Hepatitis Alcohólica Aguda:

¿qué hay de nuevo en 2019?

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DIGESTIVO
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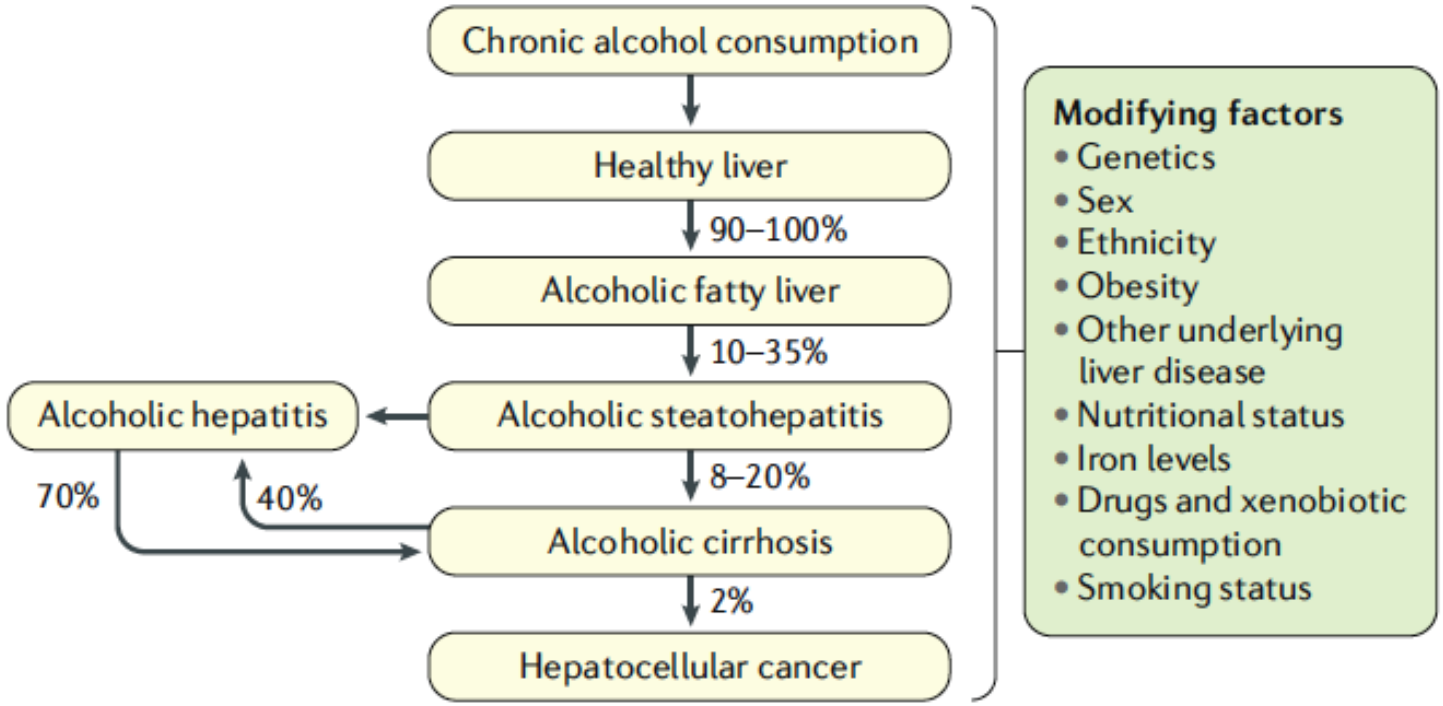
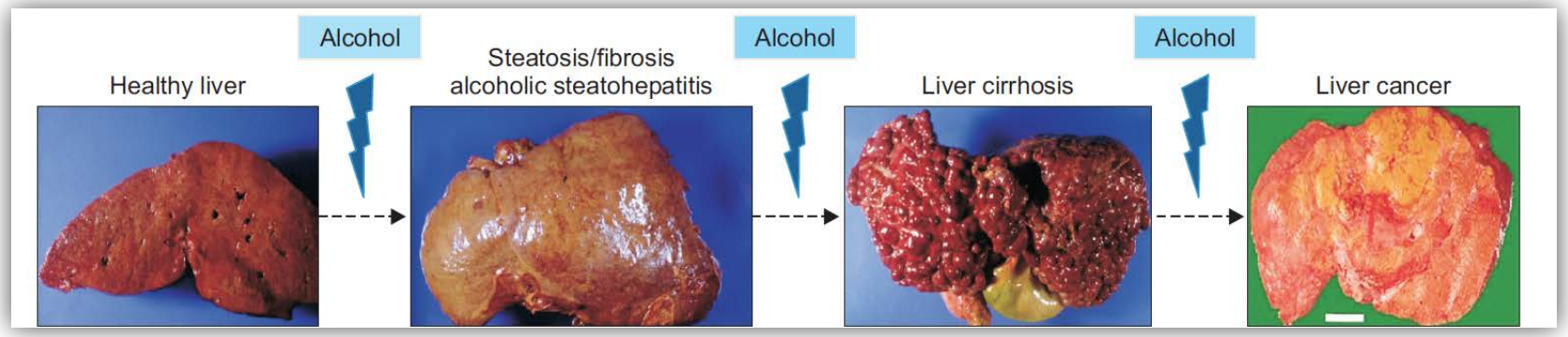
Natural History of Alcoholic Liver Disease [ALD]





Mathurin P, Bataller R. J Hepatol. 2015;62(1 Suppl):S38-46. Seitz HK, et al. Nat Rev Dis Primers. 2018;4(1):16.
Stickel F, et al. Gut Liver. 2017;11(2):173-88.. Gao & Bataller. Gastroeterology 2011

Alcoholic Hepatitis. Definition

Clinical Syndrome:

- Acute onset of JAUNDICE [Bilirubin >3mg/dl].
- Active alcohol consumption (at least previous 4-8 weeks)
  - >100g/OH/day. *Binge drinking*.
- AST, ALT <300-400 UI/mL, ratio 2:1
- Rule out other causes of liver injury.

PROBABLE Alcoholic Hepatitis

DEFINITE Alcoholic Hepatitis
- with liver biopsy

POSSIBLE Alcoholic Hepatitis (uncertain / confounding)

Crabb DW et al. Gastroenterology. 2016. EASL Clinical Practice Guidelines: Management of alcohol-related liver disease. J Hepatol. 2018;69(1):154-81.
Singal AK, et al. ACG Clinical Guideline: Alcoholic Liver Disease. Am J Gastroenterol. 2018.

Clinical presentation: signs and symptoms

- **JAUNDICE**
- Nausea/vomiting
- Abdominal pain (usually right upper quadrant/midepigastric)
- Fatigue
- Weakness
- Anorexia
- Fever
- Increased abdominal girth with ascites
- Tender hepatomegaly
- Hepatic decompensation: variceal bleeding, hepatic encephalopathy

Stigmata of chronic liver disease:

- Spider angiomata
- Palmar erythema
- Gynecomastia
- Parotid enlargement
- Increased collateral vessels
- Dupuytren's contractures

Dugum MF & McCullough AJ. Clin Liv Dis 2016

Burden / Why treat these patients?

Mortality:

- 28 days: 25-40%.
- 90 days: 20-50%

Issues strongly associated with **mortality** during hospitalization (6,8-15%):

- Age.
- **Sepsis.**
- **Infections: SBP, pneumonia, UTI.**
- **Acute kidney injury [AKI]**
- Hepatic Encephalopathy.
- Coagulopathy.

*SBP: Spontaneous bacterial peritonitis; UTI: urinary tract infection

Lucey MR, et al. New England Journal of Medicine. 2009;360(26):2758-69.
Mathurin P, Bataller R. J Hepatol. 2015;62(1 Suppl):S38. Liangpunsakul S. J Clin Gastroenterol. 2011;45(8):714. Dunn W, et al. Hepatology. 2005;41(2):353

Prognostic Score to indicate treatment

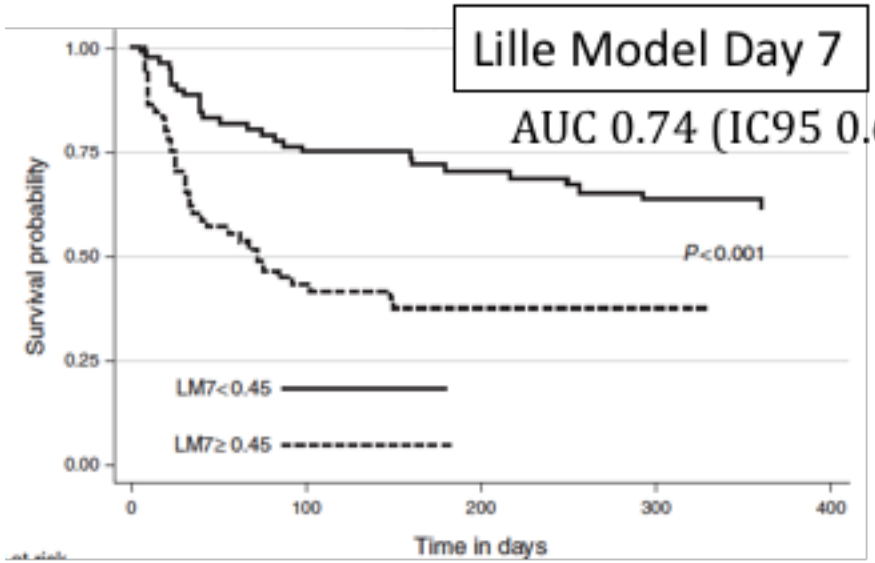
	Bilirubin	PT/INR	Creatinine Urea	Leukocytes	Age	Albumin	Severity
MADDREY DF	✔	✔					> 32
MELD	✔	✔	✔				>20
GAHS	✔	✔	✔	✔	✔		>9
ABIC	✔	✔	✔		✔	✔	≥6,71
LILLE*	✔	✔	✔		✔	✔	≥0,45
AHHS - Alcoholic Hepatitis Histologic System: fibrosis, neutrophil infiltration, bilirubinostasis, megamitochondria. Severe ≥ 6 points.							

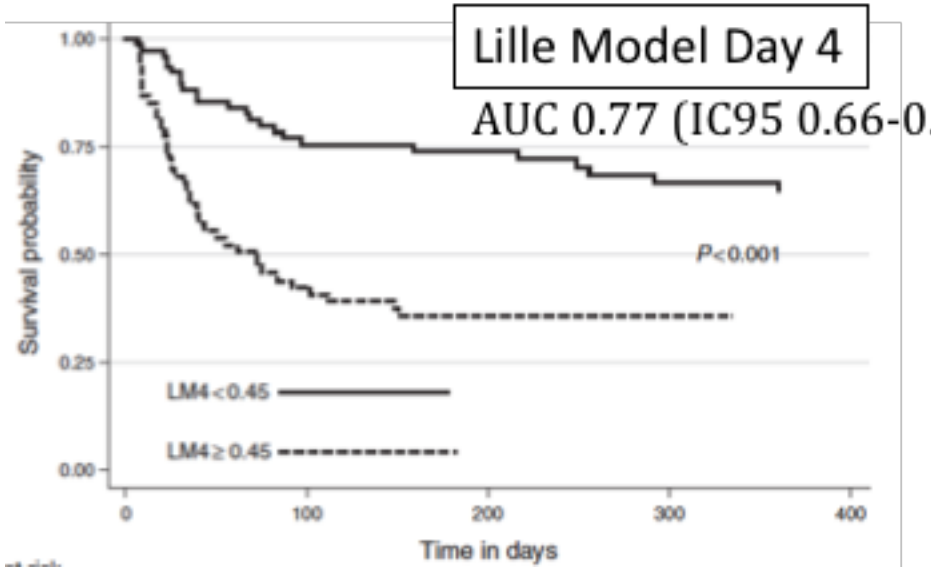
* Bilirubin at baseline and day 7 / day 4

**PT: prothrombine time. INR: International Normalized Ratio.

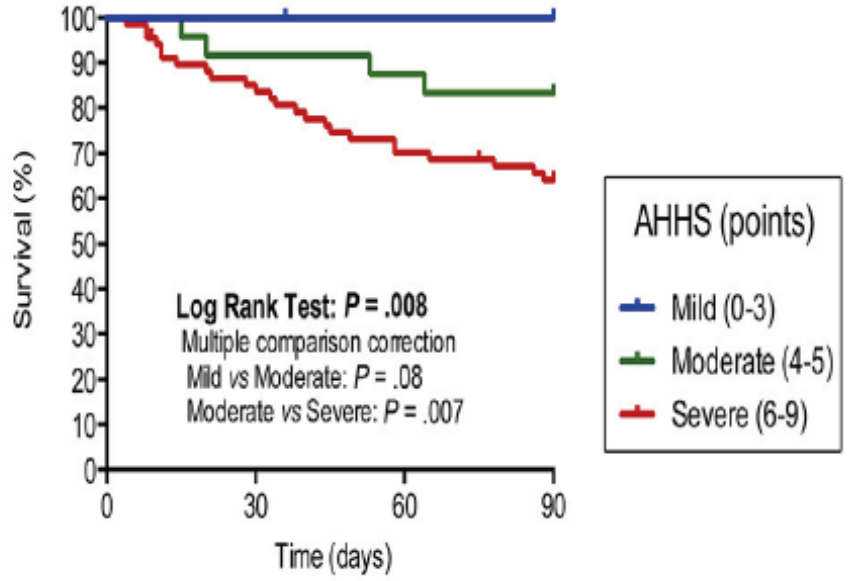
Altamirano J et al. Gastroenterology. 2014. EASL Clinical Practice Guidelines: Management of alcohol-related liver disease. J Hepatol. 2018;69(1):154-81.
Garcia-Saenz-de-Sicilia M, et al. Am J Gastroenterol. 2017;112(2):306

Lille 4





AHHS



	Points
Stage of fibrosis	
No fibrosis or portal fibrosis	0
Expansive fibrosis	0
Bridging fibrosis or cirrhosis	+3
Bilirubinostasis	
No	0
Hepatocellular only	0
Canalicular or ductular	+1
Canalicular or ductular plus hepatocellular	+2
PMN infiltration	
No/Mild	+2
Severe	0
Megamitochondria	
No megamitochondria	+2
Megamitochondria	0

Altamirano J et al. Gastroenterology. 2014
Garcia-Saenz-de-Sicilia M et al. Am J Gastroenterol. 2017;112(2):306

Serum bile acid profiles distinguish severe alcoholic hepatitis from decompensated alcohol-related cirrhosis

BACKGROUND & AIMS

- Accurate diagnosis of severe alcoholic hepatitis (SAH) is important in determining therapy
- However, surveys suggest only a minority of patients undergo liver biopsy due to high cost and potential complications
- **Aim:** Determine a new non-invasive diagnostic test for steatohepatitis that would distinguish SAH from its most common differential, acute decompensation (DC) of alcohol-related cirrhosis

METHODS

- SAH patients had biopsy-proven steatohepatitis with MDF ≥32
- Serum BAs measured by mass spectrometry in two cohorts

	Exploratory cohort		Validation cohort	
	SAH	DC	SAH	DC
N=	68	21	65	40
Mean age (years)	49	54	47	51
Median MELD	23	26	25	30
Mean bilirubin (µmol/L)	378	246	323	261
Median MDF	54	65	56	79

- Analyzed by OPLS-DA and AUROC

Tyson LD, et al. ILC 2019; PS-174

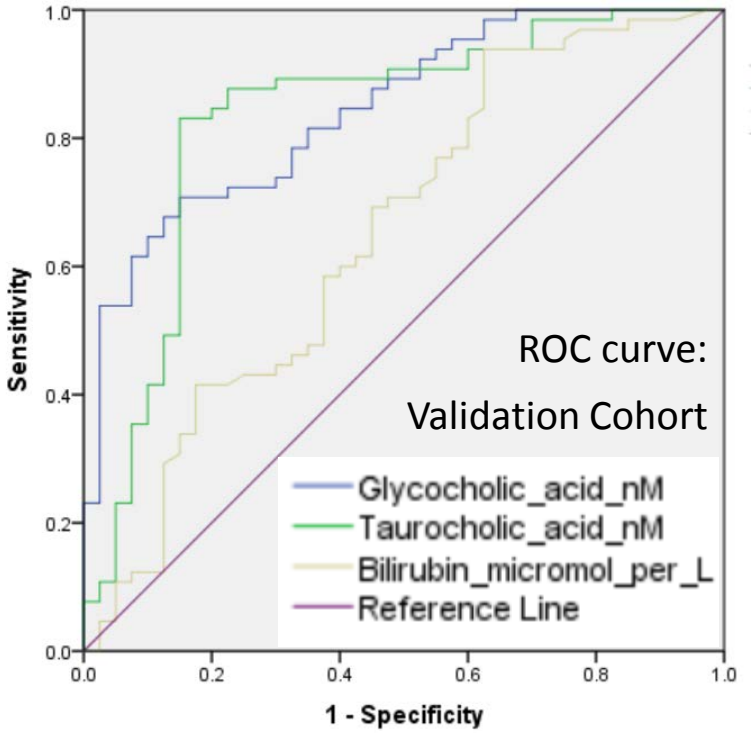
Serum bile acid profiles distinguish severe alcoholic hepatitis from decompensated alcohol-related cirrhosis

RESULTS

- OPLS-DA accurately discriminated AH from DC in both cohorts:
  - GCA -**GLYCOCHOLIC** acid and TCA -**TAUROCHOLIC** acid were the dominant metabolites

	Full BA profile	GCA	TCA	Bilirubin
Exploratory cohort				
AUROC	0.93	0.90	0.87	0.79
95% CI	0.87–0.99	0.83–0.97	0.77–0.97	0.67–0.91
Validation cohort				
AUROC	0.93	0.85	0.83	0.65
95% CI	0.88–0.98	0.77–0.92	0.74–0.92	0.54–0.76

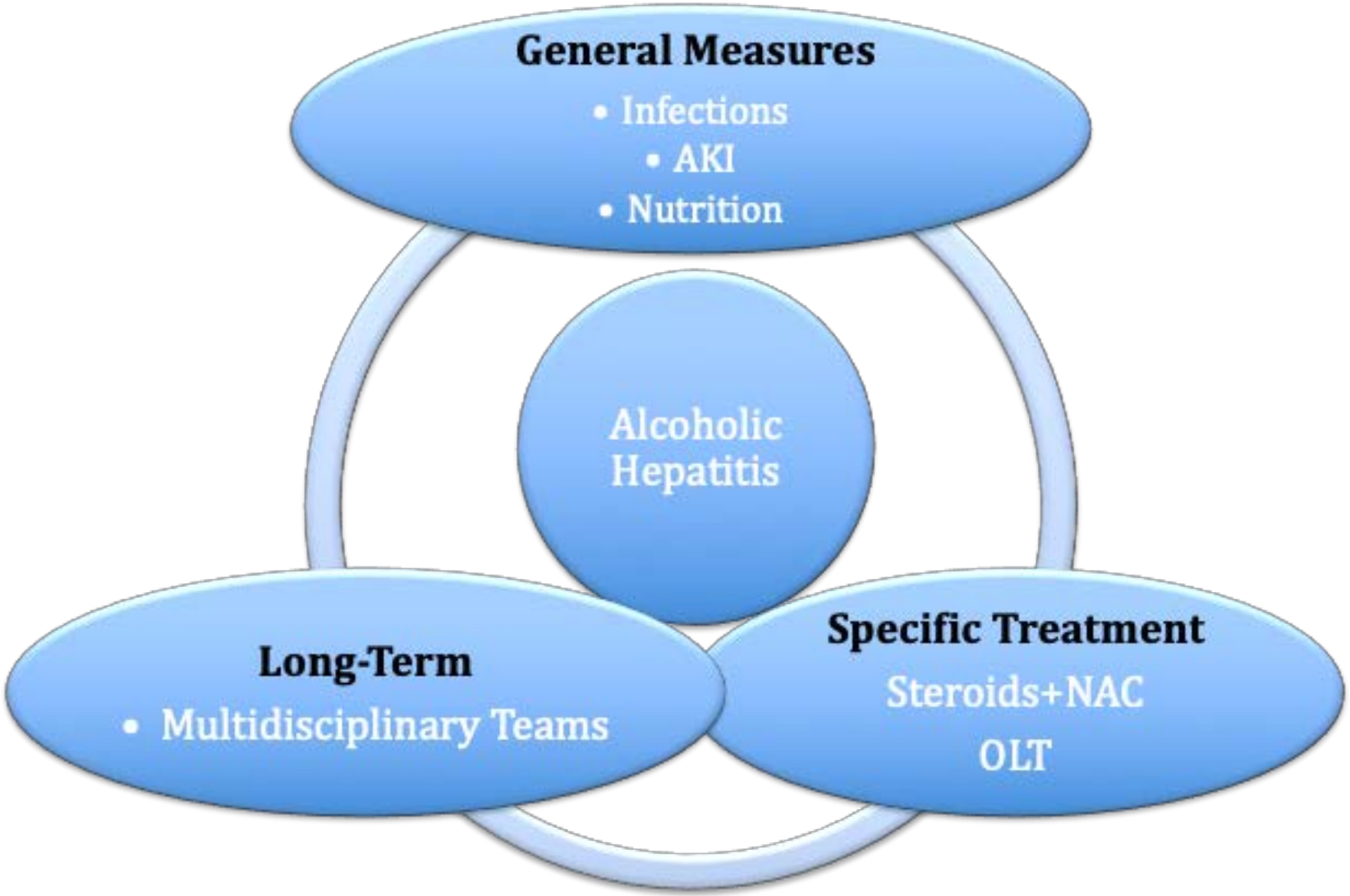
AUROC analyses for serum BAs and bilirubin



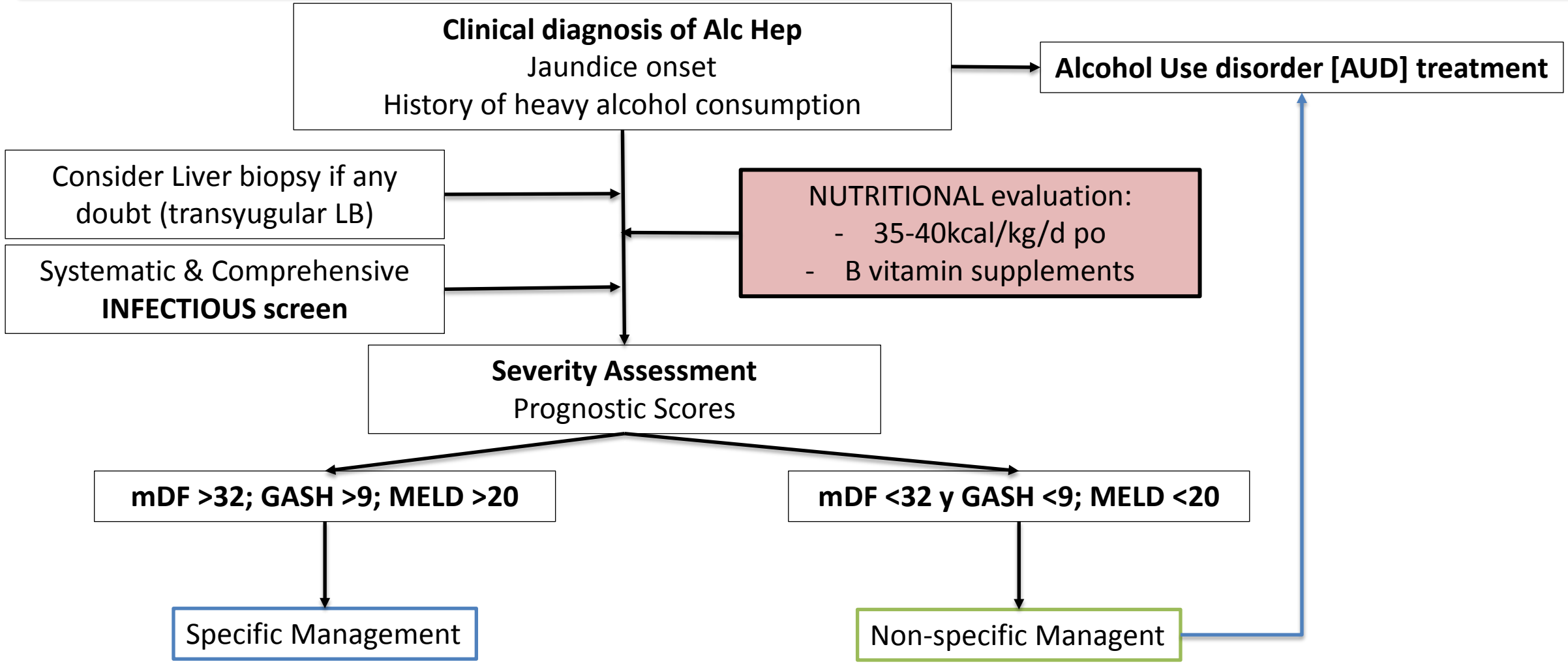
CONCLUSIONS SAH has a serum BA profile distinct from patients with DC and similar liver dysfunction. The entire BA profile and individual BAs of GCA and TCA are promising non-invasive biomarkers for SAH, and may reduce the need for liver biopsy

Tyson LD, et al. ILC 2019; PS-174

Alcoholic Hepatitis Treatment



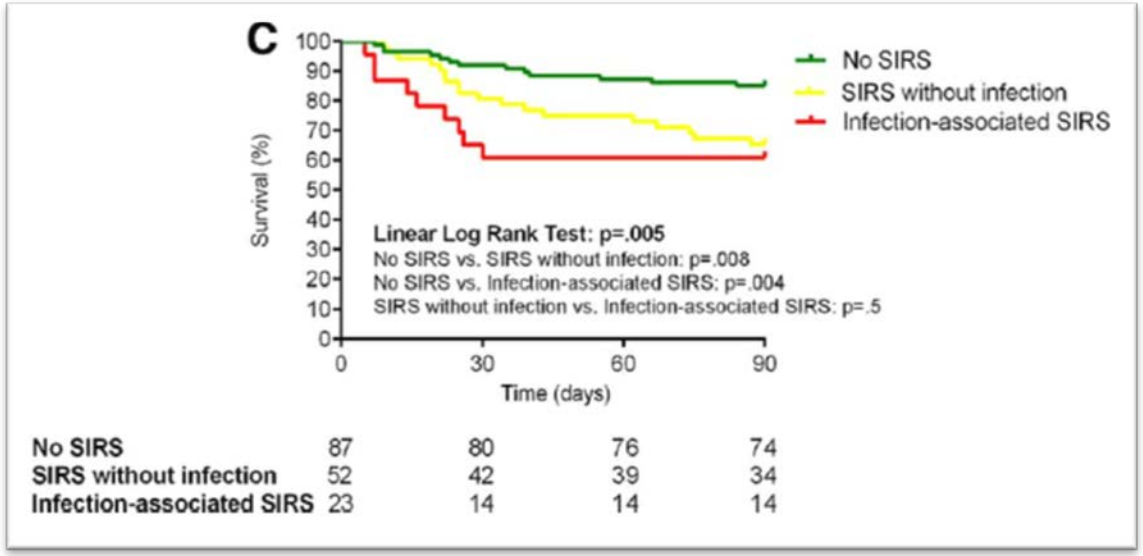
Algorithm to manage Alcoholic Hepatitis [Alc Hep]



EASL Clinical Practice Guidelines: Management of alcohol-related liver disease. J Hepatol. 2018;69(1):154
ACG Clinical Guideline: Alcoholic Liver Disease. Am J Gastroenterol. 2018;113(2):175

– General Measures: **INFECTIONS**

At admission: **25%** of the patients have infections
20-60% also have Systemic Inflammatory Response Syndrome [SIRS]



SIRS associated infection:
- **Procalcitonin** 0,45ng/mL (PPV 83.3; NPV 71%)

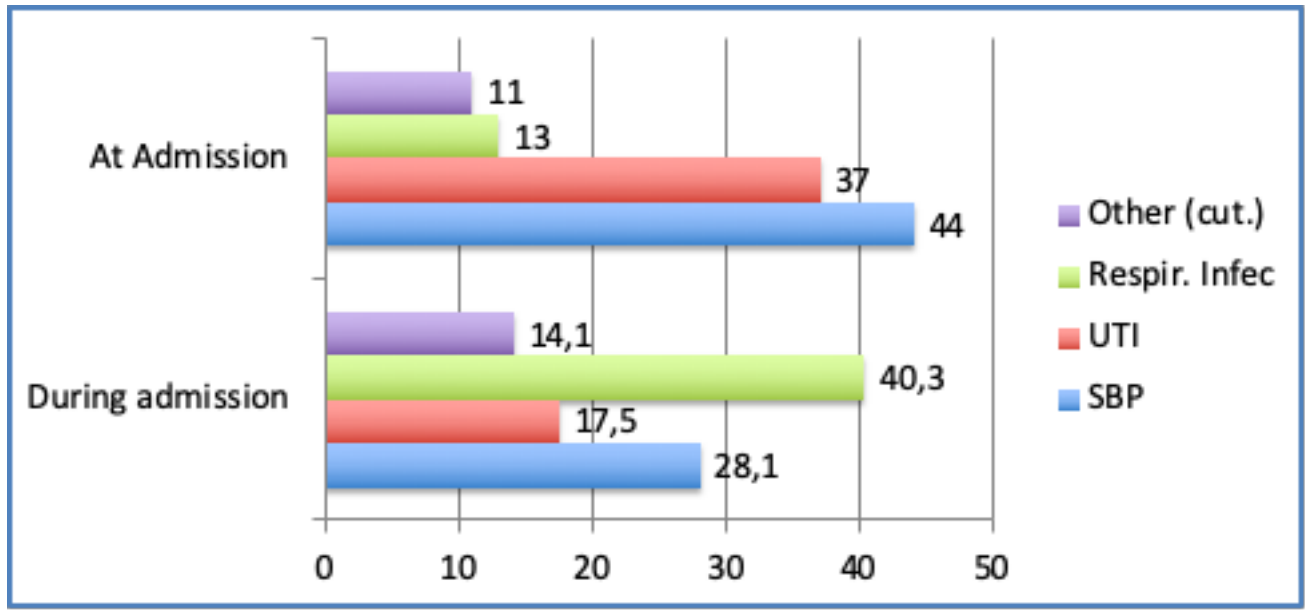
Definición de SIRS: ≥ 2:
1. Tª <36 or >38º C
2. HR >90 bpm
3. RR>20bpm or PaCO2 <32mmHg
4. Leukocytes >12.000 or <4.000, immature neutrophils >10%

23,7% develop infections after starting steroids.

Steroid **non-responders** are prone to infections.

It is the **first cause of death** in the first 90 days.

Infections during admission reduces 2-month survival [SV]: -> 46,4 vs 77,3%.

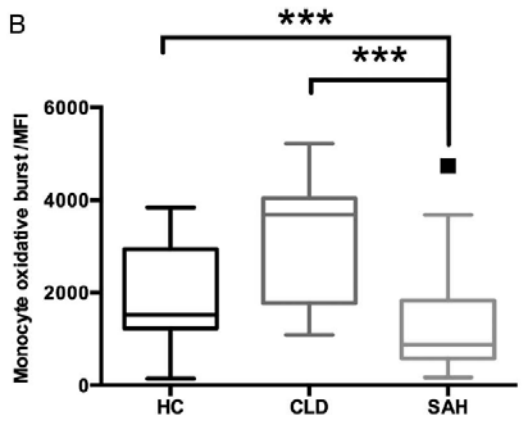


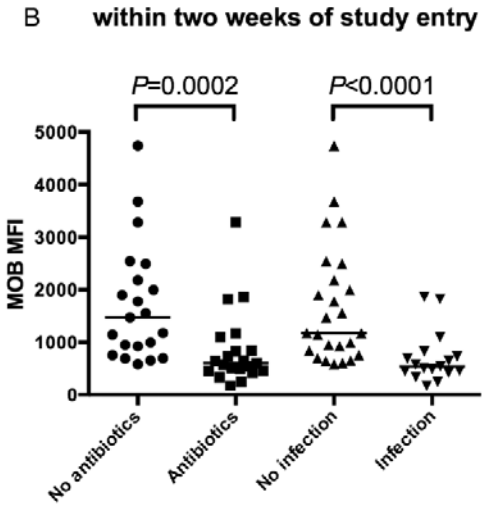
*SBP: Spontaneous bacterial peritonitis; UTI: urinary tract infection

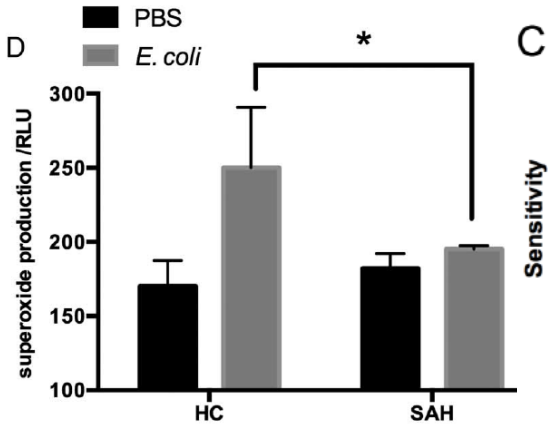
Michelena, J. Et al. Hepatology. 2015. Prado V, et al. Ann Hepatol. 2016;15(4):463-73 Orntoft NW, et al. Clin Gastroenterol Hepatol. 2014;12(10):1739-44 e1.
Louvet A, et al. Gastroenterology. 2009;137(2):541-8.

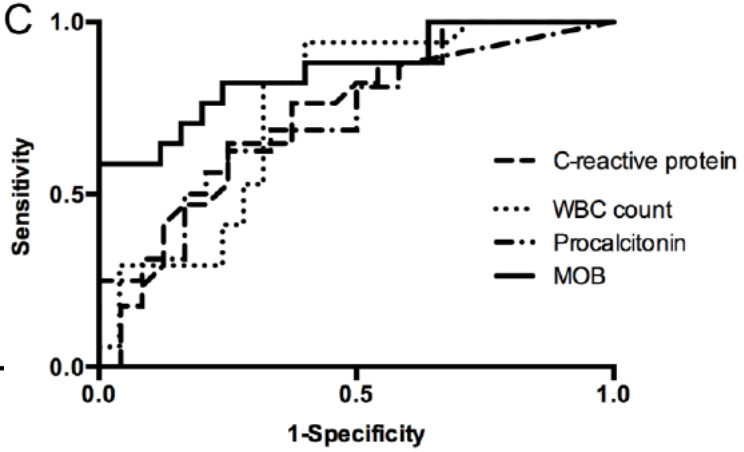
– General Measures: **INFECTION detection**

Phagocytosis and monocyte oxidative burst [MOB]









Circulating Level of Bacterial DNA

- >18pg/mL (80% specificity D7 Infection)

Table 4. Multivariate Logistic Regression Analysis Incorporating Bacterial DNA, Model for End-Stage Liver Disease, and White Blood Cell Count for Prediction of Early-Onset Infection in Patients Treated With and Without Prednisolone

	Prednisolone		No prednisolone	
Variable	OR (95% CI)	*P* value	OR (95% CI)	*P* value
^{hi}bDNA	4.68 (1.80–12.17)	.001	0.83 (0.39–1.75)	.62
MELD	1.08 (0.99–1.17)	.097	1.07 (0.99–1.15)	.08
WBC	1.06 (0.97–1.16)	.187	1.07 (0.99–1.15)	.07

MELD, Model for End-Stage Liver Disease; WBC, white blood cell count.

Vergis N, et al. Gut. 2017;66(3):519-29 .
Vergis N, et al. *Gastroenterology* 2017; **152**(5): 1068-1077

– General Measures: **INFECTIONS**

ESTUDIO PILOTO DE LA ADMINISTRACIÓN DE RIFAXIMINA EN LA HEPATITIS AGUDA ALCOHOLICA GRAVE

César Jiménez[1]; Meritxell Ventura[1,3,4]; Margarita Sala[2,3,5]; Nuria Cañete[2,3,6]; María Poca[2,3,7]; Macarena Simón-Talero[1,3]; José Altamirano[1]; Ramón Bataller[4]; Víctor Vargas[1,2,3] InTeam Consortium Study Investigators[6]

[1]Servicio de MI-Hepatología. Hospital Vall d'Hebron; [2]Universidad Autónoma de Barcelona. [3]CIBEREHD; [4]Division of Gastroenterology, Hepatology and Nutrition. University of Pittsburgh; [5]Hospital Germans Trias i Pujol; [6]Hospital del Mar; [7]Hospital de la Santa Creu i Sant Pau; [8]InTeam Consortium Study Investigators

Severe Alc Hep, n=19 vs Historic Controls n=19.

GRÁFICO 1

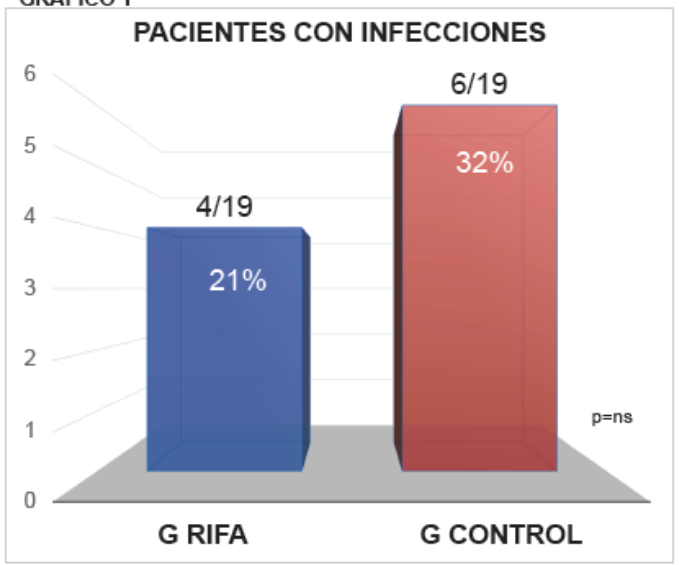


GRÁFICO 2

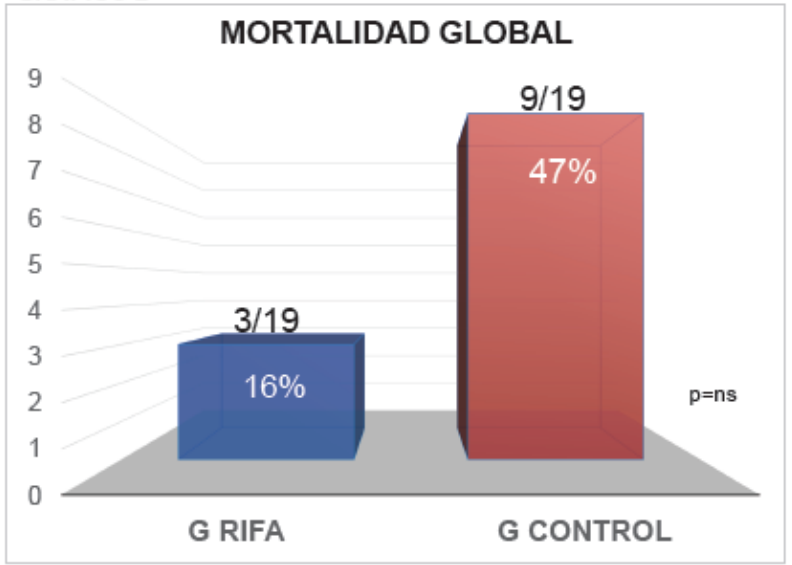
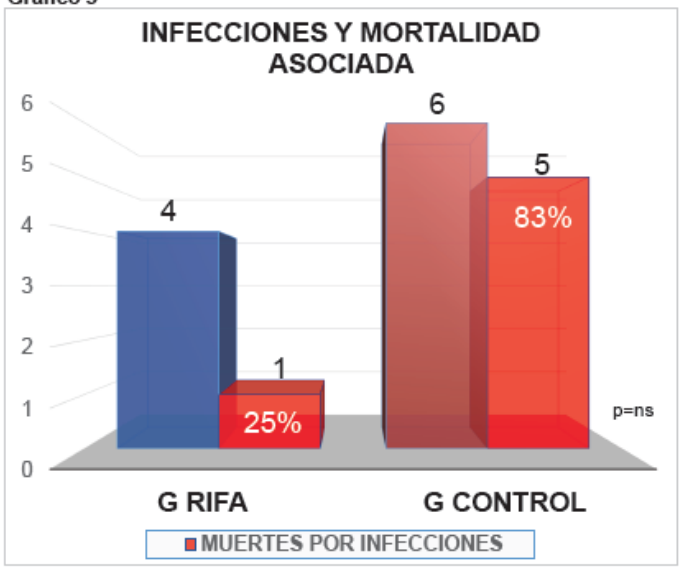


Gráfico 3



No relevant adverse events

– General Measures: **INFECTIONS**

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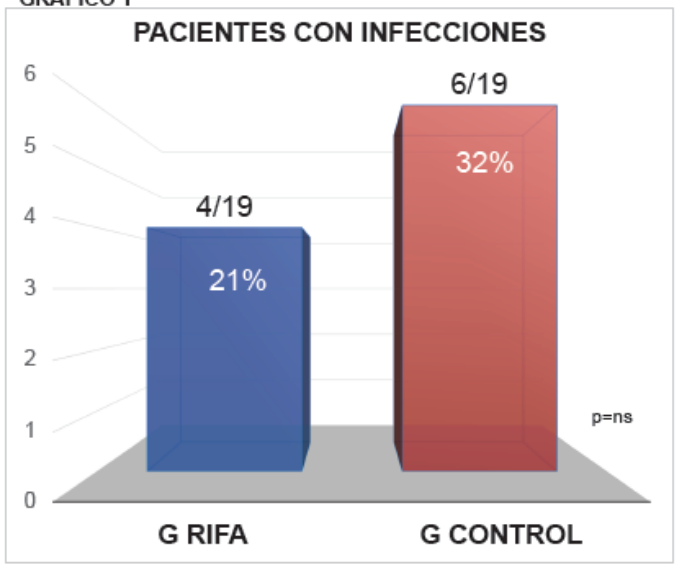


GRÁFICO 2

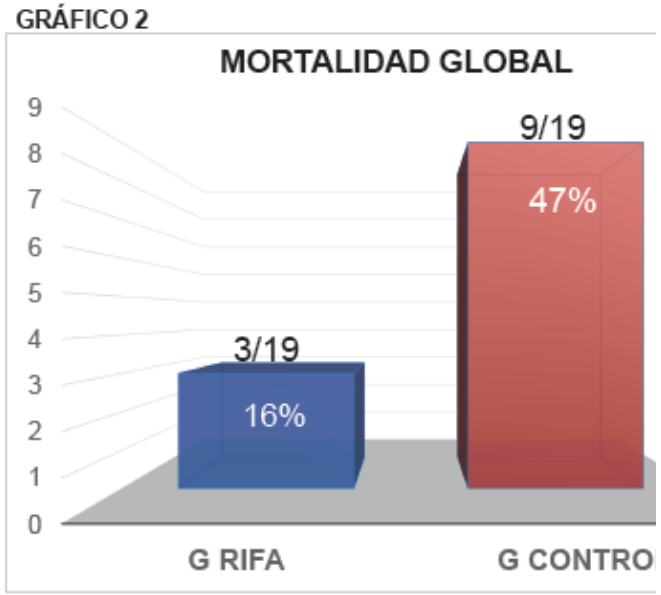
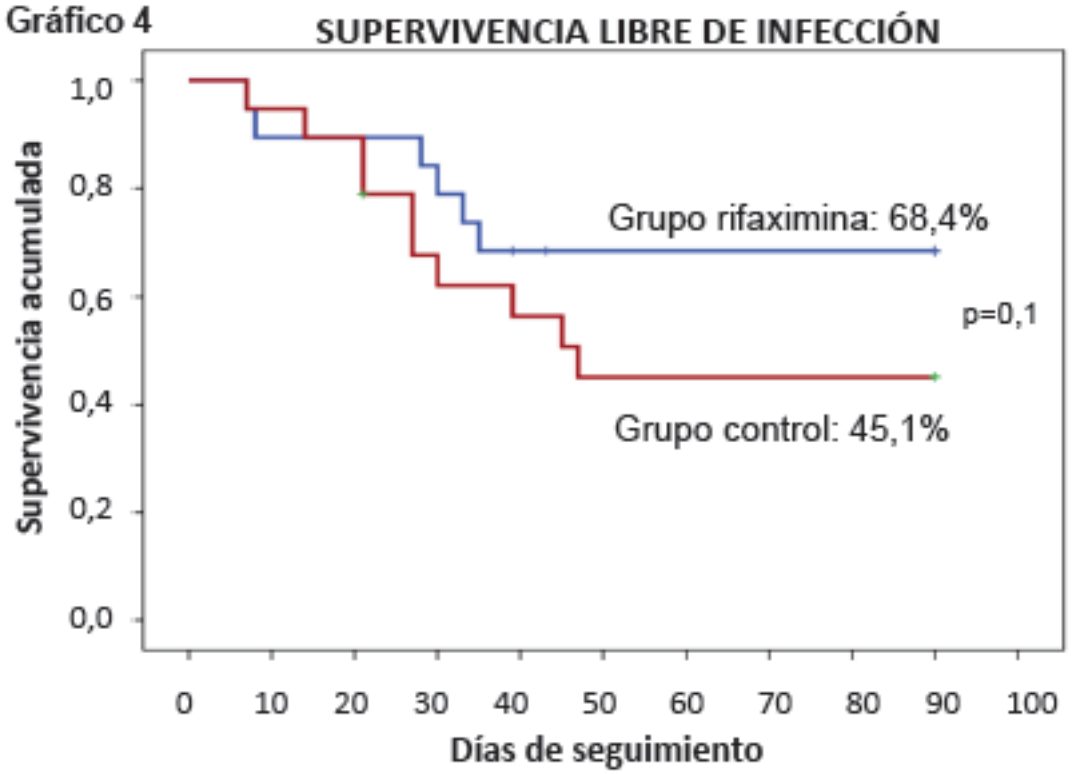


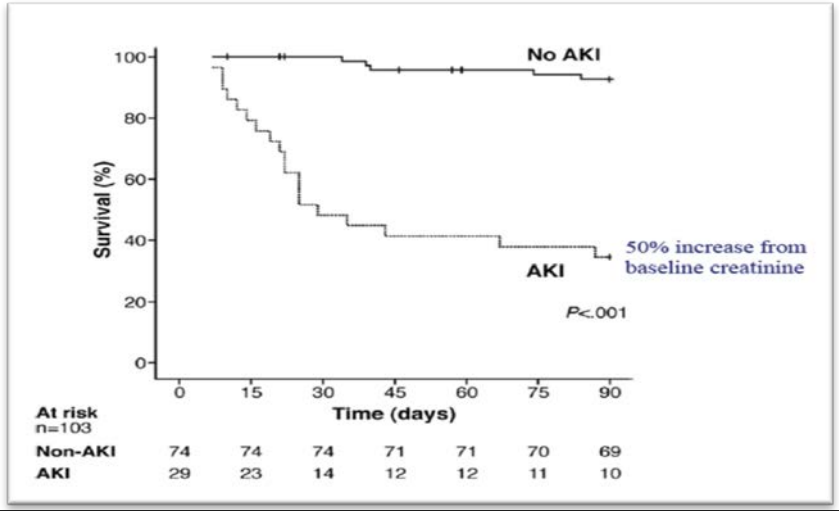
Gráfico 4



No relevant adverse events

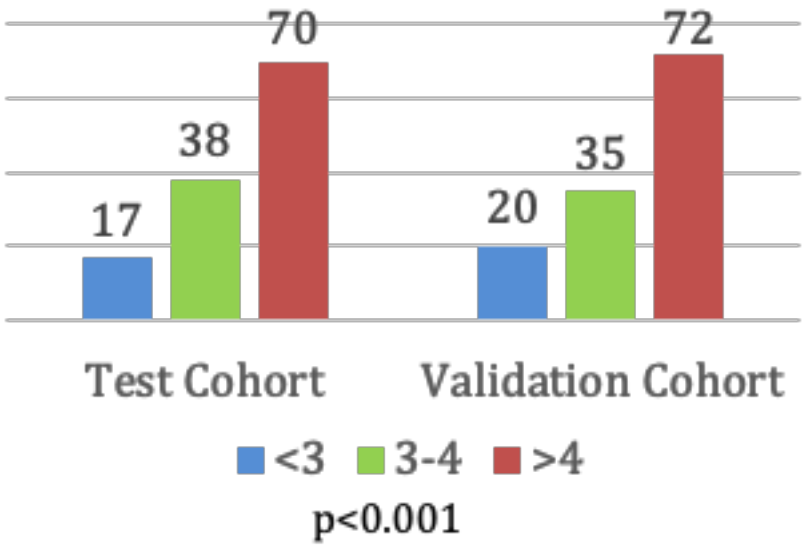
– General Measures: **ACUTE KIDNEY INJURY**

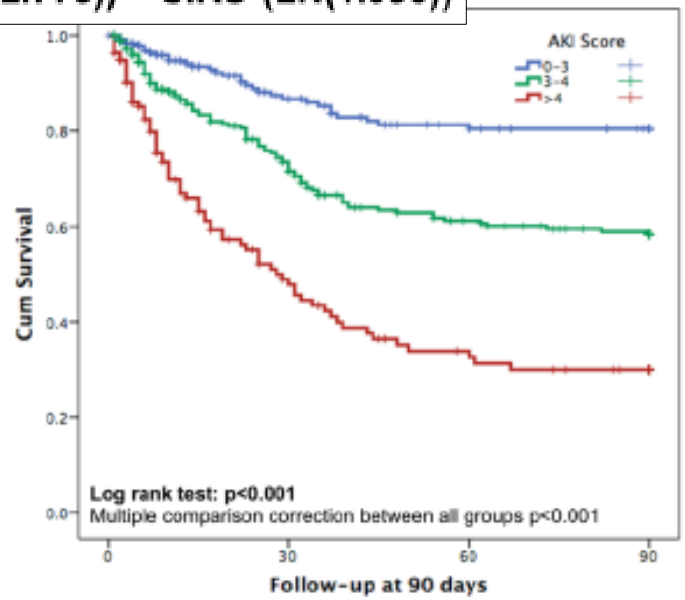
- Early predictor of mortality:
  - 23%*-32% AKI
  - 90-day mortality: 65% vs 7%.
- AKI precictors*:
  - SIRS at admission
  - Bilirubin
  - INR
- **AKI risk score [0-4]:**
  - Hepatic Encephalopathy.
  - SIRS
  - MELD



AKIN criteria:
- ≥ 0.3mg/dl
- ≥ 50% baseline

AKI-AH Risk Score = MELD*(LN(1.109)) + HE*(LN(2.775)) + SIRS*(LN(1.993))





Altamirano J. et al. CGH 2012. Serste T, et al. Liver Int. 2015;35(8):1974.
Sujan R, et al. Liver transplantation. 2018;24(12):1655

Baseline neutrophil-to-lymphocyte ratio indicates infection and acute kidney injury, and is related to corticosteroid Lille response in alcoholic hepatitis

BACKGROUND & AIMS

- Neutrophil-to-lymphocyte ratio (NLR) has been shown to reflect sepsis and inflammation
- This study assessed the role of the NLR in the prognosis of alcoholic hepatitis

METHODS

- NLR calculated from 789 patients in the **STOPAH trial**
- Patients were randomized to prednisolone treated or no prednisolone treatment groups
- Prevalent infections treated prior to randomization; infections developing after inclusion were recorded
- Prevalent AKI was defined by initial creatinine ≥133 µmol/L. Incident AKI was defined as an increase of serum creatinine by 26.5 µmol/L, or by 50% by Day 7 in those without baseline AKI
- OR and t-tests were used for comparative analysis

RESULTS

- Higher NLR found in patients with prevalent AKI (11.1 vs. 6.0; p=0.001 [2.6, 7.6]) and with prevalent infection (7.8 vs. 6.3; p=0.02 [0.2, 2.8]) vs those without such features
- Higher NLR values were seen in those patients with incident AKI and in those who developed infection (*Table*)
- If NLR ≥5, a favourable Lille score was more likely with prednisolone treatment (*Figure)*

Forrest E, et al. ILC 2019; GS-11

Baseline neutrophil-to-lymphocyte ratio indicates infection and acute kidney injury, and is related to corticosteroid Lille response in alcoholic hepatitis

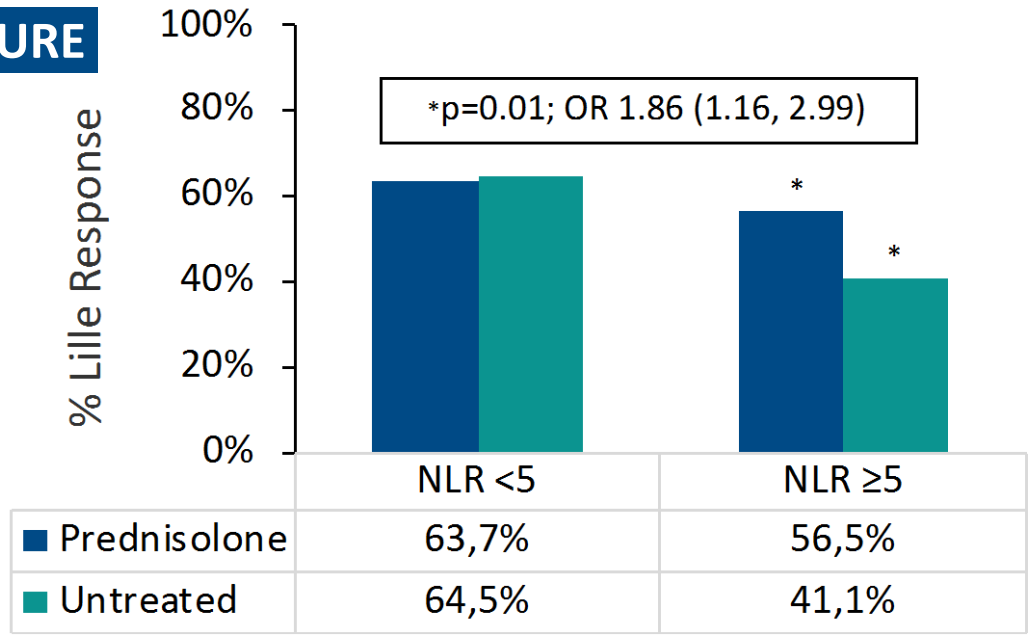
RESULTS (Cont.)

- Risk of developing infection and incident AKI after prednisolone treatment greater if **NLR >8** vs ≤8:
  - Infection by Day 7: 17.3% vs 7.4%: p=0.006; OR 2.60
  - Infection by Day 28: 30.6% vs 20.0%: p=0.031; OR 1.76
  - Incident AKI: 20.8% vs 7.0%: p=0.008; OR 3.46

TABLE

		NLR	
Incident AKI	Present (n=67)	7.5 (6.4, 8.7)	p=0.0056
	Absent (n=403)	6.0 (5.6, 6.4)	
Infection by Day 7	Present (n=94)	7.8 (6.3, 9.2)	p=0.035
	Absent (n=695)	6.1 (5.8, 6.5)	
Infection by Day 28	Present (n=185)	7.1 (6.3, 8.0)	p=0.025
	Absent (n=604)	6.1 (5.6, 6.5)	

FIGURE

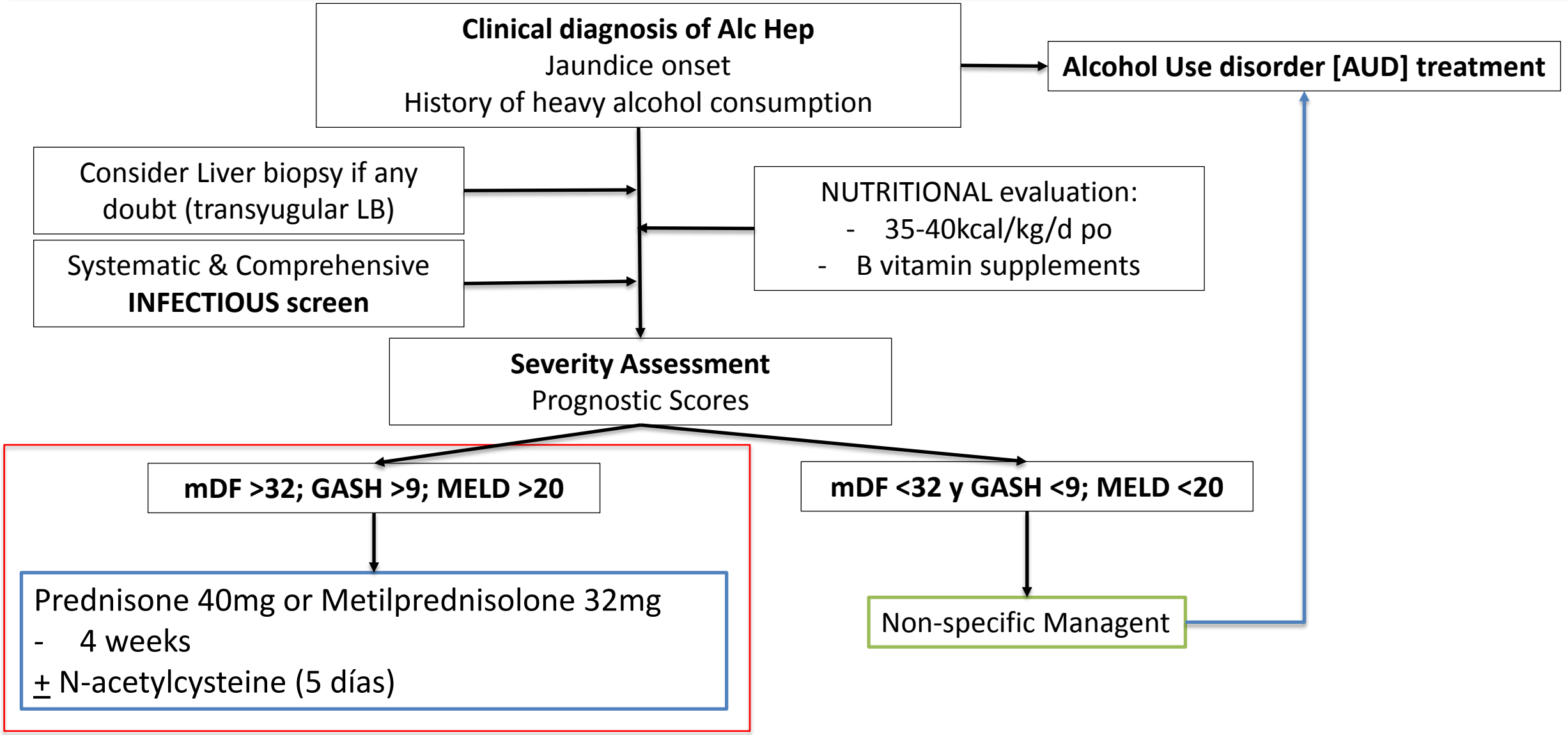


CONCLUSIONS

High NLR associates with prevalent AKI and infection in alcoholic hepatitis. A Lille response to prednisolone is more likely if NLR ≥5, but development of infection or AKI after prednisolone treatment is greater if NLR >8

Forrest E, et al. ILC 2019; GS-11

Specific Management

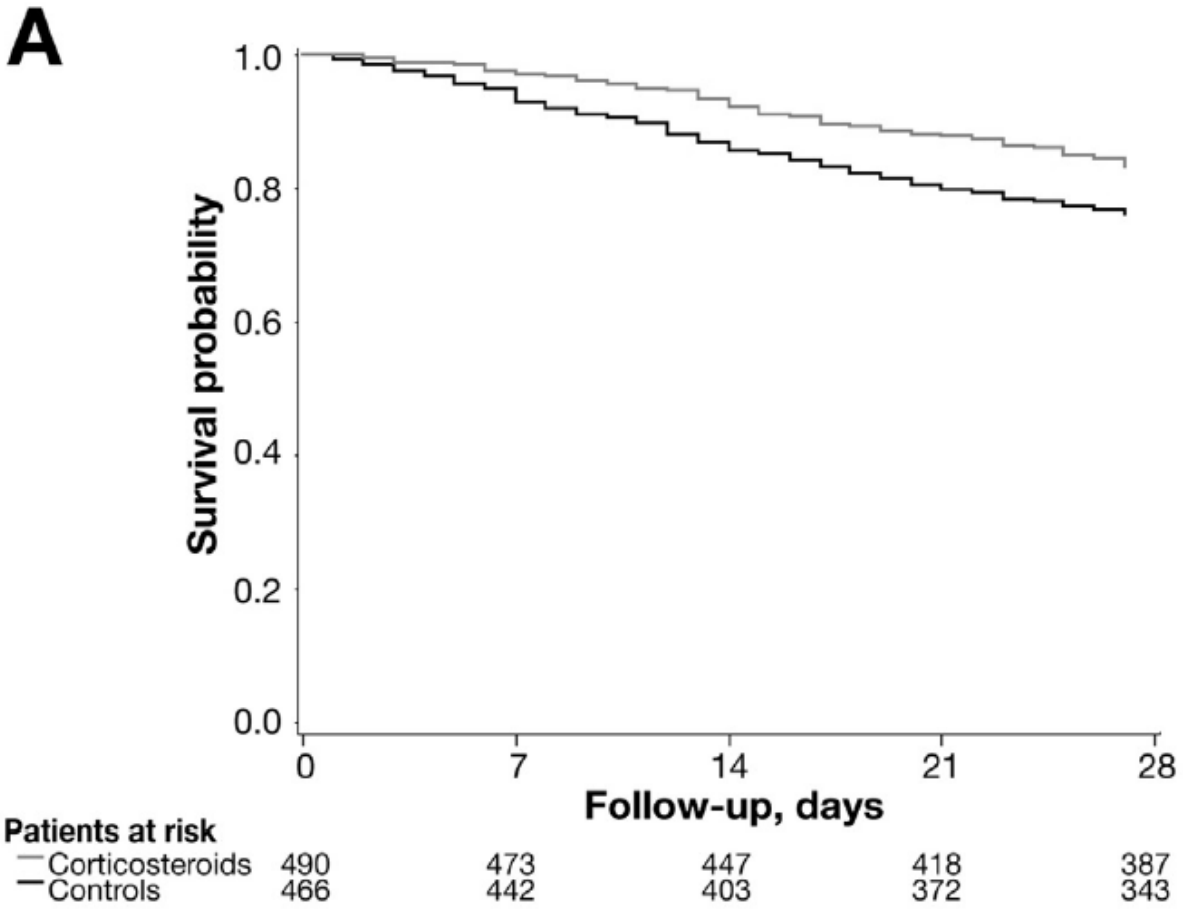


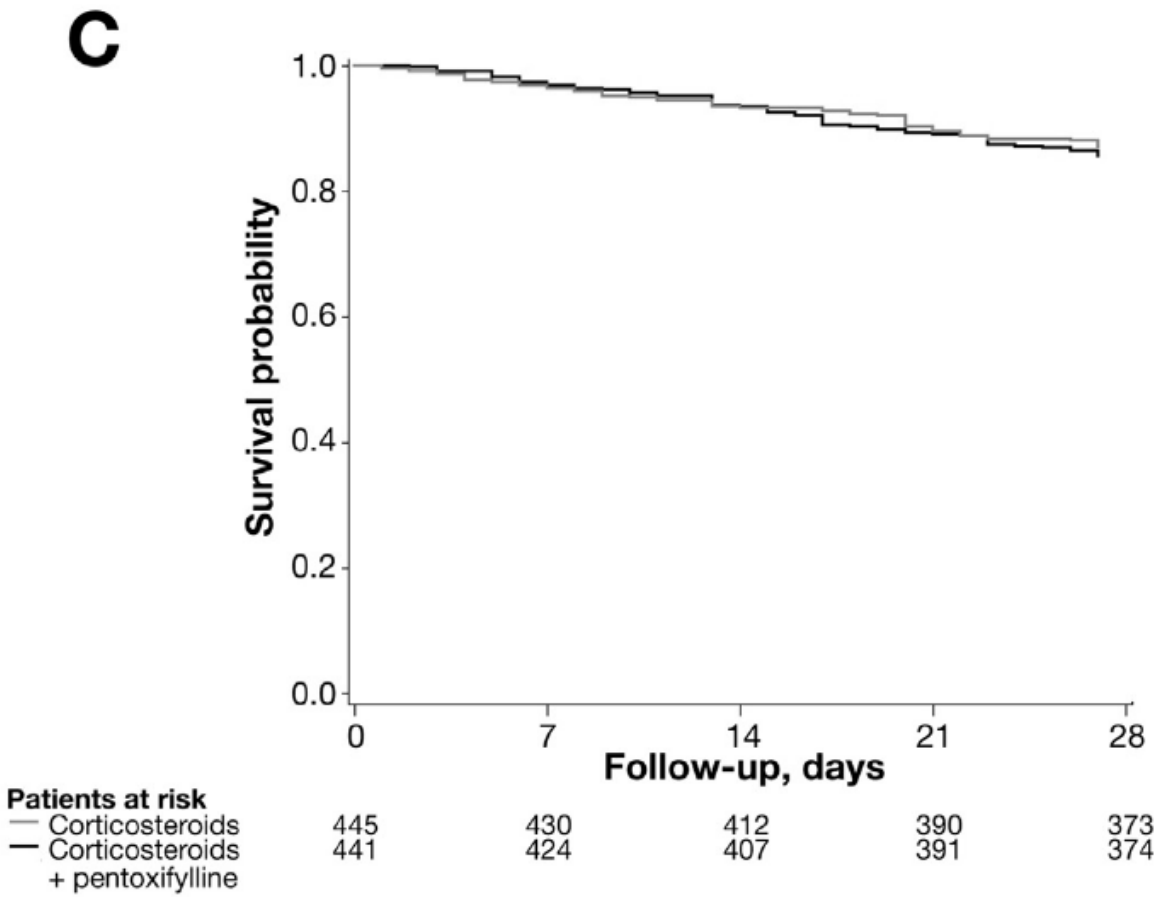
EASL Clinical Practice Guidelines: Management of alcohol-related liver disease. J Hepatol. 2018;69(1):154
ACG Clinical Guideline: Alcoholic Liver Disease. Am J Gastroenterol. 2018;113(2):175

Specific Management: STEROIDS

Prednisolone 40mg po for 28 days (stop/tapered dose for 3 weeks)

Meta-analysis: 11 studies – 2111 patients – Primary End Point: 28-day Mortality.





Louvet A, et al. Gastroenterology. 2018;155(2):458

Specific Management: STEROIDS

EVALUACIÓN DE UNA PAUTA DESCENDENTE RÁPIDA DE CORTICOIDES EN LA HEPATITIS ALCOHÓLICA GRAVE

Berta Cuyàs Espí (1), Maria Poca Sans (1,2), Elida Oblitas Susaníbar (1), Eva Mª Román Abal (1, 2, 3), Carlos Guarner Aguilar (1,2), Germán Soriano Pastor (1,2)

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3. Escola Universitària d'Infermeria EUI-Sant Pau

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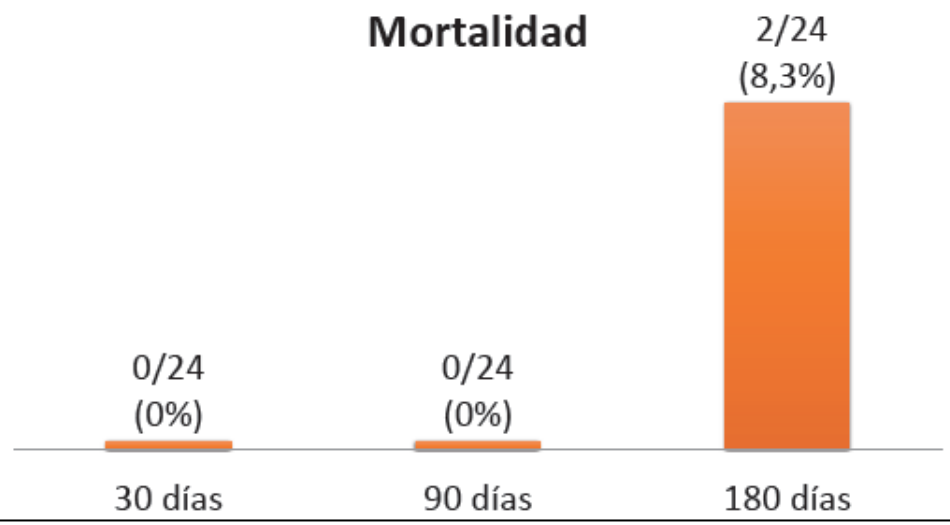
43 CONGRESO anual 2018
Asociación Española para el Estudio del Hígado

Retrospectivo. Prednisona 40mg, 7días – descenso de 10mg/sem hasta suspender

Tabla 2. Tratamiento (n=24)	
Corticoterapia	24 (100%)
Duración corticoterapia días	34 ± 9,2
Antibiótico profiláctico	18 (75%)
Pentoxifilina concomitante	14 (58,3%)
Nutrición enteral	5 (20,8%)
Suplementos nutricionales	23 (95,8%)
Abstinencia a los 180 días	14 (58,3%)

Resultados expresados en frecuencias (%) y medias ± desviación estándar



Literatura (Louvet, Hepatology 2007):	5%	10%	15%

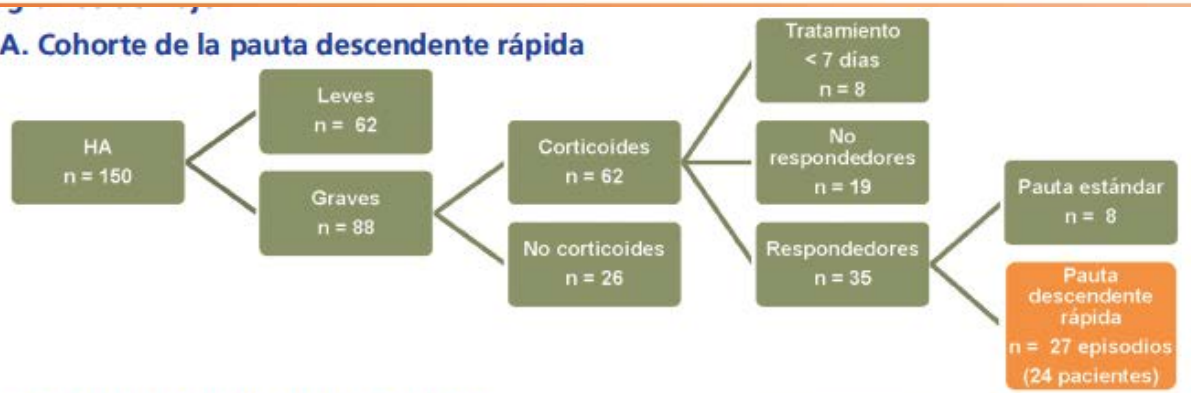
Cuyas B et al. AEEH 2018

COMPARACIÓN ENTRE UNA PAUTA DESCENDENTE RÁPIDA DE CORTICOIDES Y LA PAUTA ESTÁNDAR EN LA HEPATITIS ALCOHÓLICA GRAVE

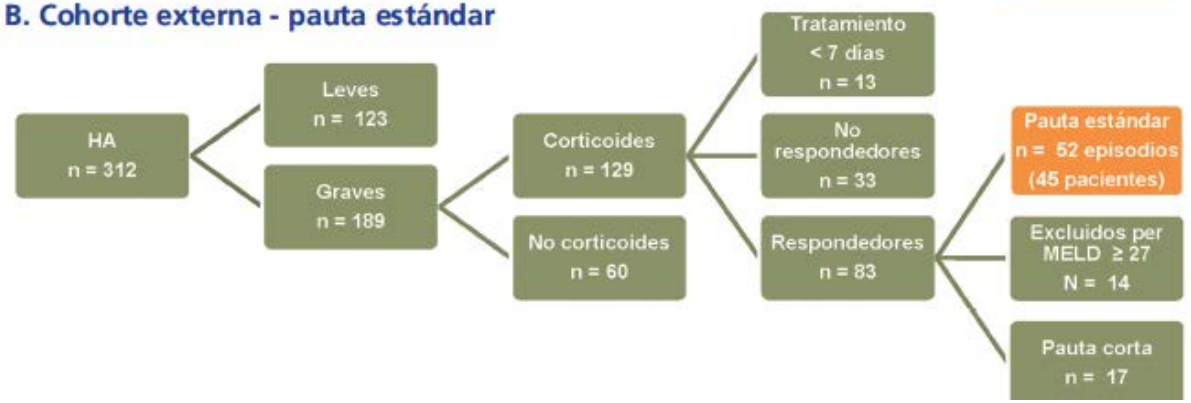
Berta Cuyàs[1]; Elida Oblitas[1]; Marc Batlle[2]; Gerard Suris[3]; Alberto Amador[3]; Margarita Sala[4,5]; Helena Masnou[4]; José Castellote[3]; Nuria Cañete[2]; Eva Román[1,5,6]; Carlos Guarner[1,5]; Germán Soriano[1,5]; Maria Poca[1,5]

1- Servicio de Patología Digestiva, Hospital de la Santa Creu i Sant Pau, UAB, Barcelona | 2- Sección de Hepatología, Servicio de Aparato Digestivo, Hospital del Mar, UAB, IMIM, Barcelona. | 3- Unidad de Hepatología, Servicio de Aparato Digestivo. Hospital Universitari de Bellvitge, UB. IDIBELL | 4- Unidad de Hepatología, Servicio de Digestivo. Hospital Universitari Germans Trias i Pujol. Badalona | 5- CIBERehd | 6- Escola Universitària d'Infermeria EUI-Sant Pau

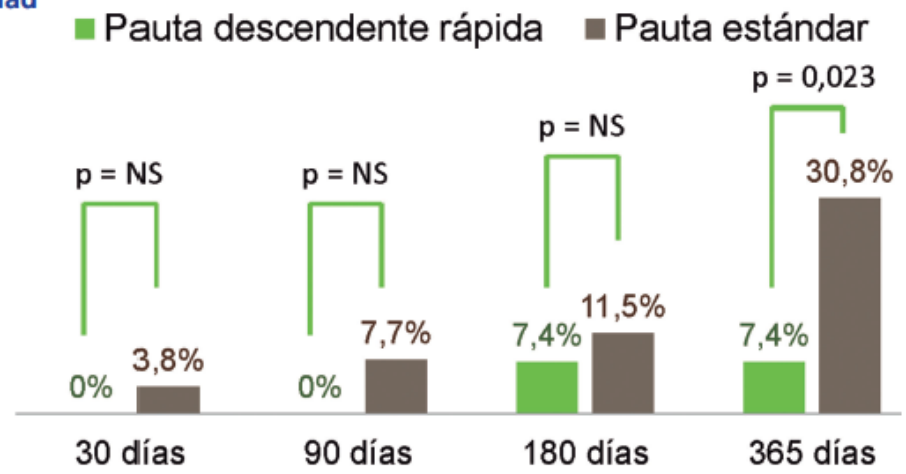
A. Cohorte de la pauta descendente rápida



B. Cohorte externa - pauta estándar



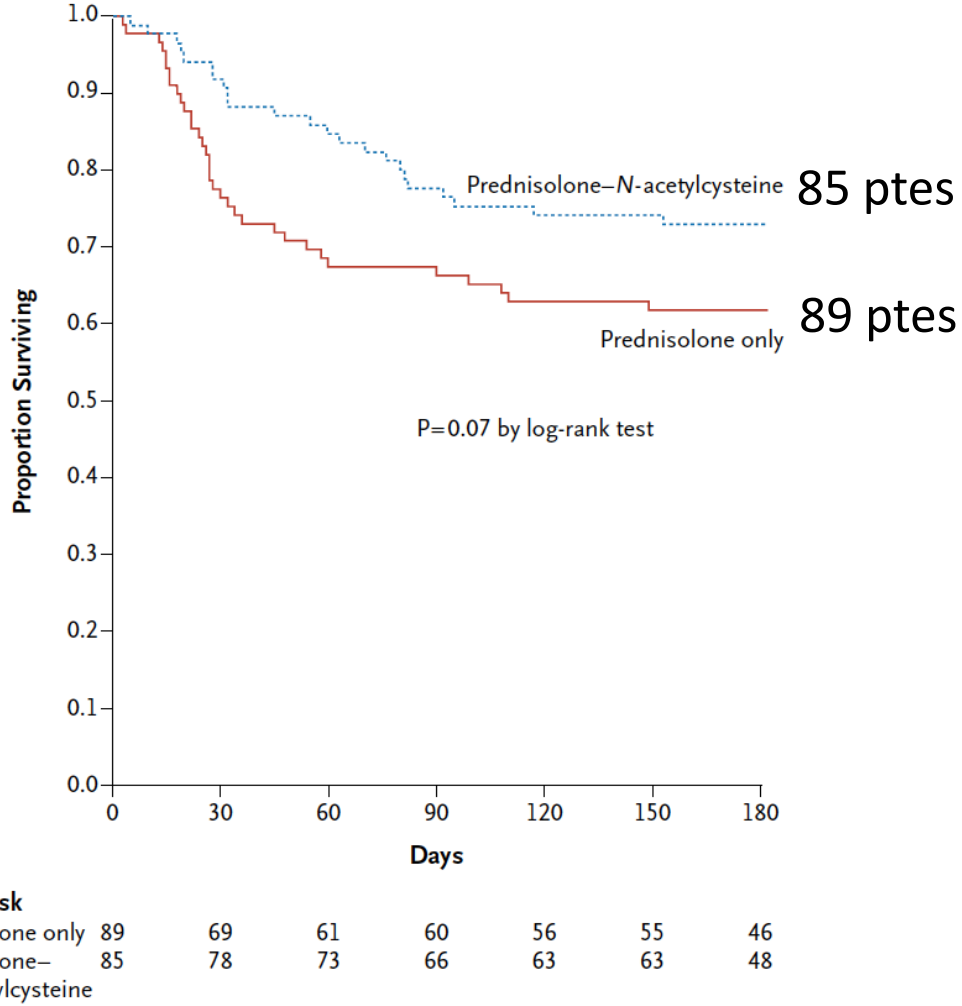
4. Mortalidad



*El grupo de pauta rápida, asoció más frecuentemente antibiótico profiláctico (77% vs 44%) y un valor menor de albúmina (24 vs 26 g/L)

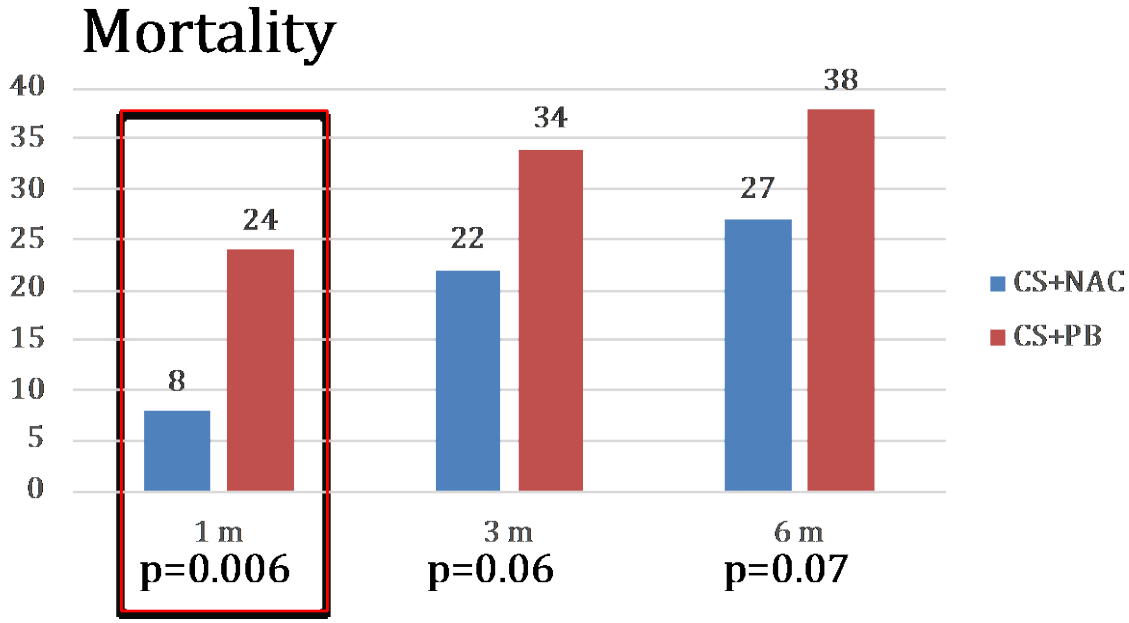
Specific Management: N-Acetyl-cysteine [NAC]

NAC: 100mg/kg/day for 5 days (+prednisolone [CS])



85 ptes

89 ptes



Mortality due to HRS NAC group (6 months):

- 9% vs 22% (p=0.02)

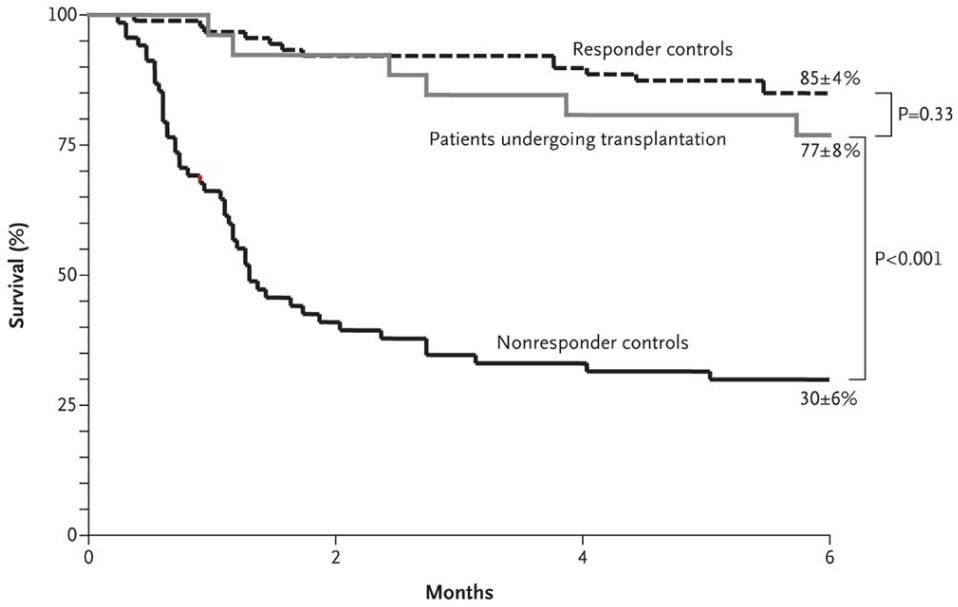
Infections were less frequent in NAC group:

- 19% vs 42% (p=0.001)

*HRS: Hepatorenal Syndrome

Nguyen-Khac E et al. The New England journal of medicine. 2011;365(19):1781

Specific Management: **Liver Transplant**



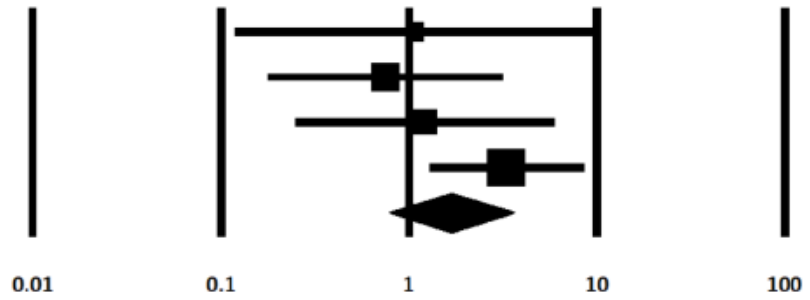
Non-responders to steroids.

Highly selected patients

2/26 alcohol relapsers. Short follow-up.

Alcohol Relaps risk

Study name	Subgroup within study	Comparison	Outcome	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Immordino 2007	Histological ASH	2_ASH transplanted vs. alcoholic cirrhosis transplanted	Alcohol relapse	1.071	0.121	9.480	0.062	0.951
Lee 2017	Severe ASH	2_ASH transplanted vs. alcoholic cirrhosis transplanted	Alcohol relapse	0.747	0.180	3.107	-0.401	0.689
Tomé 2002	Histological ASH	2_ASH transplanted vs. alcoholic cirrhosis transplanted	Alcohol relapse	1.208	0.249	5.861	0.235	0.814
Wells 2007	Histological ASH	2_ASH transplanted vs. alcoholic cirrhosis transplanted	Alcohol relapse	3.312	1.303	8.420	2.515	0.012
Pooled estimate risk				1.683	0.791	3.582	1.351	0.177



Systematic Review and Meta-analysis: – 11 studies

Mathurin P et al. N Engl J Med 2011;365:1790-1800
Marot A, et al. PLoS One. 2018;13(1):e0190823

Long Term Management

398 patients with Severe Alc Hep, steroid treated. 60% were responders.

Follow-up: 42 months [11-88]. Short-term prognosis: MELD and Lille.

- Long term prognosis: **EtOH relaps** (>30g/d). Proportional to amount and Lille.
- Relaps: 1st-year- 25,2%, 3rd-y año- 33.7%, 5th-y - 35,2%.

	Short-Term			
Factors	Patients		Univariate HR (IC95%); p	Multivariate HR (IC95%); p
	At risk	Death		
Relaps				
No	1445	139	1.00 (ref)	-
Yes	161	9	1.56 (0,74-3.30); p=0.24	-
Lille				
<0,45	238	46	1.00 (ref)	
≥0,45	160	102	**6.08 (4.26-8,65);p<0.0001**	**1.35 (1.27-1.43); <0.0001**
MELD Each 5 points	373	137	**1.64 (1.45-1.85); p<0.0001**	**1.29 (1.12-148); <0.0001**

Louvet A, et al. Hepatology. 2017

Long Term Management

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	Long-Term			
Factors	Patients		Univariate HR (IC95%); p	Multivariate HR (IC95%); p
	At risk	Deaths		
Relaps				
No	7860	44	**1.00 (ref)**	**4.14 (2,76-6.20); <0.0001**
Yes	2554	55	**3,90 (2,61-5,82); <0.0001**	
Lille				
<0,45	183	78	1.00 (ref)	-
≥0,45	35	21	**1.83 (1.12-2.98); 0.015**	-
MELD Each 5 points	209	97	0,94 (0.76-1.15); 055	-

Louvet A, et al. Hepatology. 2017

Long Term Management

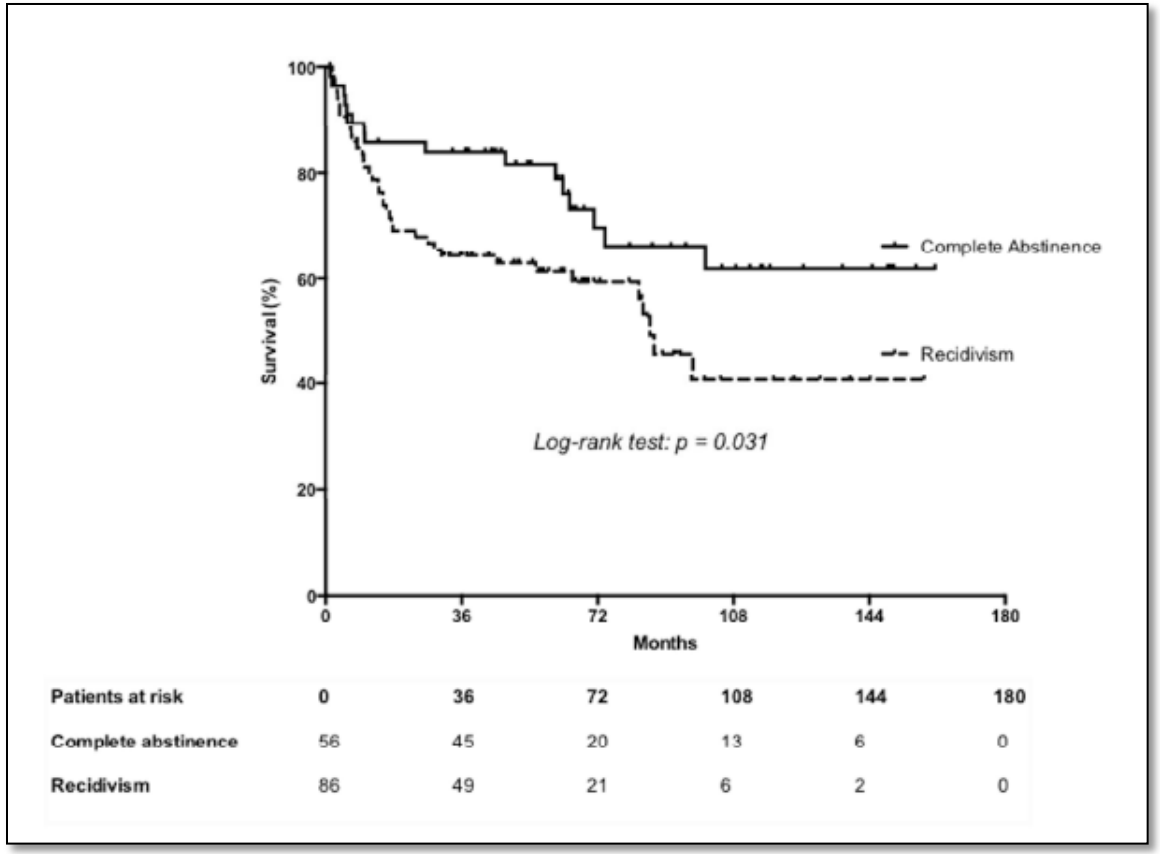
Abstinence is the main factor that predicts survival after an alcoholic hepatitis episode.

N=162 patients (Deaths: during admission 20, in the follow-up 54)

- Median of follow-up: 55 months [IQR 17-85]
- Complete abstinence: 39%.

Relapse predictors:

- No previous AUD treatment.
  - Age (<48 years-old)



Patients at risk	0	36	72	108	144	180
Complete abstinence	56	45	20	13	6	0
Recidivism	86	49	21	6	2	0

Treatment retention rate in Alcohol Programs:

- MELD in short-term; Long-term: High-Risk Alcoholism Relaps Scale (HRAR>3), psychiatric disorders.
- **To receive alcohol therapy in a center different from hospital where admission was -< Relaps** (OR 5,4)

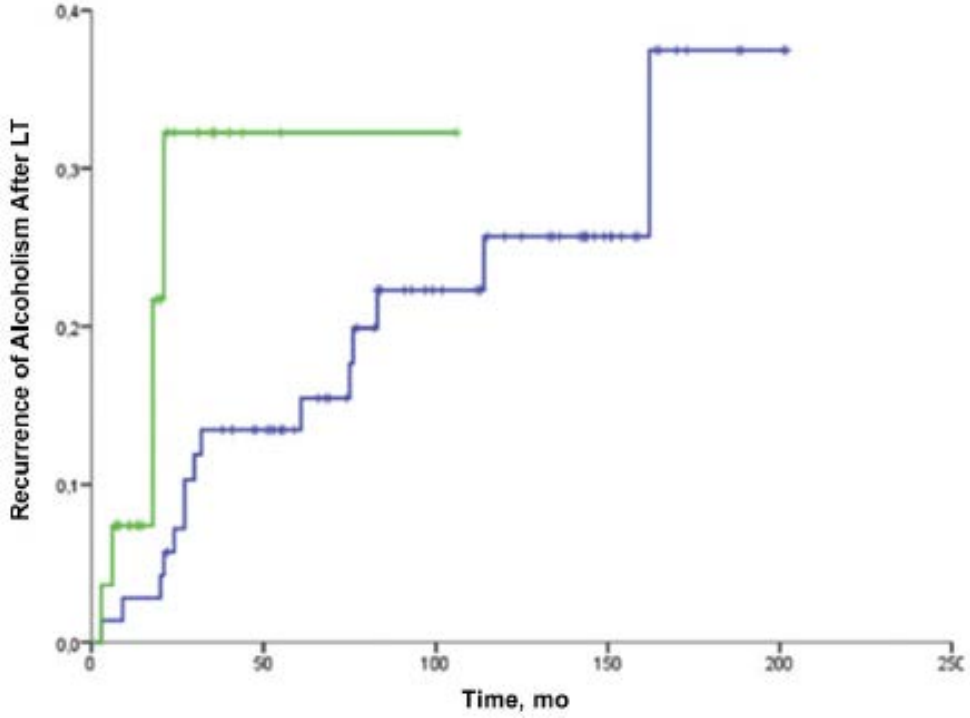
Altamirano J, Lopez-Pelayo H et al. Hepatology 2017
Lopez-Pelayo H et al. Journal of psychosomatic research. 2019;116:75

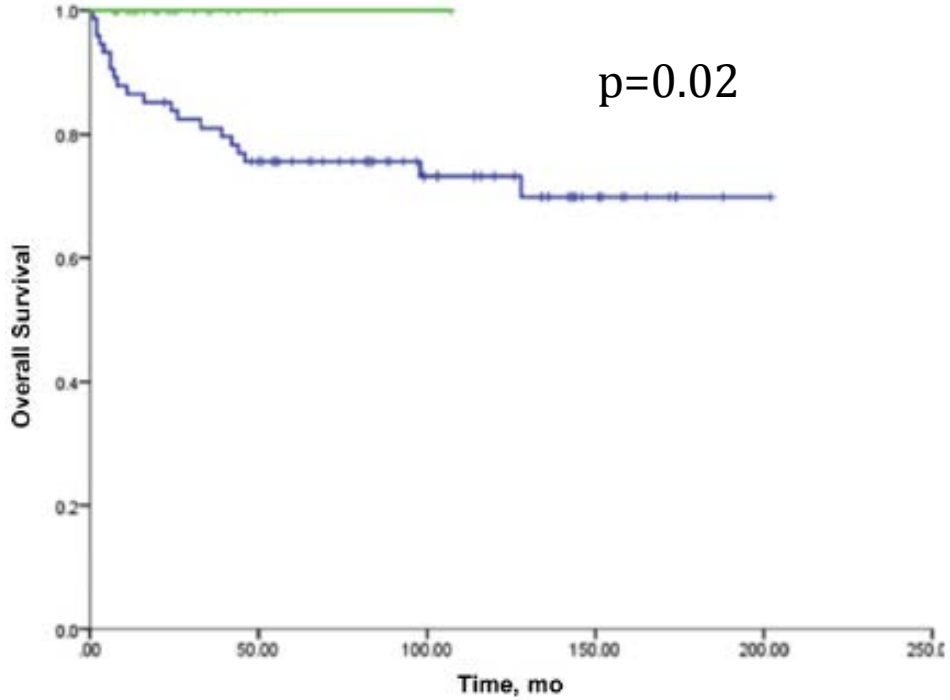
Multidisciplinary Teams

Multidisciplinary Team [MT]: Surgeons, Gastroenterologists, Addiction Specialists, Psychiatrists/psycologists + ***Alcohol biomarkers*** (CDT, EtG).

N= 102 patients with liver transplant due to alcoholic cirrhosis.

- 28 patients were evaluated by MT

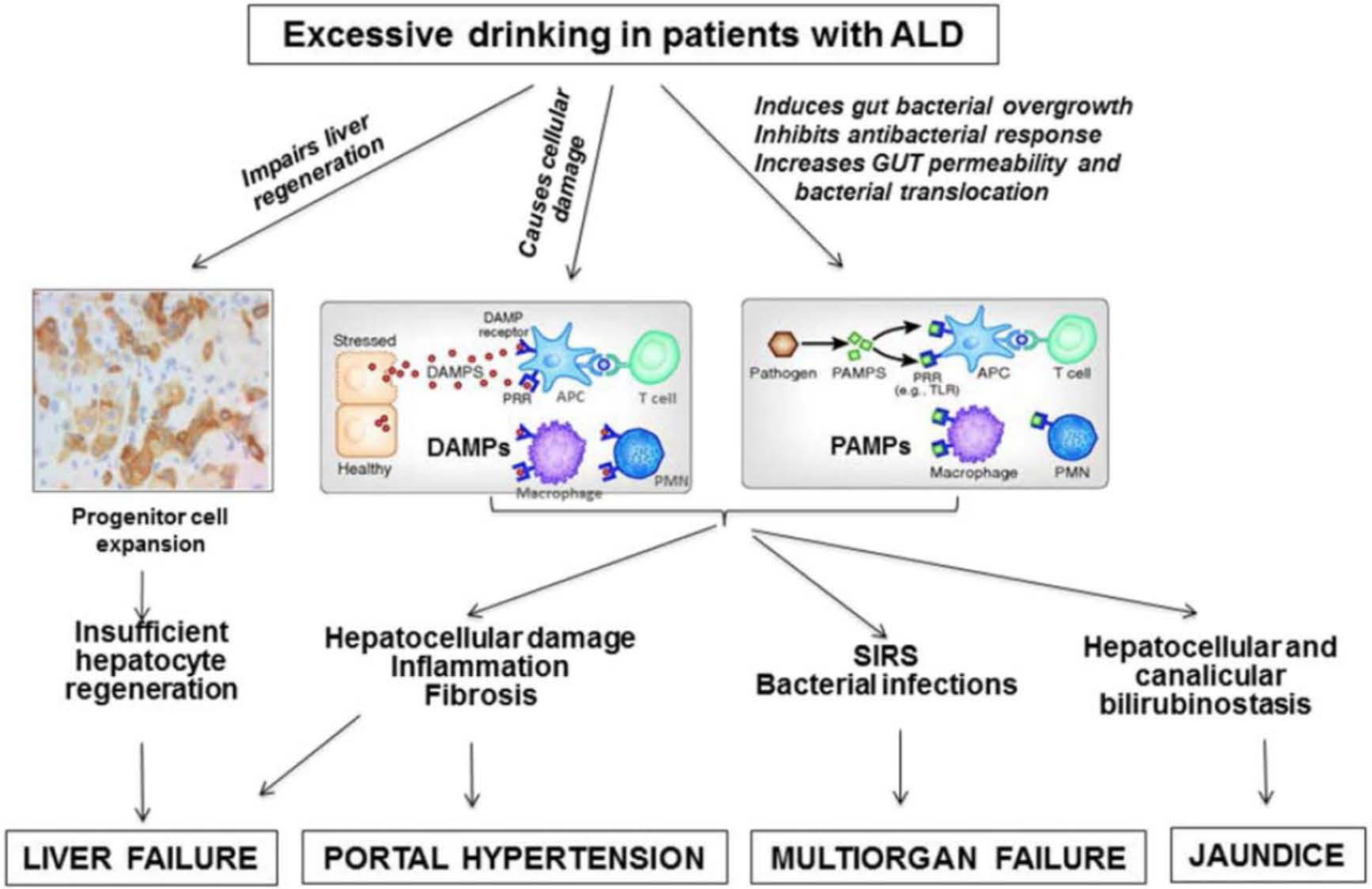




* **CDT**: Carbohydrate-deficient transferrin; **EtG**: ethyl glucuronide

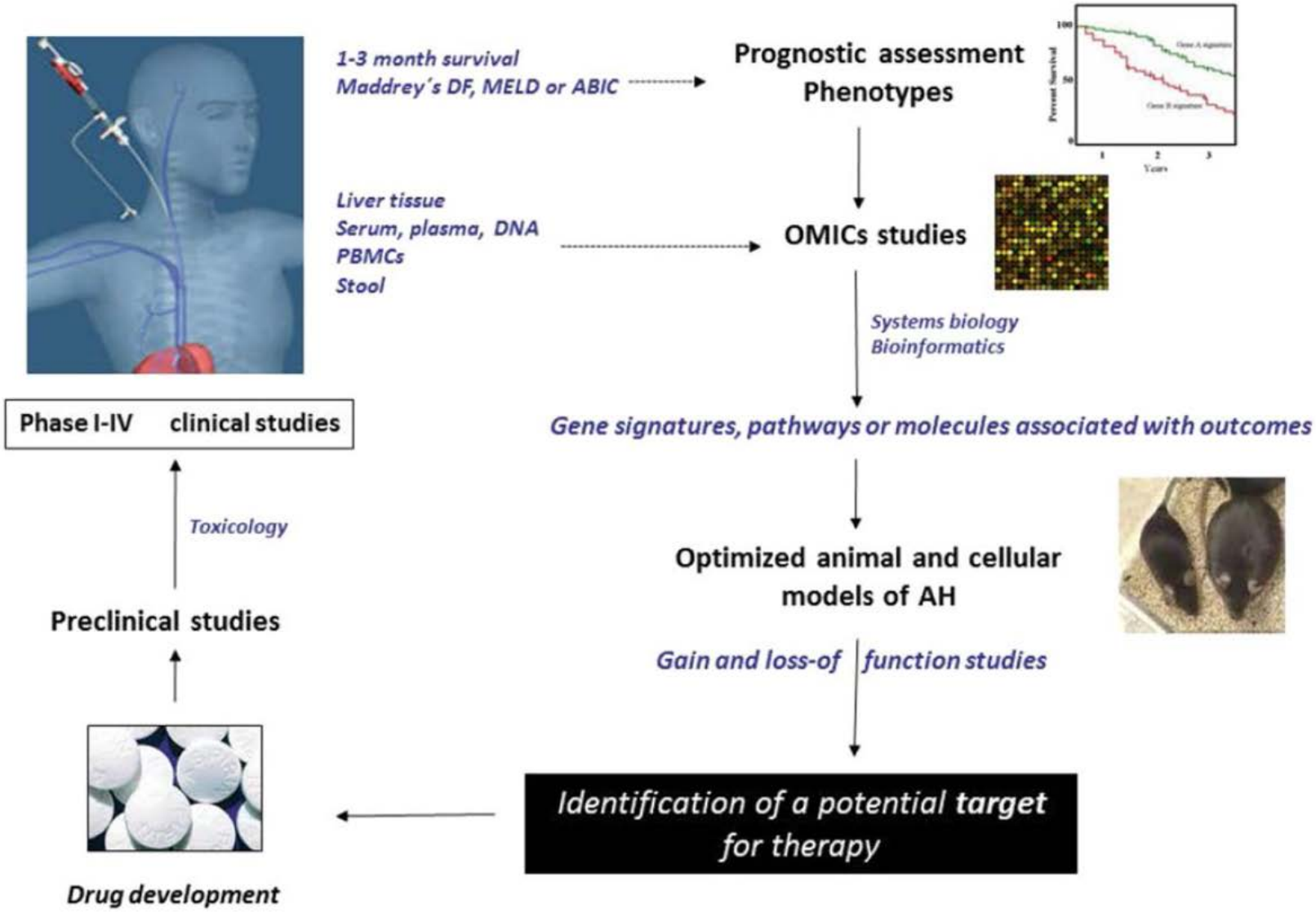
Magistri P, et al. Transplantation proceedings. 2019;51(1):187

Where we can go? – Pathogenesys in Alcoholic Hepatitis



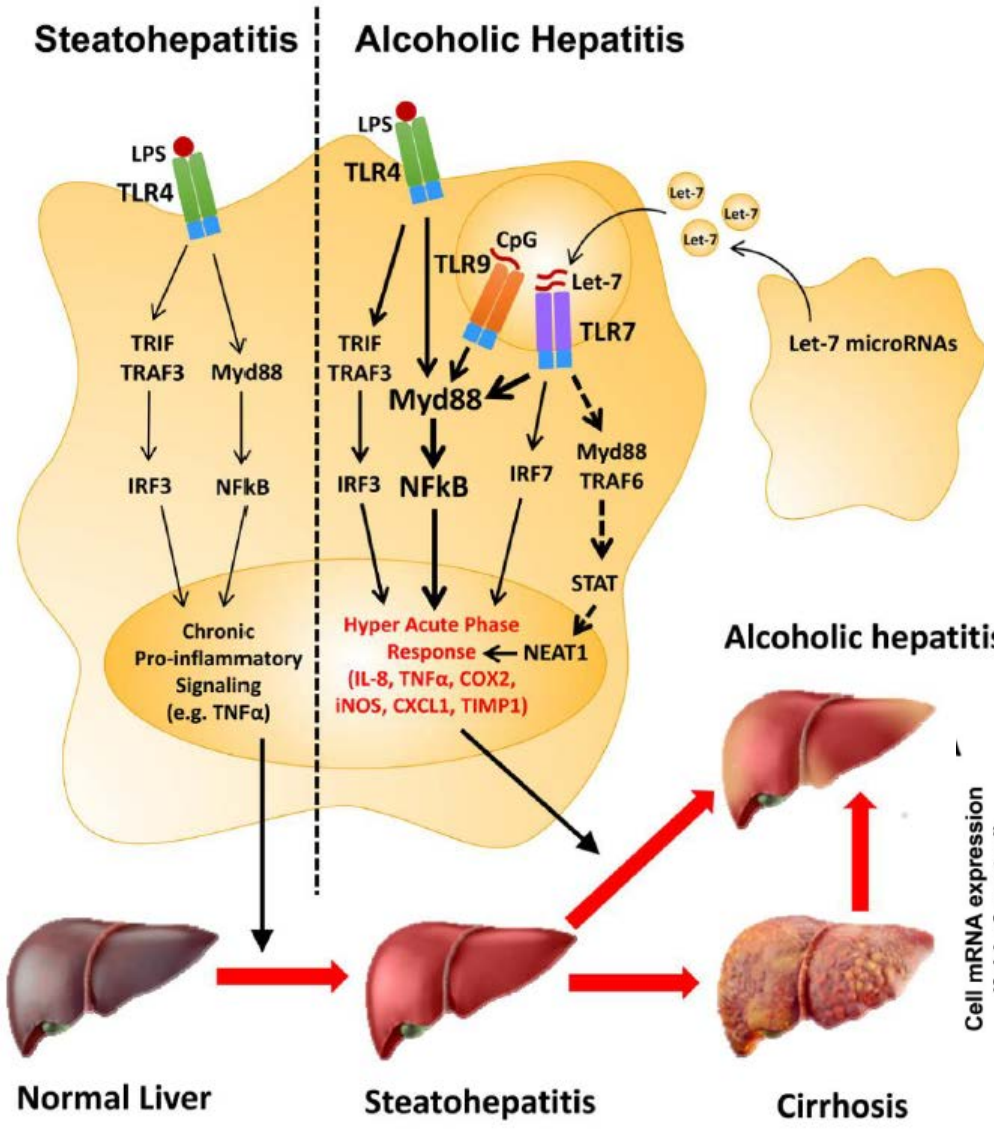
Mandrekar P, Bataller R, Tsukamoto H, Gao B. Alcoholic hepatitis: Translational approaches to develop targeted therapies. Hepatology. 2016;64(4):1343-55.

Where we can go?

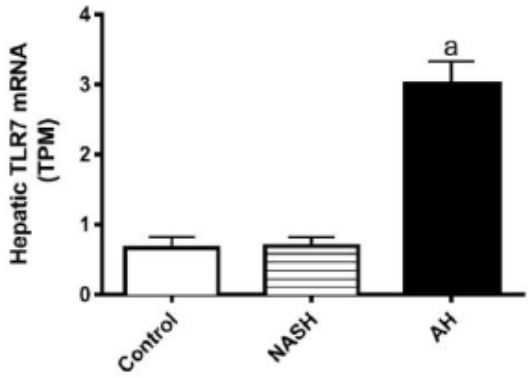


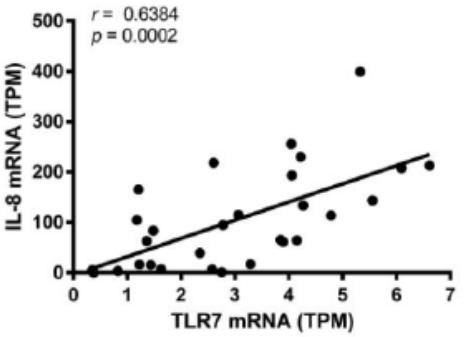
Mandrekar P, Bataller R, Tsukamoto H, Gao B. Alcoholic hepatitis: Translational approaches to develop targeted therapies. Hepatology. 2016;64(4):1343-55

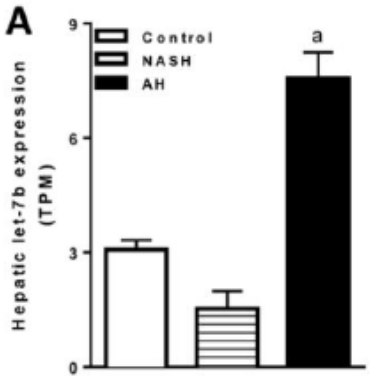
TLR7-let7 signaling contributes to ethanol-induced hepatic inflammatory response in mice and in alcoholic hepatitis



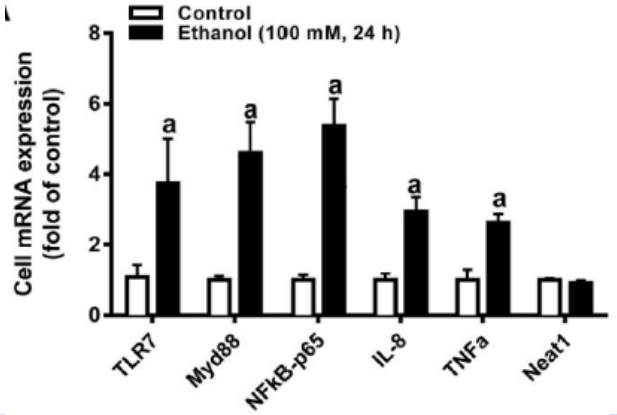
DeepSeq

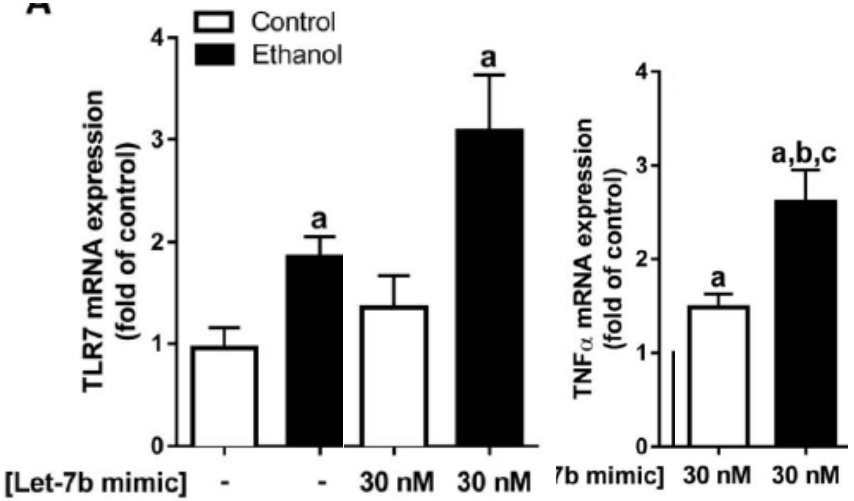






Mice – **Primary Hepatocytes - VL-17A**





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Massey VL, et al. *Alcohol Clin Exp Res* 2018; **42**(11): 2107-2122

La progresión de la enfermedad hepática por alcohol a la hepatitis alcohólica grave se caracteriza por el descenso en la actividad en los factores de transcripción implicados en la diferenciación del hepatocito

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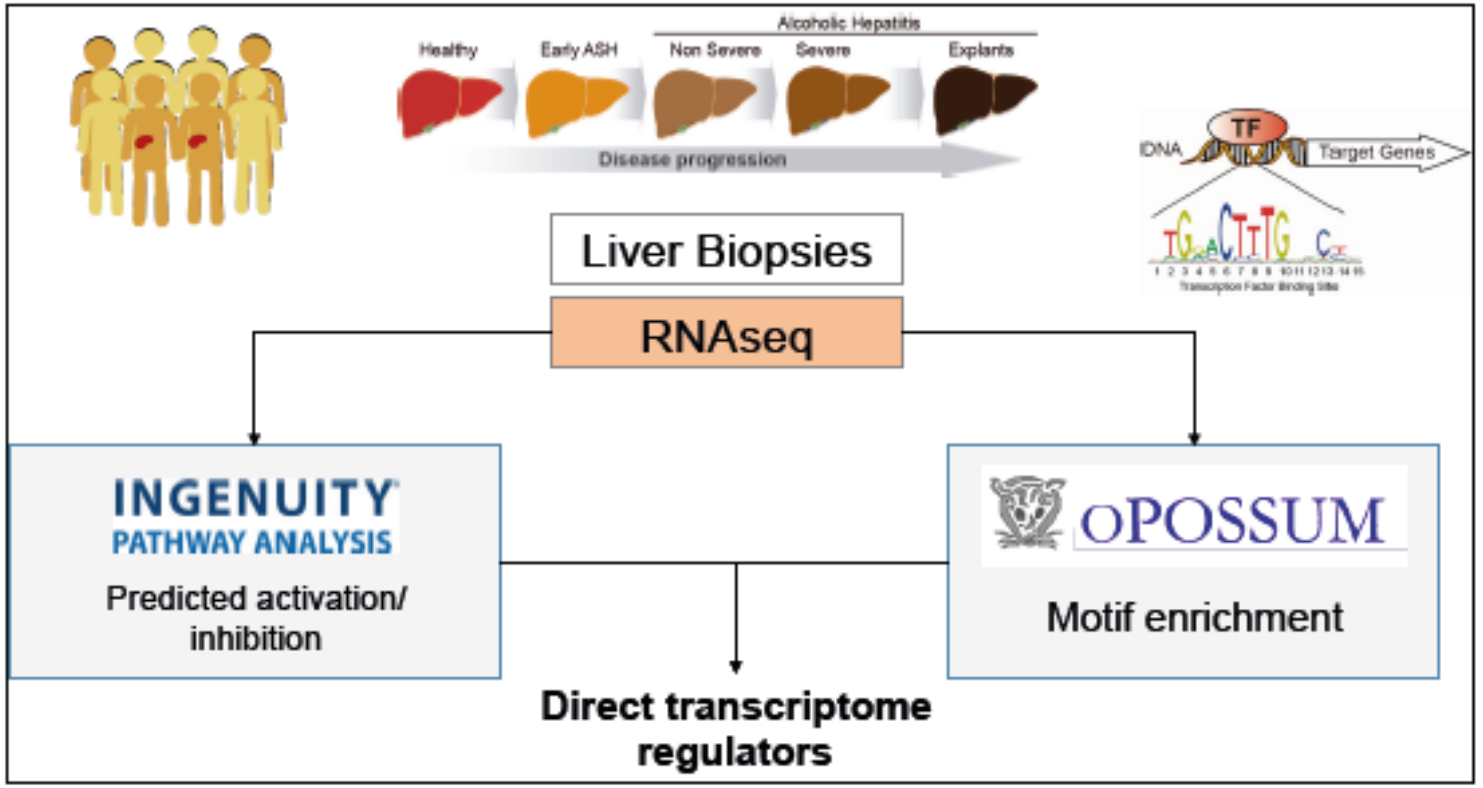
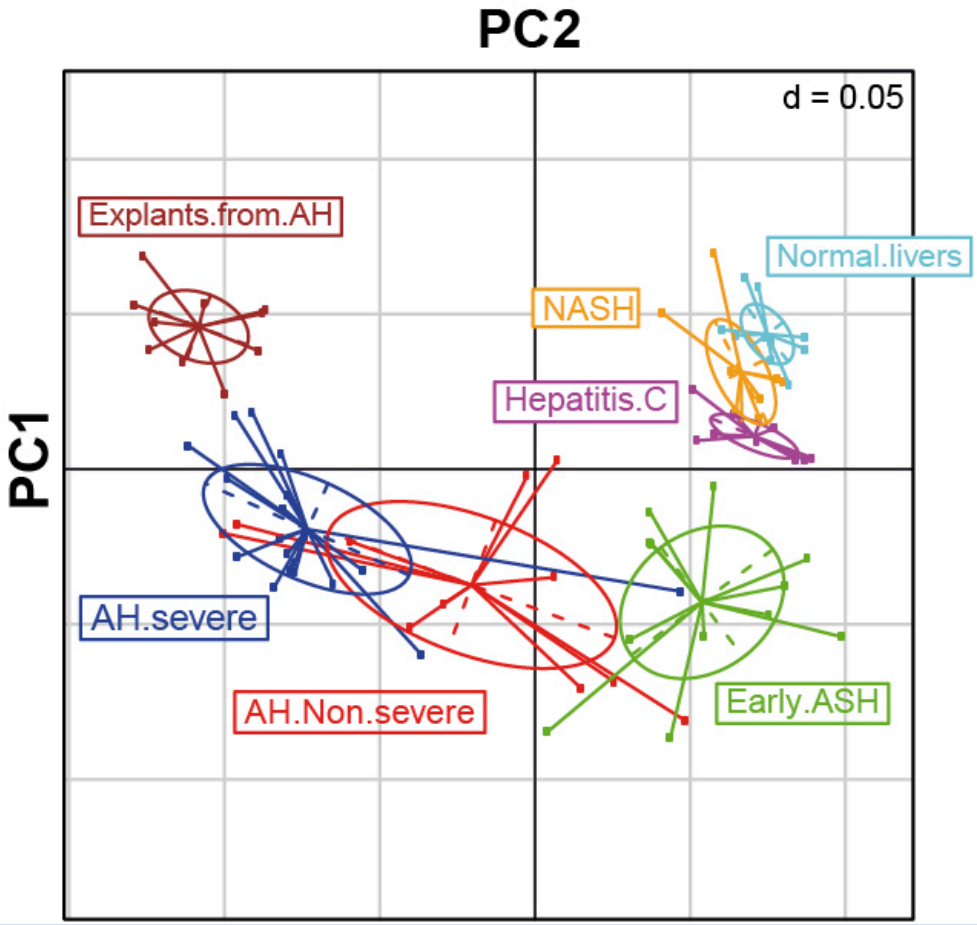
1. Gastroenterology and Hepatology, Hospital Marques de Valdecilla, Instituto de Investigación Valdecilla – IDIVAL. Santander, Spain; 2. Pittsburgh Liver Research Center, University of Pittsburgh Medical Center. Pittsburg, PA. USA. 3. Liver Unit, Clinica Universidad de Navarra, Pamplona, Spain; 4. Bowles Center For Alcohol Studies, University of North Carolina at Chapel Hill, Chapel Hill, NC; 5. Bioinformatic Platform, CIBER de Enfermedades Hep.ticas y Digestivas (CIBERehd), Barcelona, Spain; 6. CIMA - University of Navarra, Pamplona, Spain; 7. Liver Transplant Unit, Hospital Clinic, Barcelona, Spain; 8. CIBER de Enfermedades Hepáticas y Digestivas (CIBERehd), Barcelona, Spain; 9. Cliniques Universitaires Saint-Luc, Universit. Catholique de Louvain, Brussels, Belgium; 10. LIRIC-Lille Inflammation Research International Center-U995, Univ. Lille, Inserm, CHU Lille, Lille, France; 11. Division of Gastroenterology and Hepatology, University of North Carolina at Chapel Hill, Chapel Hill, NC; 12. Vall d'Hebron Institut de Recerca, Barcelona, Spain; 13. Liver Unit, Hospital Clinic, Barcelona, Spain; 14. Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain.





DIGESTIVO
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Cabezas et al. AEEH 2018

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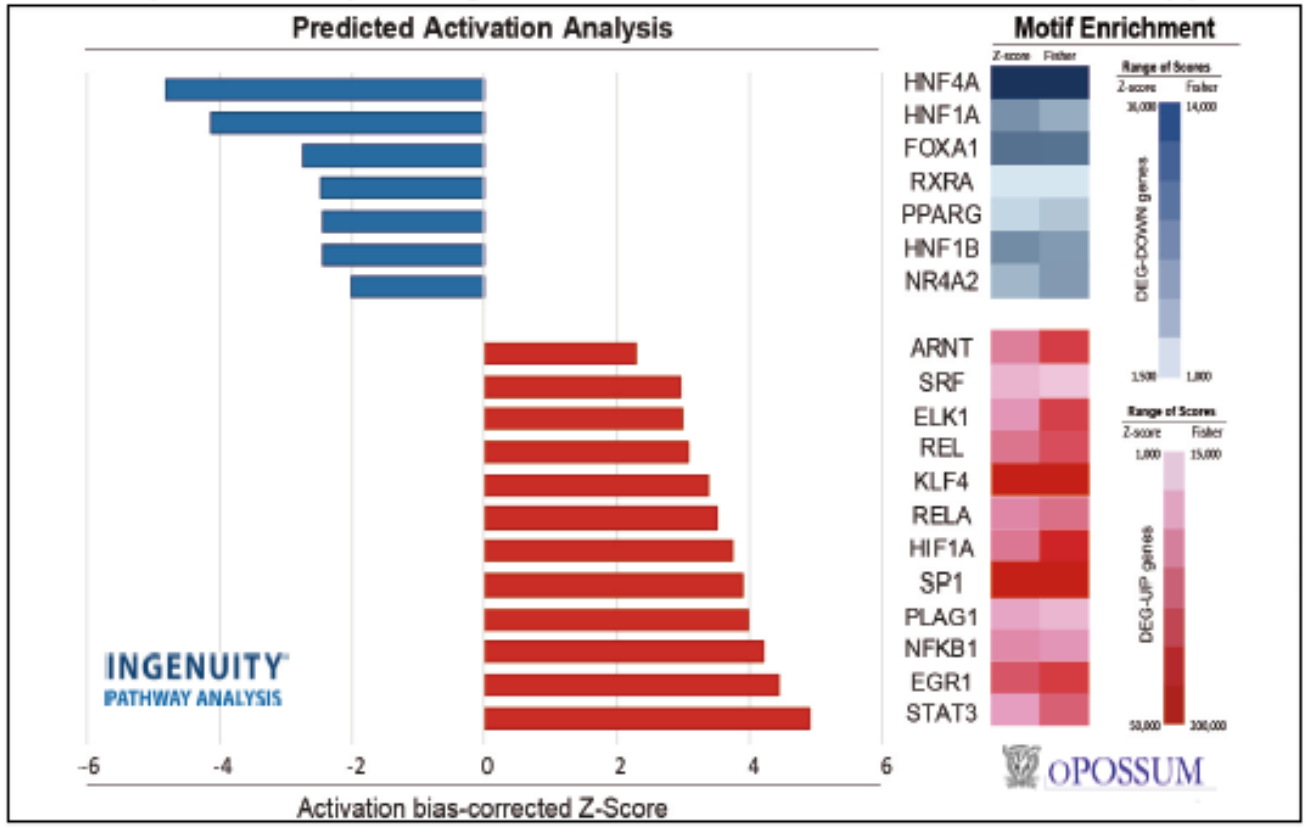

Figura 4. Las huellas de los factores de transcripción hepato-específicos (HNF4A, HNF1A y FOXA1) se vieron enriquecidos en los genes downregulados.

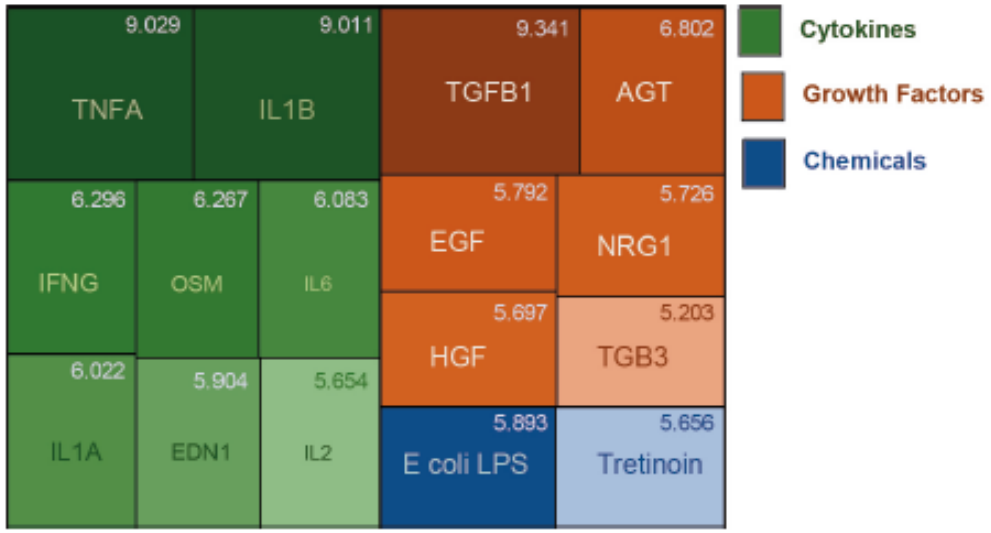

Figura 5. En el análisis de reguladores "*upstream*" del transcriptoma en la progresión de la enfermedad, con Ingenuity Pathway Analysis destaca la presencia de mediadores de inflamación, factores de crecimiento y LPS. TGFβ y EGF fueron seleccionados para los estudios mecanísticos.

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TGFβ y la vía de EGFR modulan los niveles de HNF4A.

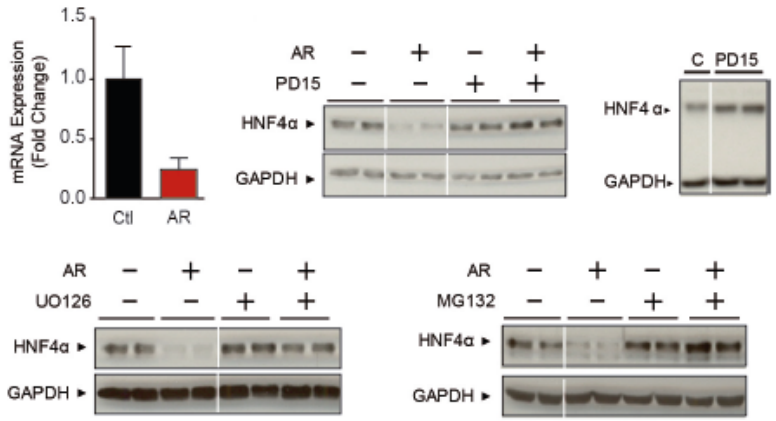


Figura 6. El tratamiento de células Hep3B con el ligando de EGFR, anfirregulina (AR), mostró que el eje EGFR-MEK-ERK está implicado en la expresión y estabilidad de HNF4α *in vitro*.

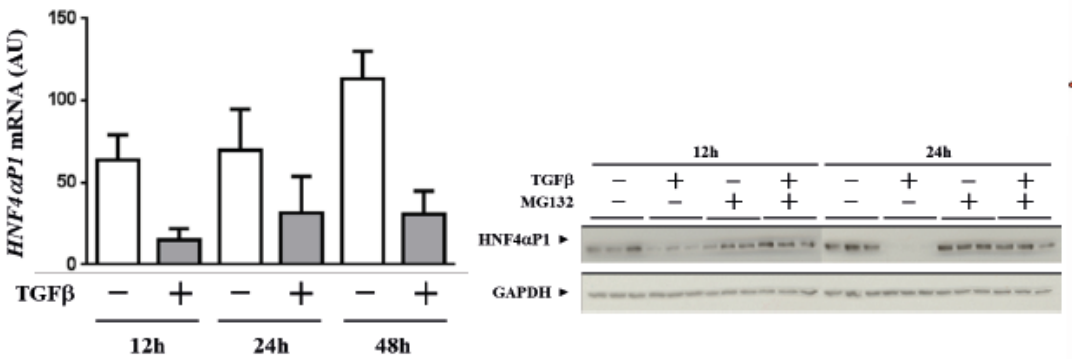
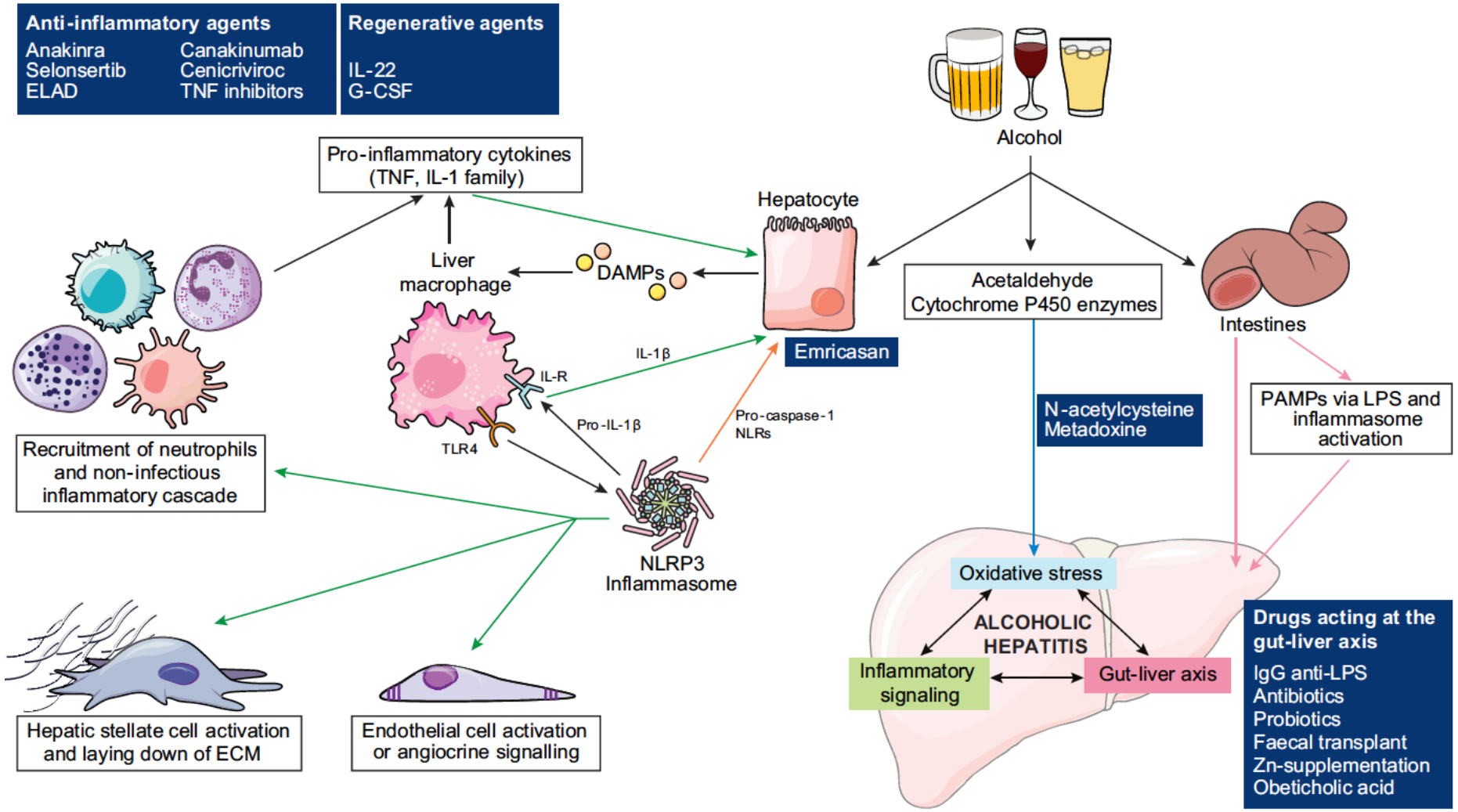


Figura 7. El tratamiento células Hep3B con TGFβ mostró que la expresión y la estabilidad de HNF4A están fuertemente influenciadas por este factor.

CONCLUSIONES

- La progresión de la enfermedad hepática por alcohol (EHA), de fases tempranas a más avanzadas como la Hepatitis Alcohólica se caracteriza por un intenso descenso de la función de Factores de Transcripción hepato-específicos (*Liver enriched transcription factors*, LETFs).
- HNF4A, HNF1A y otros LETFs aglutinan la señal transcriptómica que desciende a lo largo de la historia natural de EHA, asociándose a progresión y severidad de la Hepatitis Alcohólica.
- TGFβ y EGFR – reducen la cantidad de HNF4A y HNF1A, afectando a la expresión génica y a la estabilidad de la proteína *in vitro*.
- Terapias dirigidas a preservar la función de LETFs podrían ser útiles en el tratamiento de pacientes con Enfermedad Hepática Alcohólica.

Pathophysiology of alcoholic hepatitis and novel therapeutic targets in current clinical trials



Singal AK, Shah VH. Journal of Hepatology. 2019;70(2):305-13. doi: 10.1016/j.jhep.2018.10.026.

Treatment AUD in a PATIENT-CENTERED MANNER

GENETIC-ENVIRONMENTAL FACTORS

- Family history
- Genetic risk
- Other addictions

SOCIAOECONOMIC FACTORS

- Isolation
- Stigma
- Transportation
- Insurance

COMMON ASSOCIATED CONDITIONS

- PTSD
- Sexual abuse
- Depression
- Anxiety
- Sleep
- Pain

MULTIDISCIPLINARY ALD CLINIC

- ***Specialized nurse***
- ***Addiction therapist***
- ***Social worker***
- ***Financial counselor***
- ***Hepatologist / GI doctor***

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THANK YOU

Take home mesages:

- Alcoholic Hepatitis management needs an integral and simultaneous assessment:
  - **General Measures:** Nutritional / Prevention and early detection of infections
- In order to apply **Specific Measures**:
  - **Pharmacological treatment:**
    - CORTICOSTEROIDS ± NAC
- Ideally, **highly selected** patients with-in a multidisciplinary team, could benefit from a **Liver Transplant** when they are classified as a severe alcoholic hepatitis that do not respond to treatment.
- To achieve long term abstinence **multidisciplinary attention under the same roof** is the key.