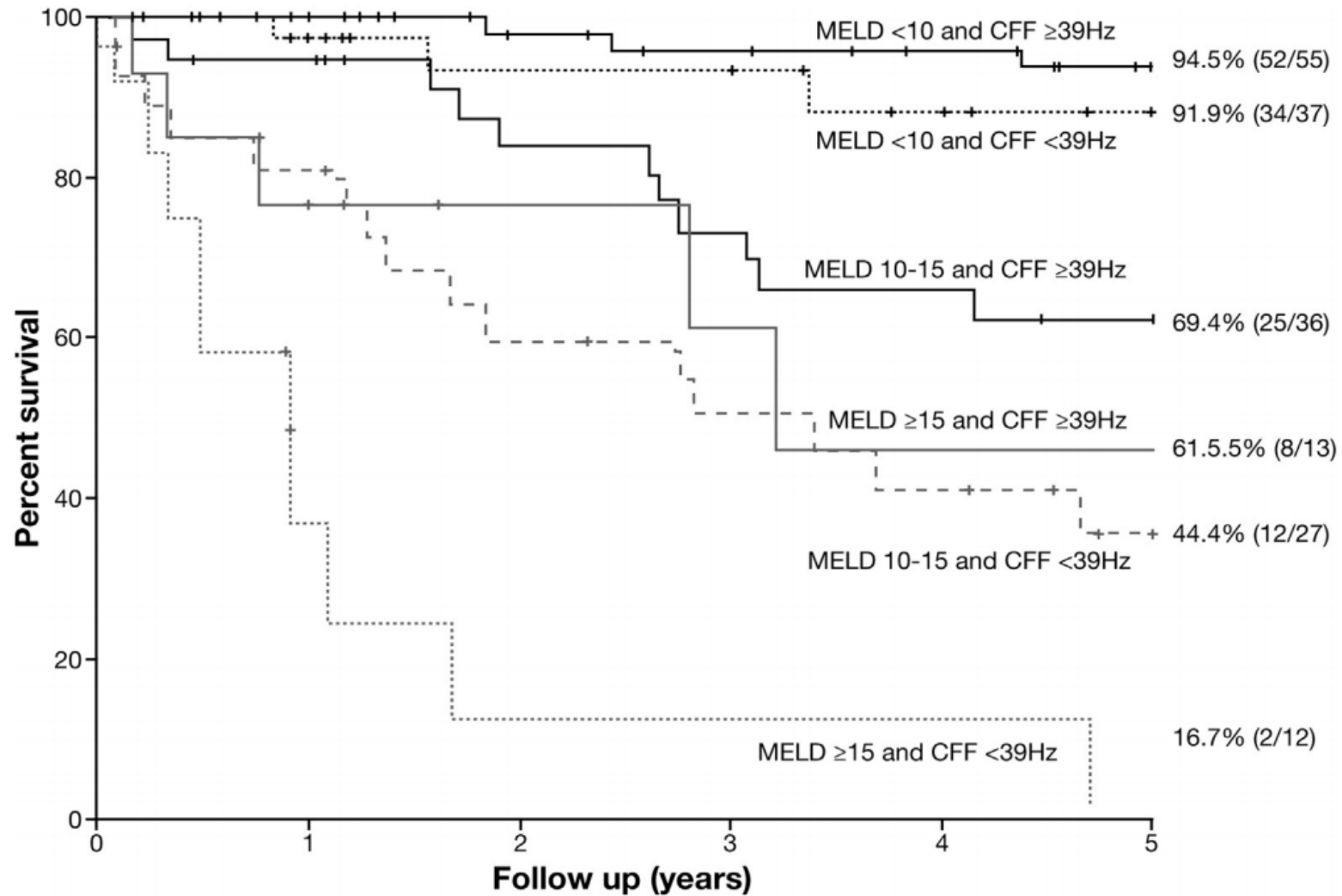


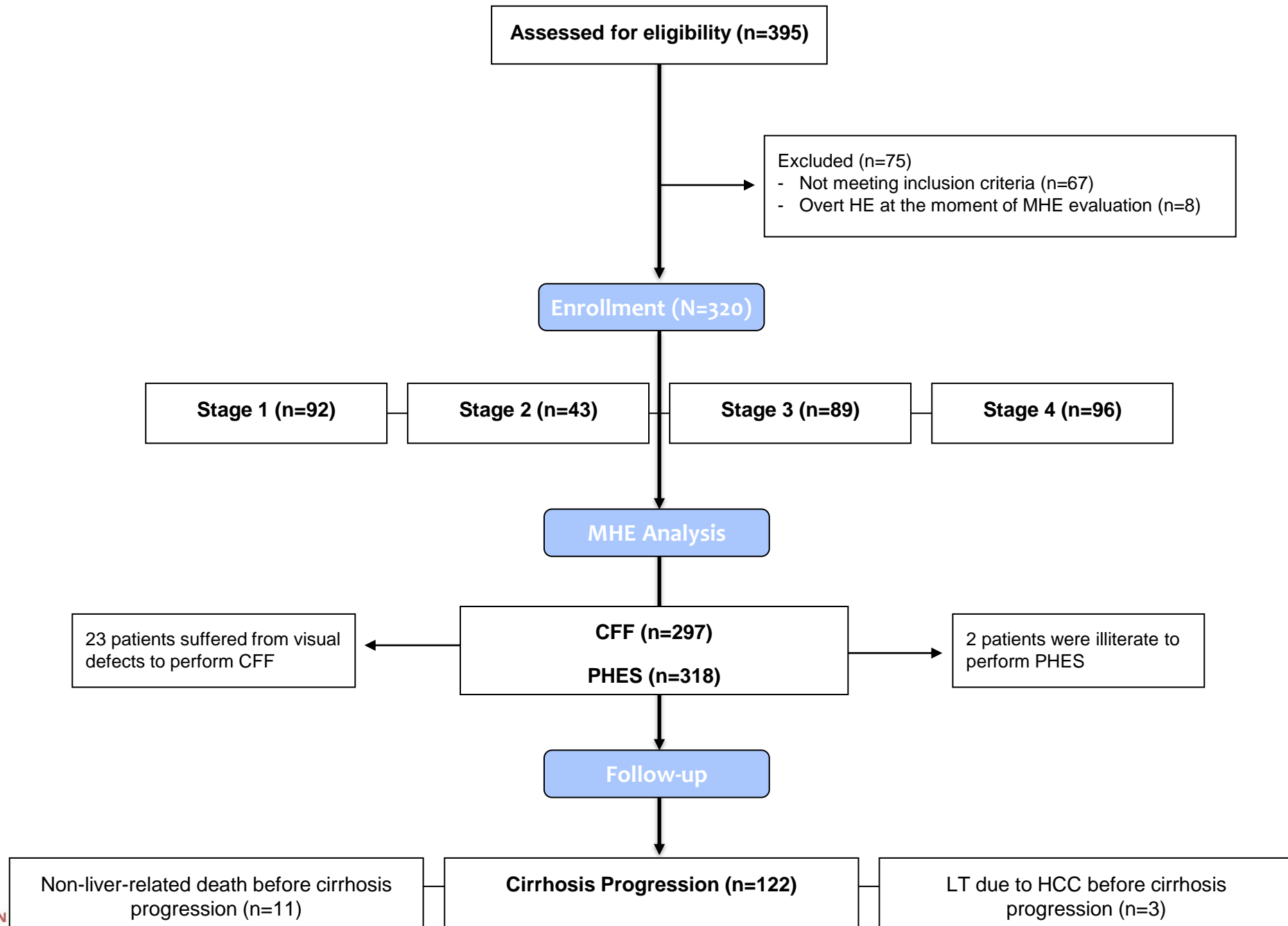
N=231 patients

— No
— MHE → **FCP < 39 HZ ó PHES < -4 puntos**

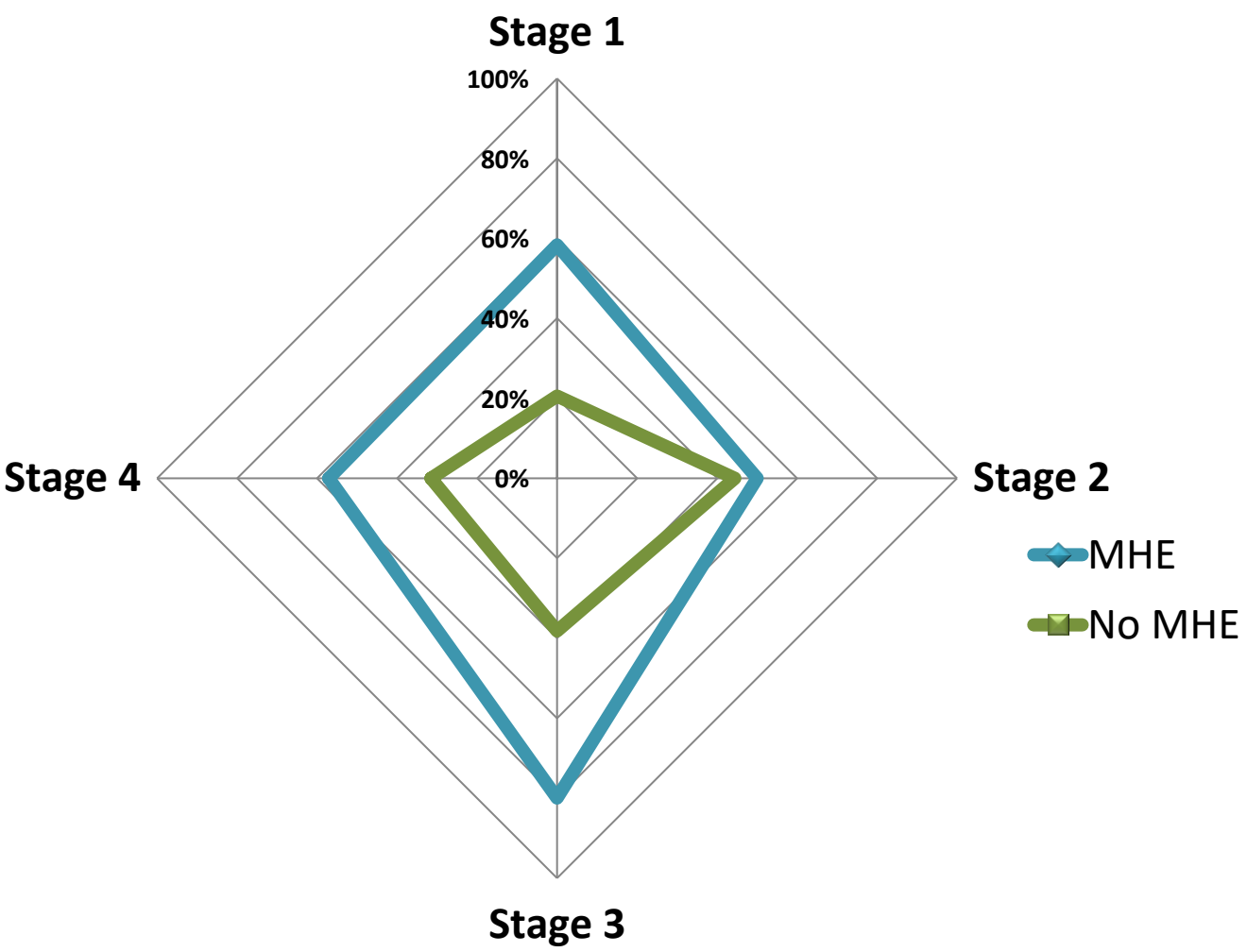


MHE & MELD & SURVIVAL

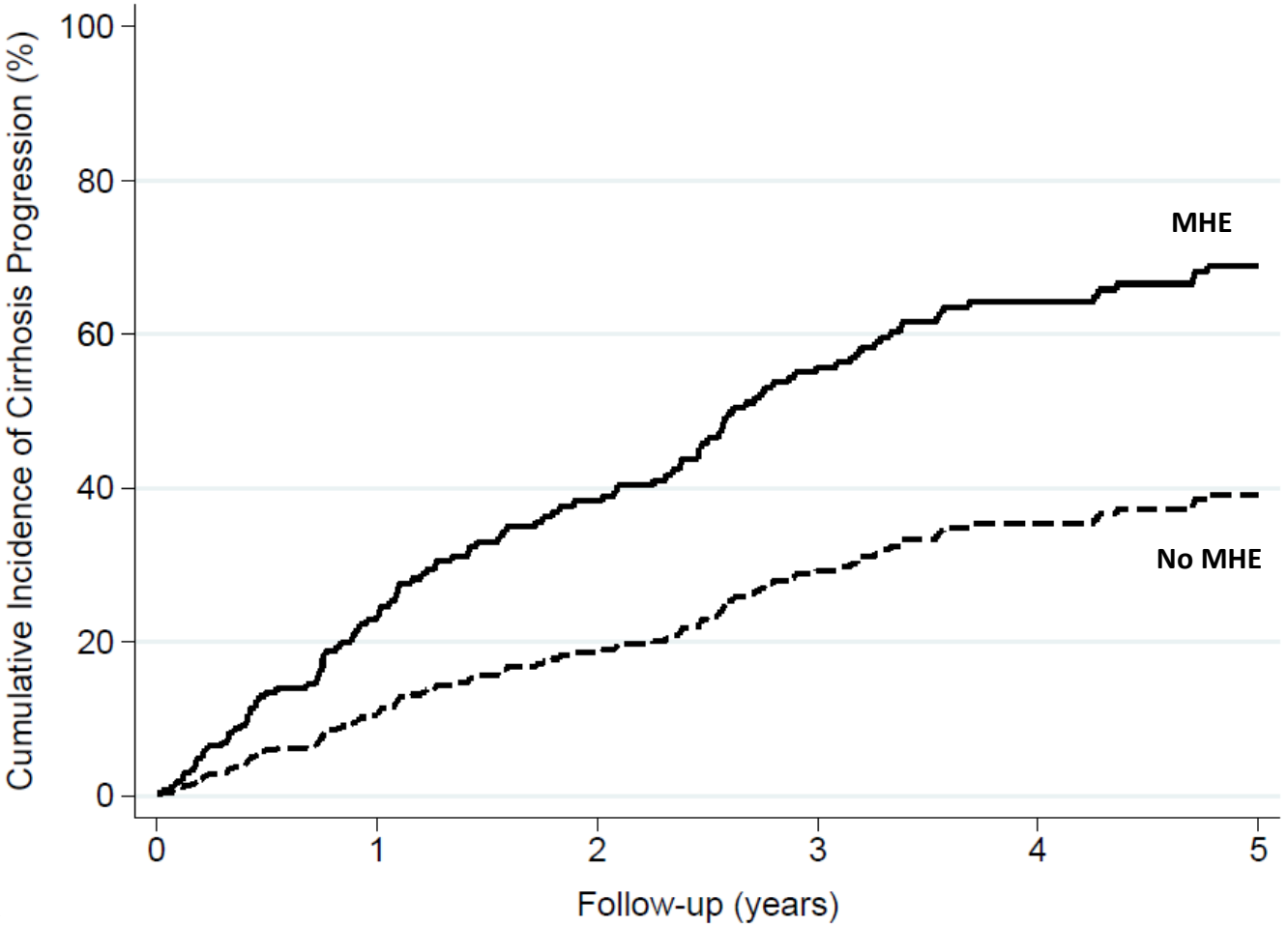




MHE is related to cirrhosis progression



MHE is related to cirrhosis progression

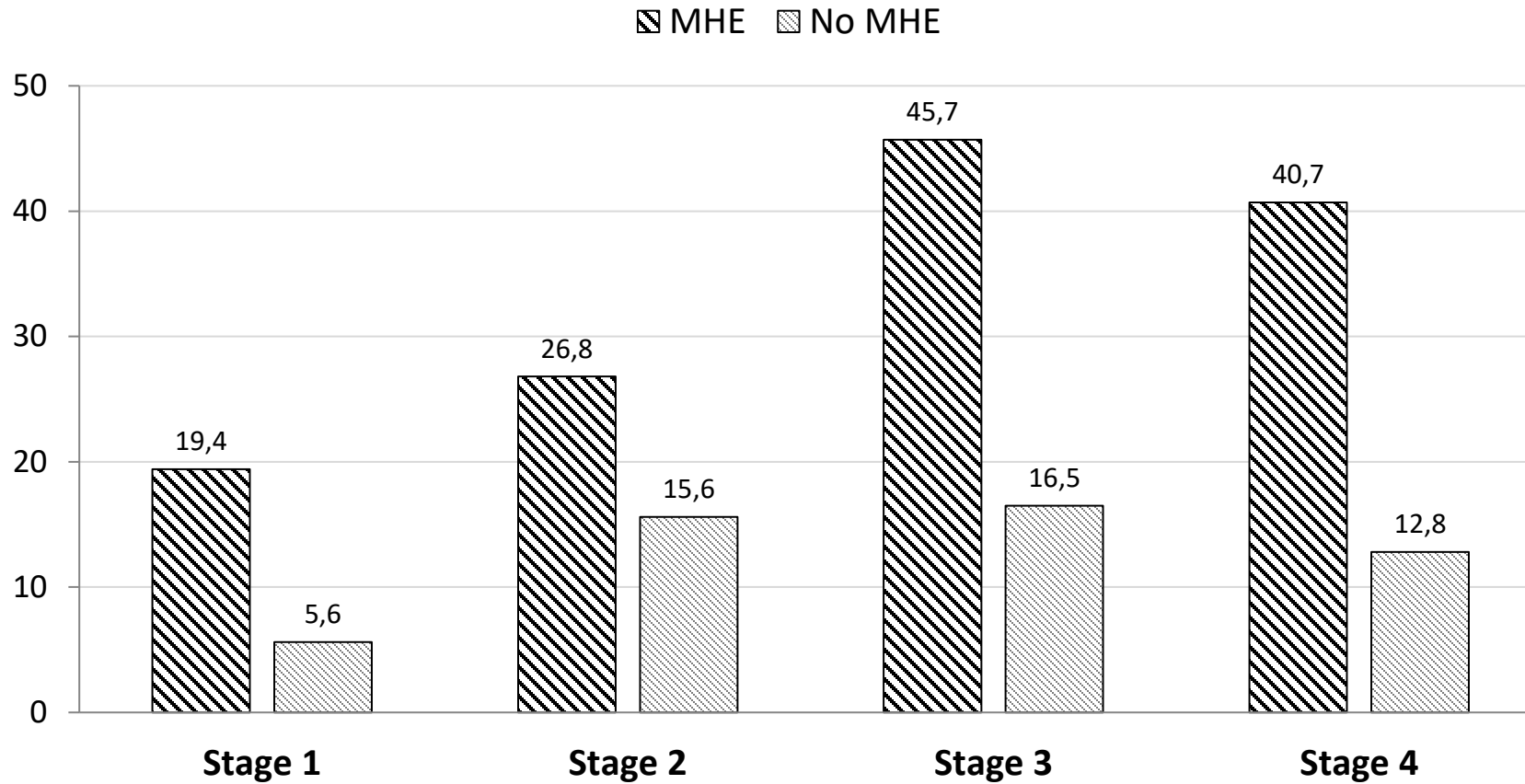


No. at risk		0	1	2	3	4	5
MHE	57	31	21	15	8	7	
No MHE	257	195	158	126	91	79	



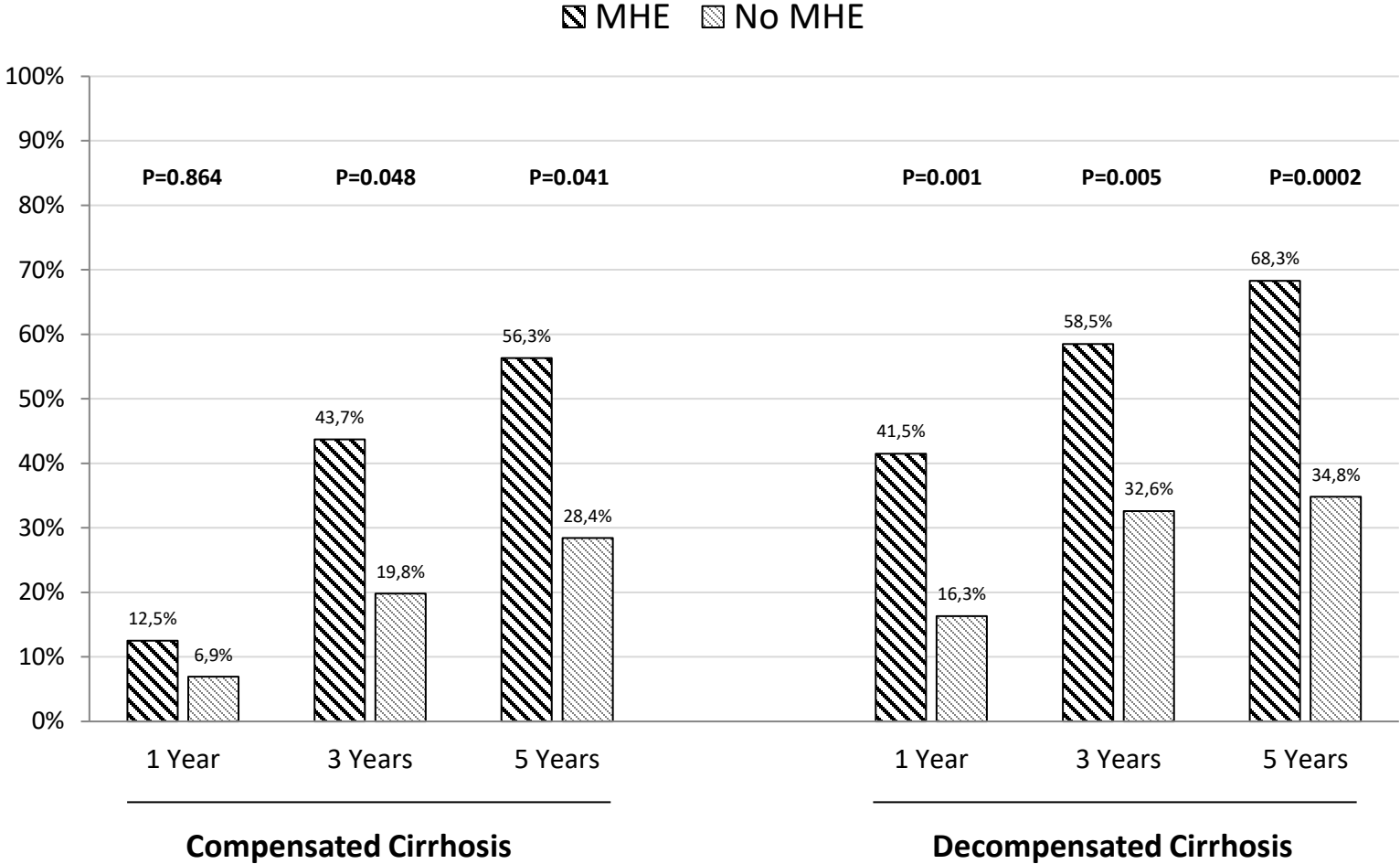
MHE is related to cirrhosis progression

Cases of Cirrhosis Progression per 100 person-years



MHE is related to cirrhosis progression

Cumulative Incidence of Cirrhosis Progression



MHE is related to cirrhosis progression

Table 3 Competing risk regression to evaluate the impact of MHE on the cirrhosis progression

Variables	Multivariable analysis					
	Model 1 [†]		Model 2 [‡]		Model 3 [§]	
	sHR (95%CI)	<i>P</i> value	sHR (95%CI)	<i>P</i> value	sHR (95%CI)	<i>P</i> value
Age	1.03 (1.00–1.05)	0.015	1.02 (1.00–1.04)	0.027	1.03 (1.00–1.05)	0.023
Sex (male)	—	—	—	—	—	—
Child–Pugh	—	—	1.40 (1.27–1.54)	0.0001	—	—
MELD	—	—	—	—	1.09 (1.03–1.16)	0.005
Albumin	0.99 (0.99–0.99)	0.001	—	—	0.99 (0.99–0.99)	0.003
INR	—	—	—	—	—	—
Creatinine	—	—	—	—	—	—
Bilirubin	1.23 (1.08–1.40)	0.002	—	—	—	—
Platelet count	0.99 (0.99–0.99)	0.026	0.99 (0.99–0.99)	0.008	0.99 (0.99–1.00)	0.057
Decompensated cirrhosis	—	—	—	—	—	—
MHE	2.34 (1.58–3.46)	0.0001	2.18 (1.43–3.33)	0.0001	2.48 (1.63–3.76)	0.0001

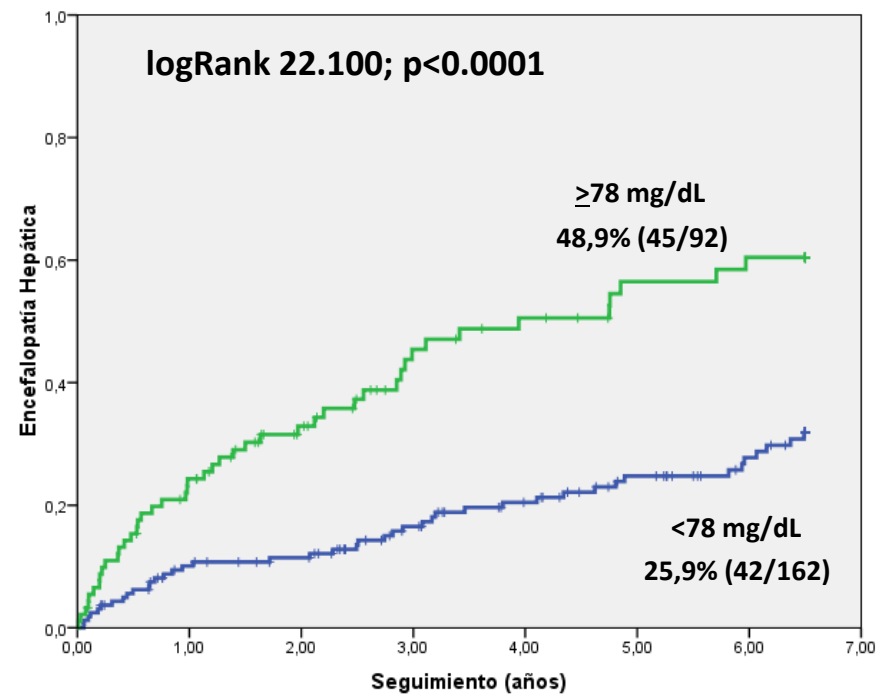
[†]Model 1 includes all variables, excluding Child–Pugh and MELD scores.

[‡]Model 2 includes Child–Pugh, excluding albumin, bilirubin, and INR.

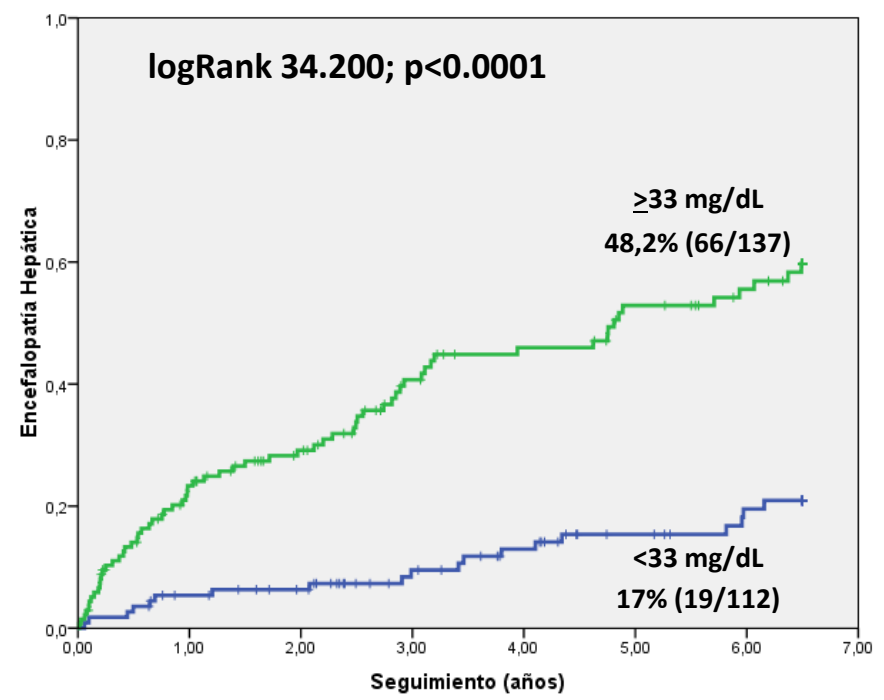
[§]Model 3 includes MELD score, excluding bilirubin, INR, and creatinine.

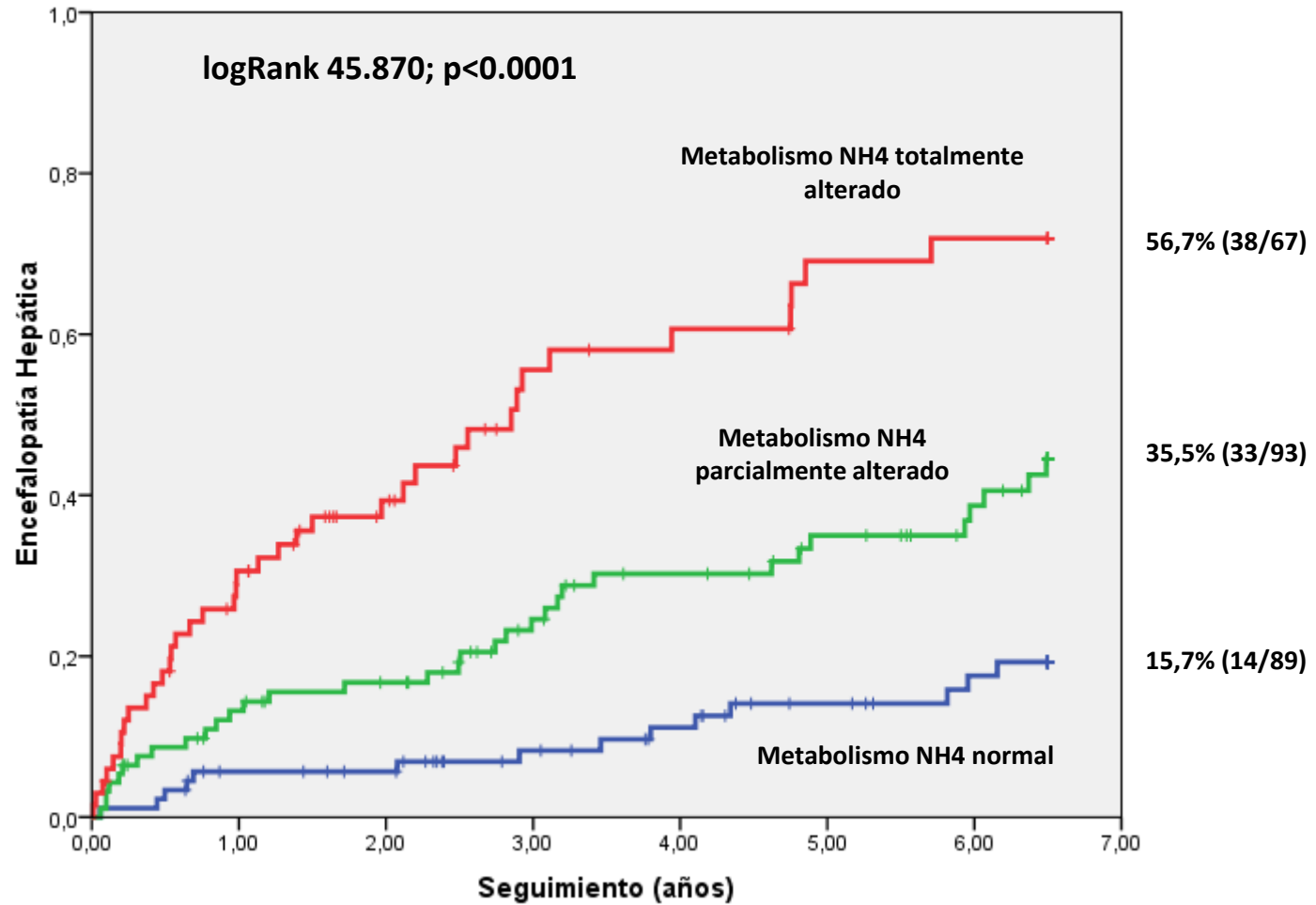
CI, confidence interval; INR, international normalized ratio; MELD, model of end-stage liver disease; MHE, minimal hepatic encephalopathy; sHR, subhazard ratio.

Amonio basal



Amonio Δ



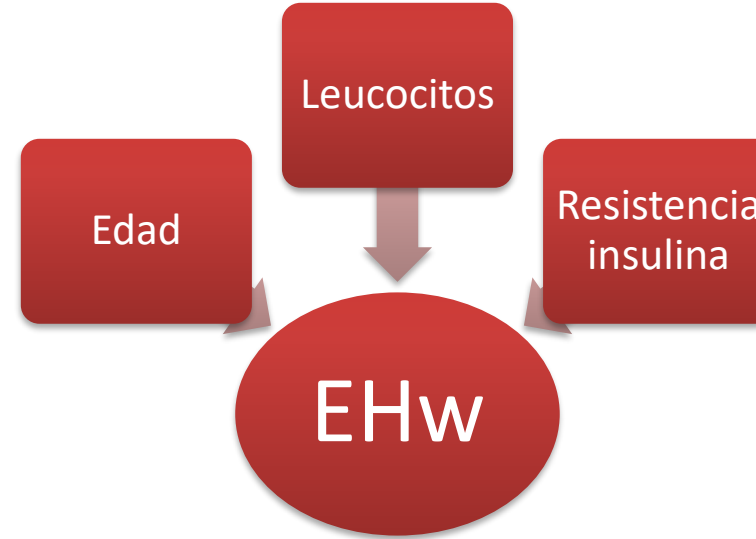


TIPO DE ENCEFALOPATÍA HEPÁTICA

Resultados

INFLAMACIÓN

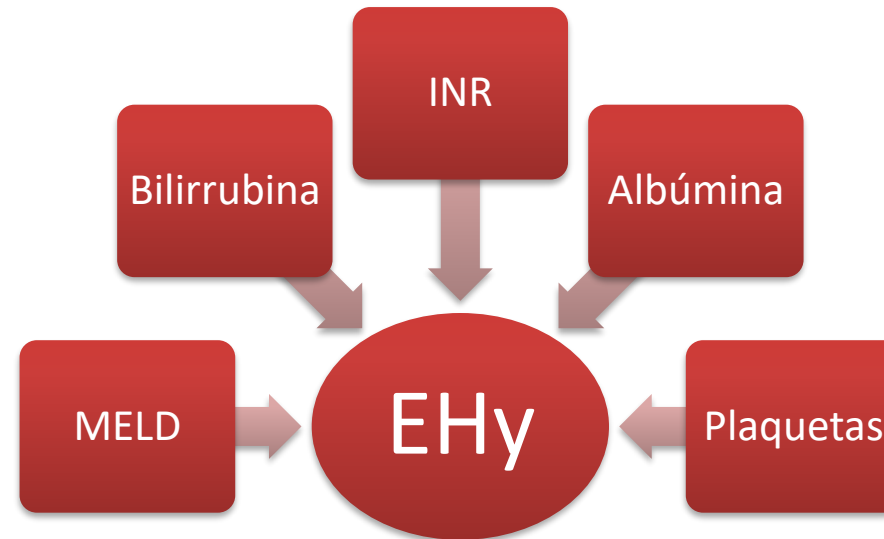
SOG NORMAL



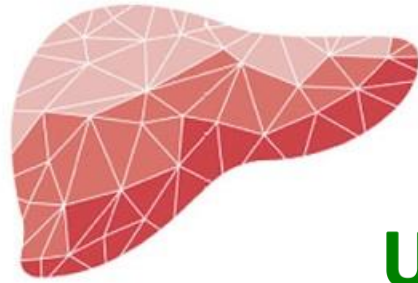
SOG ALTERADA



DISFUNCIÓN HEPÁTICA







MÁSTER EN HEPATOLOGÍA

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