Hépatite auto-immune aiguë sévère

Eleonora De Martin

Centre Hépato-biliaire, Hôpital Paul Brousse

Villejuif - France

Miss M, 26 year old

January 2018 : admitted to the hospital for acute severe hepatitis

Since 1 month: jaundice, fatigue

Biology at admission

AST IU/L	1401	Tot bili µmol/L	175	GB G/L	3.08
ALT IU/L	866	PT %	33	PNN	1.7
GGT IU/L	74	INR	2.36	Hb g/L	10.5
ALP IU/L	200	FV %	34	Plts G/L	155

Medical history

Lifestyle:
- Not married and no child
- Works in the finance
- Alcohol consumption : occasional
- Tobacco 10 cigarettes/day

Past medical history:
- Gougerot-Sjörgren Sdr + Purpura → plaquenil
  Hyperthyroidism (Basedow) → remission

Recent travel to NY, no drugs, no medications

Etiological work-up

Virology

Ac HAV, Ag HBs, Ab HBs, Ab HBc, Ab HCV, HIV, HTLV 1-2,
PCR CMV, EBV, HSV, HHV6, HHV8, HEV → NEGATIVES

Immunology

Anti-tissue Ab: **ANA > 1:1280 spickeled**

AMA, ASMA, anti-LKM1, anti-LC1 → NEGATIVES

IgG 63 (N<12.5), IgA 18.37 (N<2.54), IgM 2.07 (N<2.01)

Infection

ECBU - , Hemoc -

Toxic

Plasma and urine : -

At CT scan
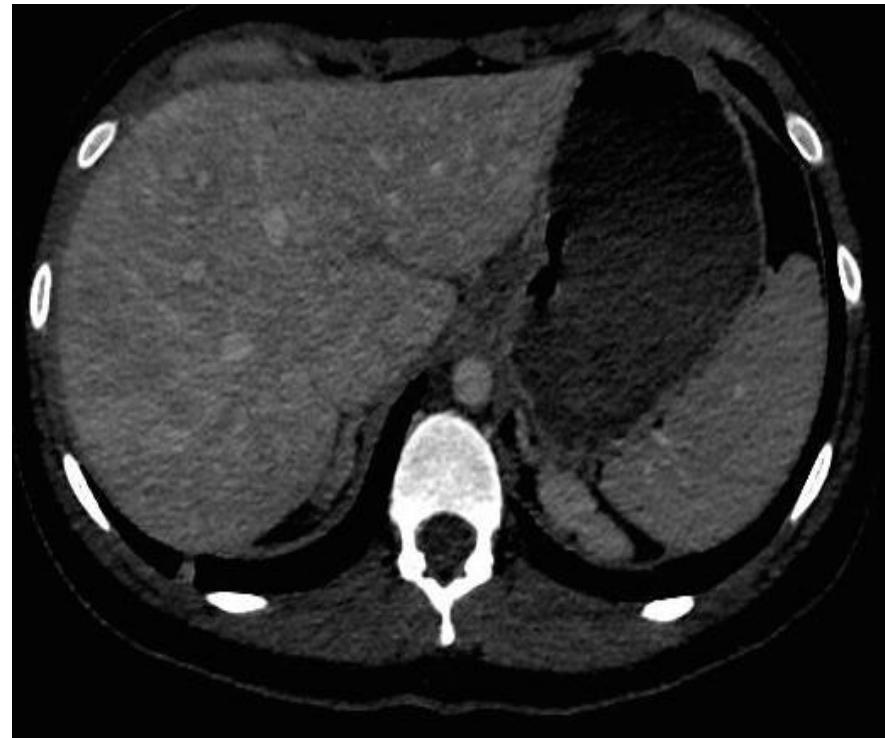
IAIHG simplified diagnostic criteria

	Parameter	Discriminator	Score
1	ANA or SMA +	≥1:40	+1
	ANA or SMA +	≥1:80 or	+2
	LKM +	≥1:40 or	+2
	SLA	Positive	+2
2	IgG Level	>Upper limit of normal	+1
		>1.1× Upper limit of normal	+2
3	Liver Histology	Compatible with AIH	+1
		Typical of AIH	+2
4	Absence of Viral Hepatitis	No	0
		Yes	+2

≥ 6 probable AIH; ≥ 7 points : definite AIH   **=6**

Hennes, Hepatology 2008
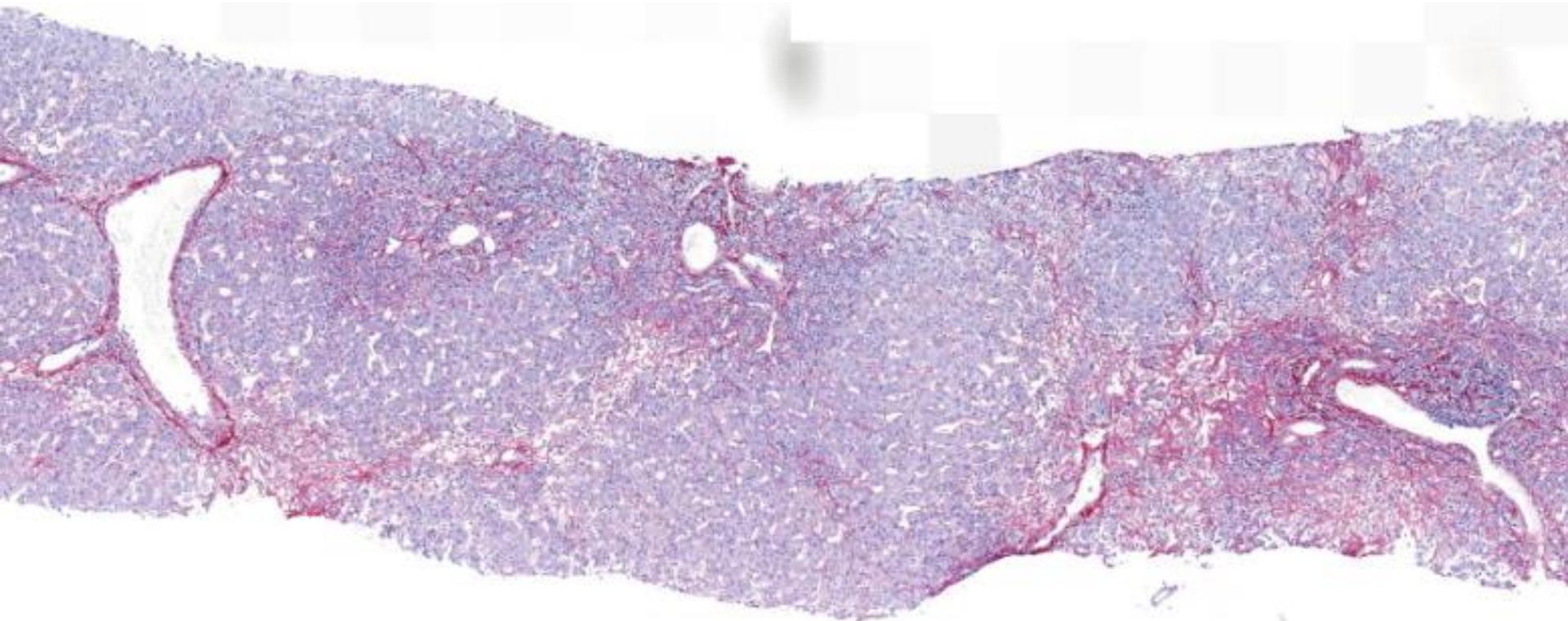
# At histology

Pour courtoisie du Dr M Sebagh

**« Subacute hepatitis (A3F2 according to METAVIR) with sub-massive necrosis…»**

At histology

« Subacute hepatitis (A3F2 according to METAVIR) with sub-massive necrosis. The presence of plasma cells is compatible with AIH»

Is acute severe autoimmune hepatitis the right diagnosis ?

Acute Severe AIH : diagnosis

Different spectrum of AIH
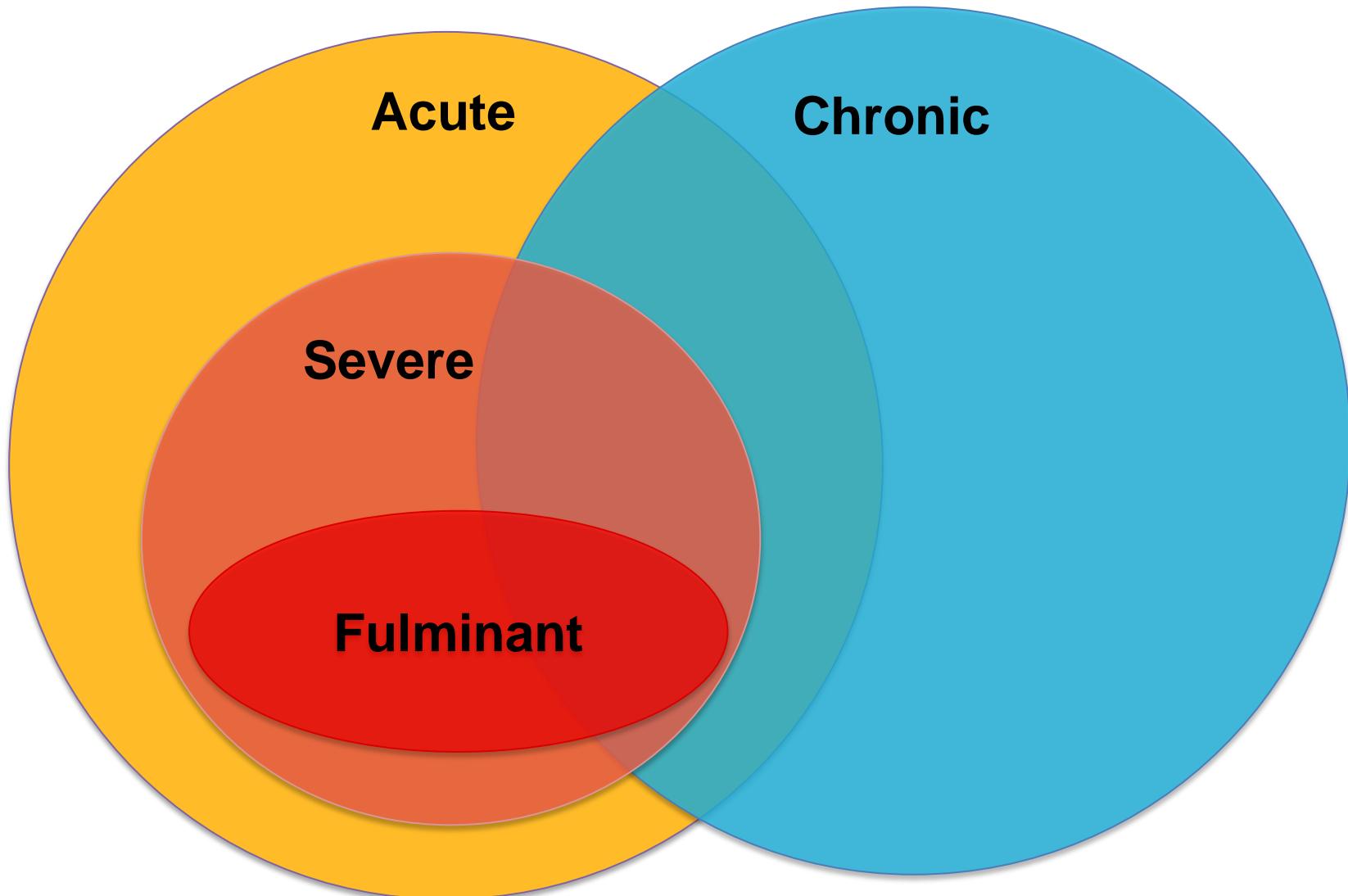
Acute onset of AIH

Multicenter retrospective Italian study, 204 patients with acute hepatitis

Characteristic	AIH Histological acute onset (83 pts)	AIH Histological acute on chronic onset (45 pts)	p
GGT, g/l	19 (16-60)	24 (9-36)	0.005
Albumin, g/l	40 (23-58)	36 (18-62)	0.02
INR	1.1 (1-1.76)	1.26 (1-3)	0.02
IgG x ULN	1.12 (0.5-2)	1.4 (0.6-3.3)	0.003
Cirrhosis	0	9 (20)	<.0001

Muratori, Dig Liv Dis 2018

IAIHG simplified diagnostic criteria

	Parameter	Discriminator	Score
1	ANA or SMA +	≥1:40	+1
	ANA or SMA +	≥1:80	+2
	LKM +		+2
	SLA		+2
2	IgG Level	...limit of normal	+1
		Upper limit of normal	+2
3	Liver Histology	Compatible with AIH	+1
		Typical of AIH	+2
4	Absence of Vir...	No	0
		Yes	+2

≥ 6 probable AIH; ≥ 7 points : definite AIH

Not validated in AS-AIH !!!

# IAIHG simplified diagnostic criteria in Fulminant Hepatic Failure

- 70 patients with non-acetaminophen FHF.

- **Simplified IAIHG criteria appears less sensitive the 1999 criteria**, in ascribing an overall (probable or definite) diagnosis of AIH (24% versus 40%).

Criteria	Sensitivity	Specificity	PPV	NPV
Simplified Criteria				
Probable diagnosis AIH (6–7)	90%	98%	97%	92%
Definite diagnosis AIH ($\geq$7)	70%	100%	100%	74%
Overall Diagnosis AIH ($\geq$6)	90%	98%	97%	92%
1999 Criteria				
Probable diagnosis AIH (10–15)	100%	97%	96%	100%
Definite diagnosis AIH ($\geq$15)	99%	98%	97%	99%
Overall Diagnosis AIH ($\geq$10)	100%	97%	97%	99%

IAIHG simplified diagnostic criteria in acute onset of AIH

	Non-severe type	Severe type	Fulminant type
n	29	14	12
Sex (male/female)[1]	4/25	4/10	4/8
Age (years)[2]	51.7 ± 14.0	48.7 ± 14.4	54.8 ± 15.8
PT (%)[3]	90 ± 17	46 ± 8	25 ± 8
ALT (IU/l)[4]	626 ± 392	600 ± 534	597 ± 625
T-Bil (mg/dl)[5]	3.3 ± 3.6	12.9 ± 8.3	20.8 ± 8.1
ANA ≥ 40 (fold)[6]	20	10	11
IgG (mg/dl)[7]	1874 ± 571	2448 ± 1400	2662 ± 885
Revised original score before treatment[8]	13.6 ± 3.4	14.8 ± 3.1	16.5 ± 3.1
Simplified score before treatment[9]	4.6 ± 1.6	4.6 ± 1.6	5.5 ± 1.1

Revised original criteria
- Nondiagnostic 9%
- Definite 40%
- Probable 51%

Simplified criteria
- Definite 11%
- Probable 29%
- Nondiagnostic 60%

Fujiwara, Liver International 2011
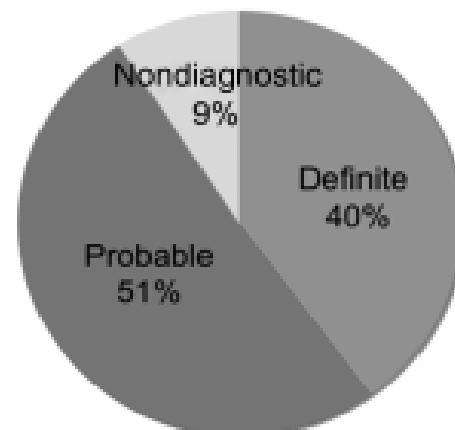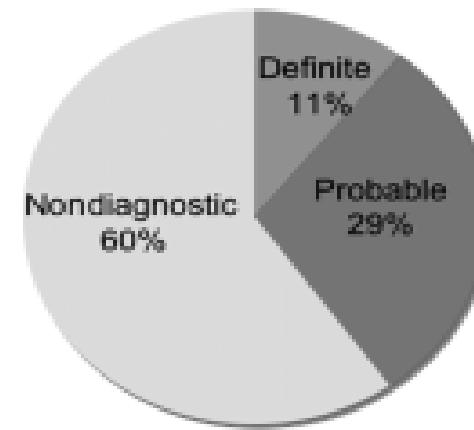
AS-AIH: diagnostic challenge

- **Auto-antibodies** : absents or weakly positives in 30%-40% of patients

- **IgG level** : normal in 25%-40% of patients

- **Histology**: typical and compatible ? Exhaustive?

EASL Guidelines, Journal of Hepatol 2015
Czaja, Dig Dis Sci 2013

Anti-nuclear antibodies (ANA)

Immunofluorescence pattern on rodent liver section
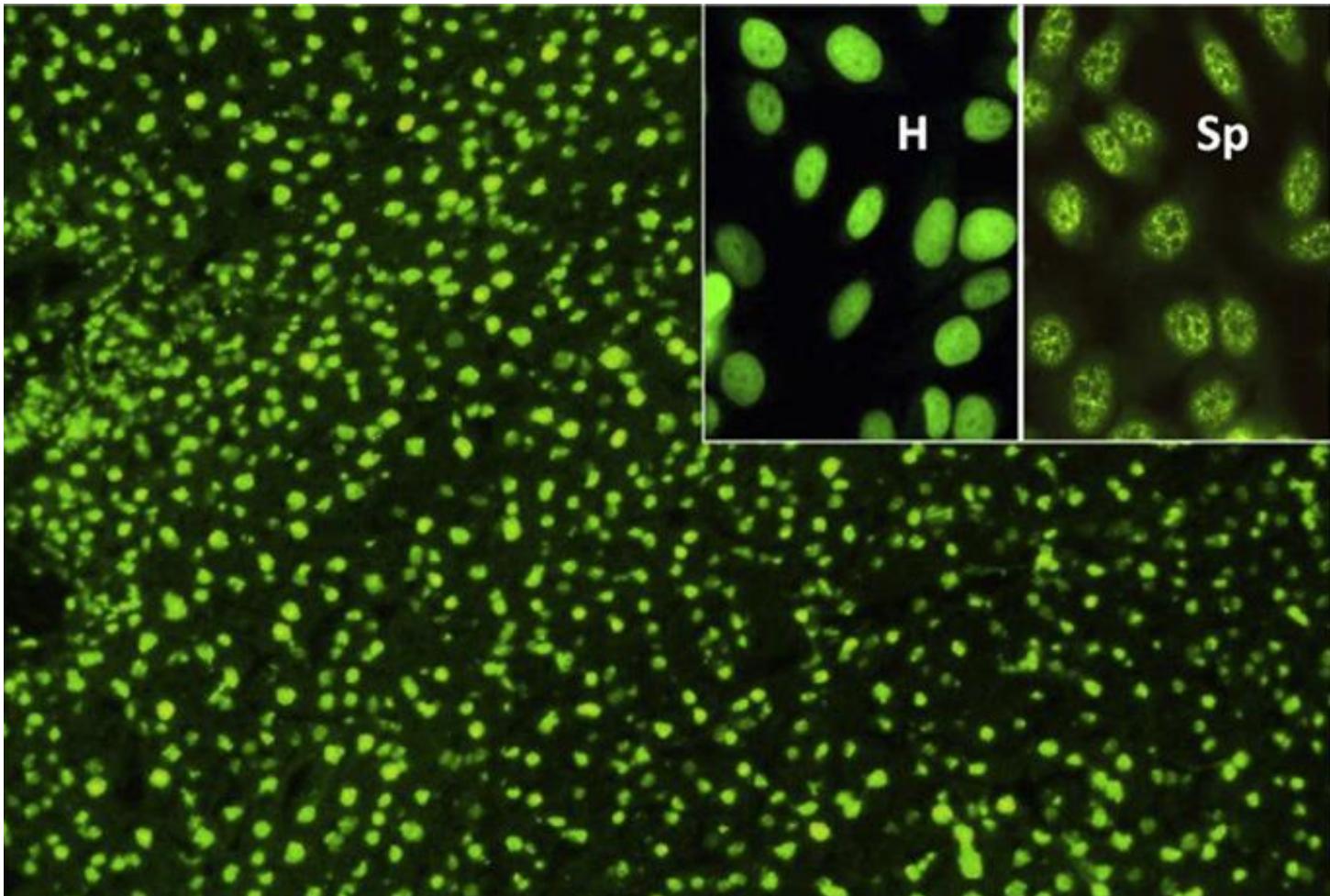
AIH Histology

Typical

- Interface hepatitis
- Lymphocytic/lymphoplasmacytic infiltrates in portal tracts and extending into the lobule
- Emperipolesis
- Hepatic rosette

Compatible

- Chronic hepatitis with lymphocytic infiltration without all the features considered typical

Histology in acute onset of AIH

Fujiwara, Liver International 2011

Centrilobular necrosis

Infiltration of Plasma Cells into Liver Tissue

	Portal areas (frequency per portal area)[a]				Central areas (no. of specimens containing plasma cells)
	<1%	1%–5%	5%–10%	>10%	
Acute AIH (n = 15)	1	6	5	3	5 (33%)
AH-HAV (n = 15)	13	2	0	0	0
AH-HBV (n = 25)	22	3	0	0	0
AH-HCV (n = 15)	12	2	1	0	0
AH-drug (n = 10)	9	1	0	0	0

Abe, Clinical Gstroenterol and Hepatol 2007

# Characteristic histological features in AIH-ALF

72 patients from the ALF Study.
The diagnosis of probable AIH-ALF was based on 4 features:

1. Massive hepatic necrosis

2. Lymphoid follicles

3. Plasma-cell infiltration

4. Central perivenulitis

Histological features of AIH-ALF predominate in the centrilobular zone

# Imaging in ALF
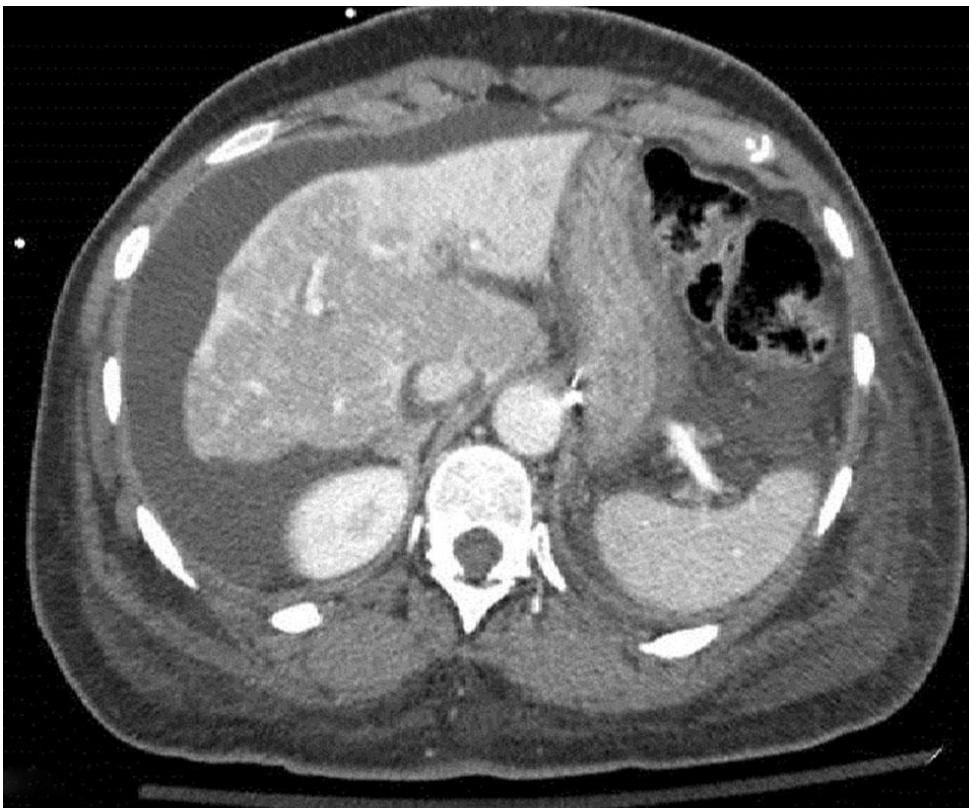
47 patients with ALF none with cirrhosis:

65% Ascites

28% Splenomegaly

23% Nodular surface

Imaging findings are variable and can resemble to cirrhosis → need for liver biopsy

Romero, Dig Dis Sci 2014

Miss M : Biological evolution
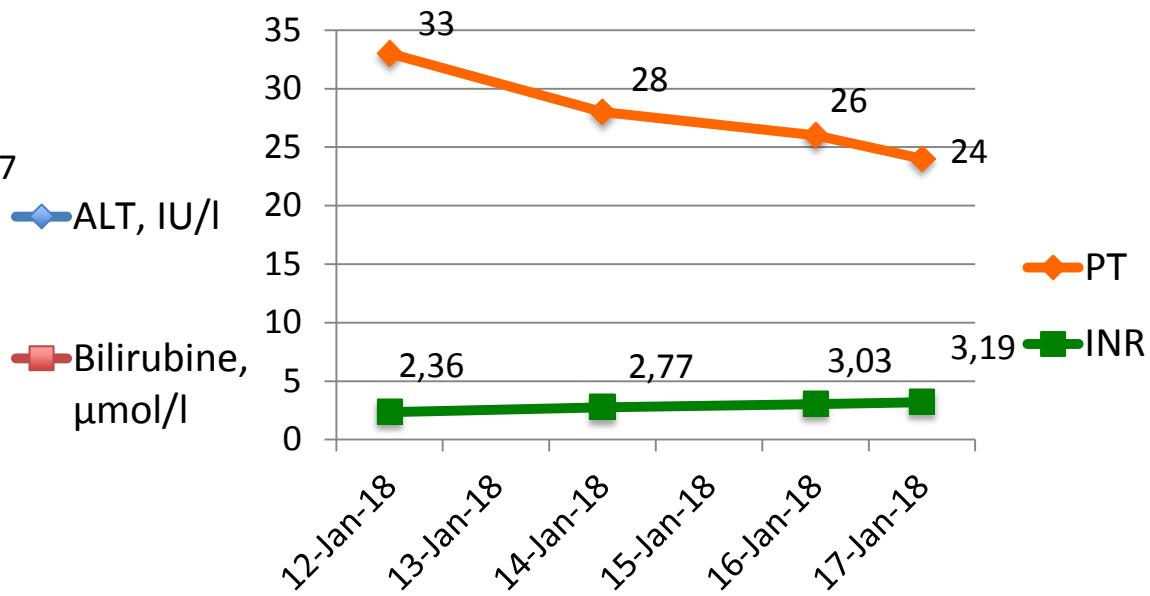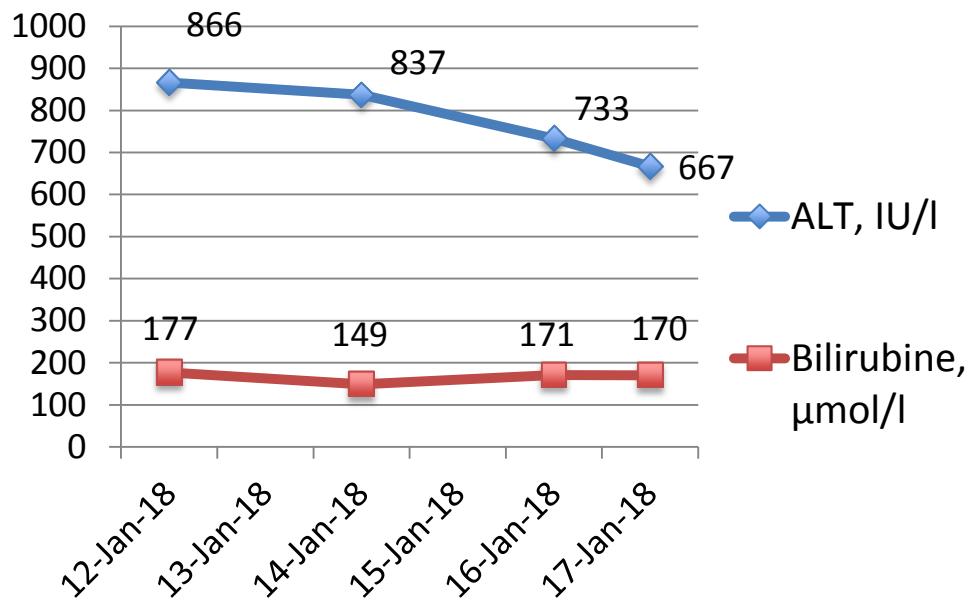
Would you treat this patients with corticosteroids and how would you evaluate treatment response ?

Acute Severe AIH : treatment

Management of AS-AIH

29. Patients with acute severe AIH should be treated with high doses of intravenous corticosteroids (≥1 mg/kg) as early as possible. Lack of improvement within seven days should lead to listing for emergency liver transplantation **(III)**

Steroid Use in Acute Liver Failure

Overall and spontaneous survival among different aetiologies of ALF
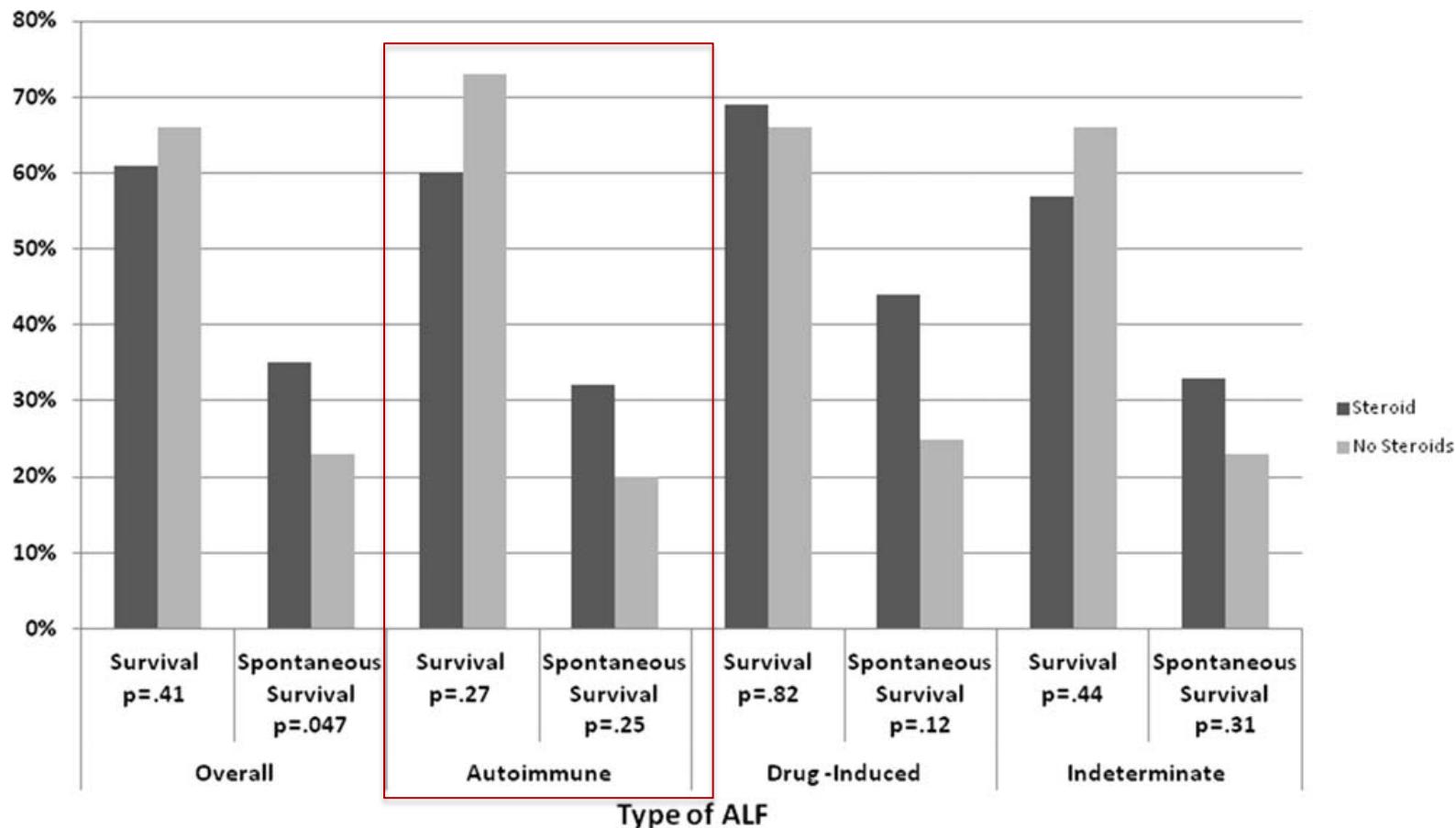
Mean INR 3.33

Karkhanis, Hepatology 2014

Uselessness of corticosteroids in severe and fulminant form of AIH

Patient Characteristics

HE grade	Coma stage	Bilirubin (μmol/L)	INR	Factor V (%)	ALT (IU/L)
3	0	301	8.5	10	505
-	-	-	-	-	-
4	1	302	6	26	1932
-	-	-	-	-	-
3	0	416	11.8	20	NA
3	0	459	4.8	9	709
-	-	-	-	-	-
4	3	400	6.7	12	150
3	0	550	11.8	25	1,403
1	0	490	7	10	69
3	0	470	10	27	706
4	2	360	11.8	10	NA
3	0	331	3.3	33	266
4	3	355	4.2	25	250
4	1	327	7.2	25	902
4	1	403	16	11	801

Median INR 6.85

12/16 (75%) treated patients

↓

10/12 (83%) liver transplantation

Ichai, Liver Transpl 2007

The role of corticosteroids in modifying outcome of AS-AIH

Parameter	AS-AIH n = 32	Acute exacerbation type n = 15	p value
Age (range)	42 (16-68)	42 (17-60)	0.30
Bilirubin µmol/L (3-20) (range)	463 (55-1208)	269 (77-574)	0.015
AST mmol/L (10-50) (range)	605 (58-2690)	706 (188-1712)	0.85
INR (0.9-1.2) (range)	2.2 (1.5-3.5)	1.9 (1.6-2.6)	0.13
Globulin g/L (25-35) (range)	39 (22-68)	47 (24-81)	0.02
Autoantibodies (≥1:80) %	56%	80%	0.19
Creatinine µmol/L (45-120) (range)	101 (26-226)	98 (69-142)	0.8
MELD score (range)	29 (22-40)	23 (16-35)	0.005
UKELD score (range)	62 (55-69)	58 (55-67)	0.006
IAIHG score	15 (10-19)	17 (10-22)	0.06
Death	19%	0%	0.15
Transplant	59%	7%	0.001

23/32 (75%) treated patients

↓

10/23 (43%) liver transplantation

Yeoman, J Hepatol 2015

Improvement of bilirubin at week 2: early prognostic factor of treatment response

- **Biochemical response after 2 weeks of corticosteroids**

* p<0.001
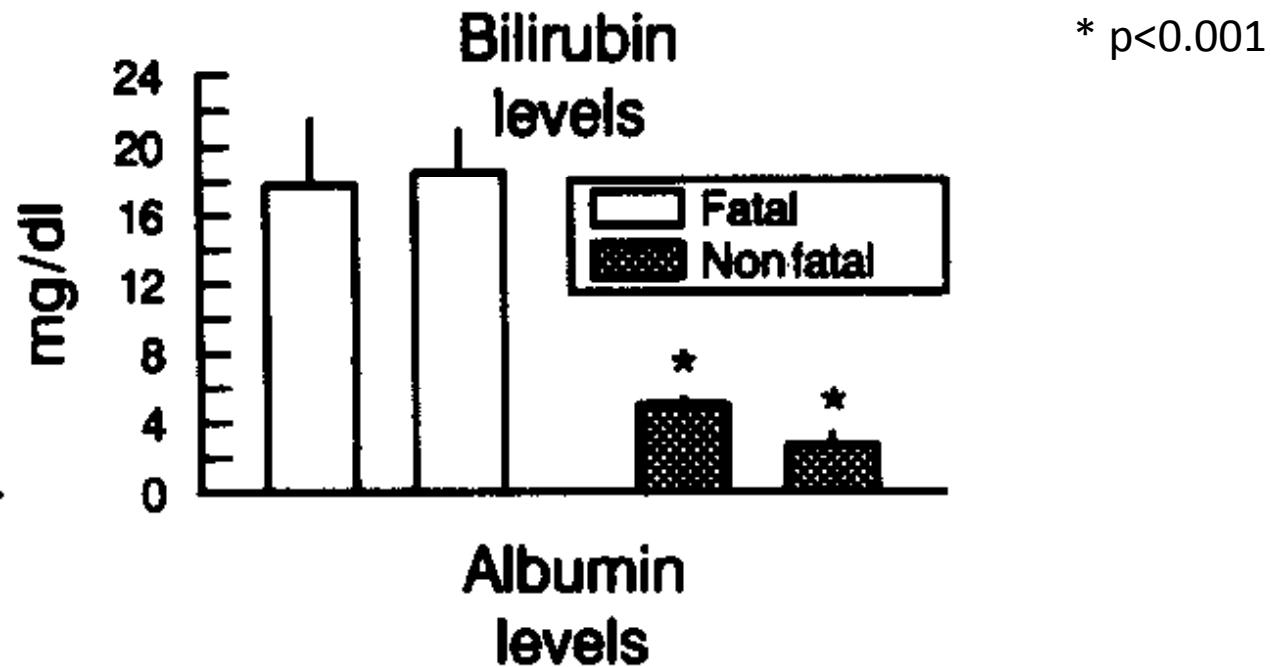
- **Histological features of patients with early mortality: multilobular necrosis**

Czaja, Gastroenterology 1988

Predictors of corticosteroid response

Characterisitcs of responders and non responders to medical therapy

| Characteristic	Responders (n = 7)	Nonresponders (n = 7)
Age	46.4 ± 12.3	44.6 ± 16.1
Female	6 (85.7%)	6 (85.7%)
Blacks	4 (57.1%)	4 (57.1%)
Cirrhosis	5 (71.4%)	2 (28.5%)
Liver panel at admission		
Bilirubin (mg/dL)	18.3 ± 13.2	22.0 ± 4.4
AST (IU/L)	869.9 ± 510.3	906.7 ± 414.3
Albumin (mg/dL)	2.7 ± 0.6	2.6 ± 0.5
Globulin (mg/dL)	4.1 ± 1.3	3.0 ± 1.1
International normalized ratio	1.9 ± 0.1	3.1 ± 1.7
MELD score at admission	23.8 ± 4.5	32.1 ± 9.0
Time from admission to starting steroids (days)	6.4 ± 5.5	2.6 ± 1.8

Verma, Hepatology 2009

Prognostic factors in AS-AIH patients treated with corticosteroids

15/17 (88%) treated patients

↓

9/15 (60%) liver transplantation

Prognostic factors :

- Massive Hepatic Necrosis type 5
- INR at presentation : cut off 2.46
- MELD at presentation : cut off 28.5

Moenne-Loccoz, J Hepatol 2016
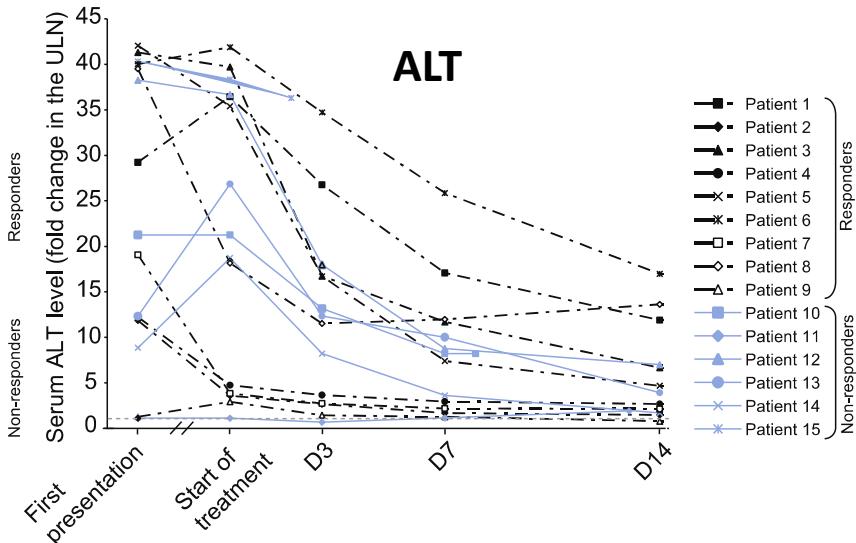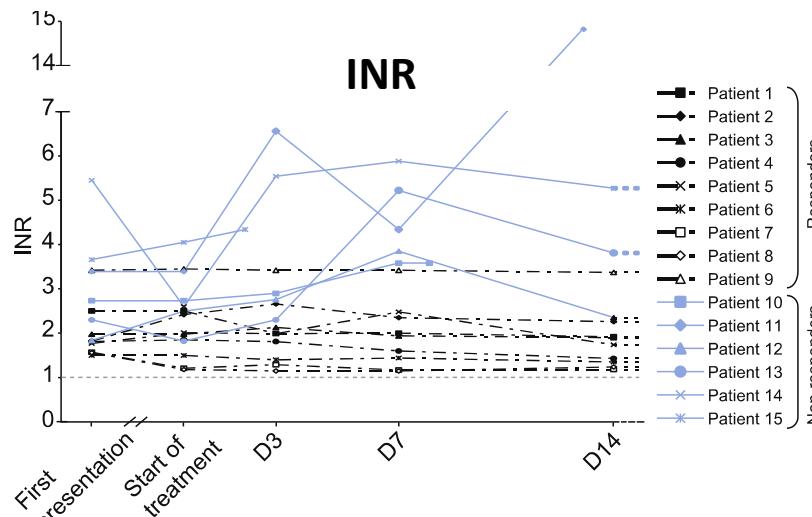
Early predictors of treatment failure in icteric AIH..

At diagnosis

- Median bilirubin

(451 lmol/L vs 262 lmol/L, P 5 0.02)

- INR (1.62 vs 1.33, P 5 0.005),

- MELD score (26 vs 20, P 5 0.02)

- MELD-Na score (27 vs 22, P 5 0.03)

- UKELD score (59 vs 57, P 5 0.01)

Analysis of area under the AUROC values at day 7

- Delta bilirubin (AUROC 0.68)

- Delta creatinine (0.69)

- Delta MELD (0.79),

- D MELD-Na (0.83)

- D UKELD (0.83)

Heterogeneous population including pediatric patients, severe and not severe AIH

SURFASA: multicenter study on AS-AIH

Multicenter French retrospective study

De Martin et al, AASLD 2017
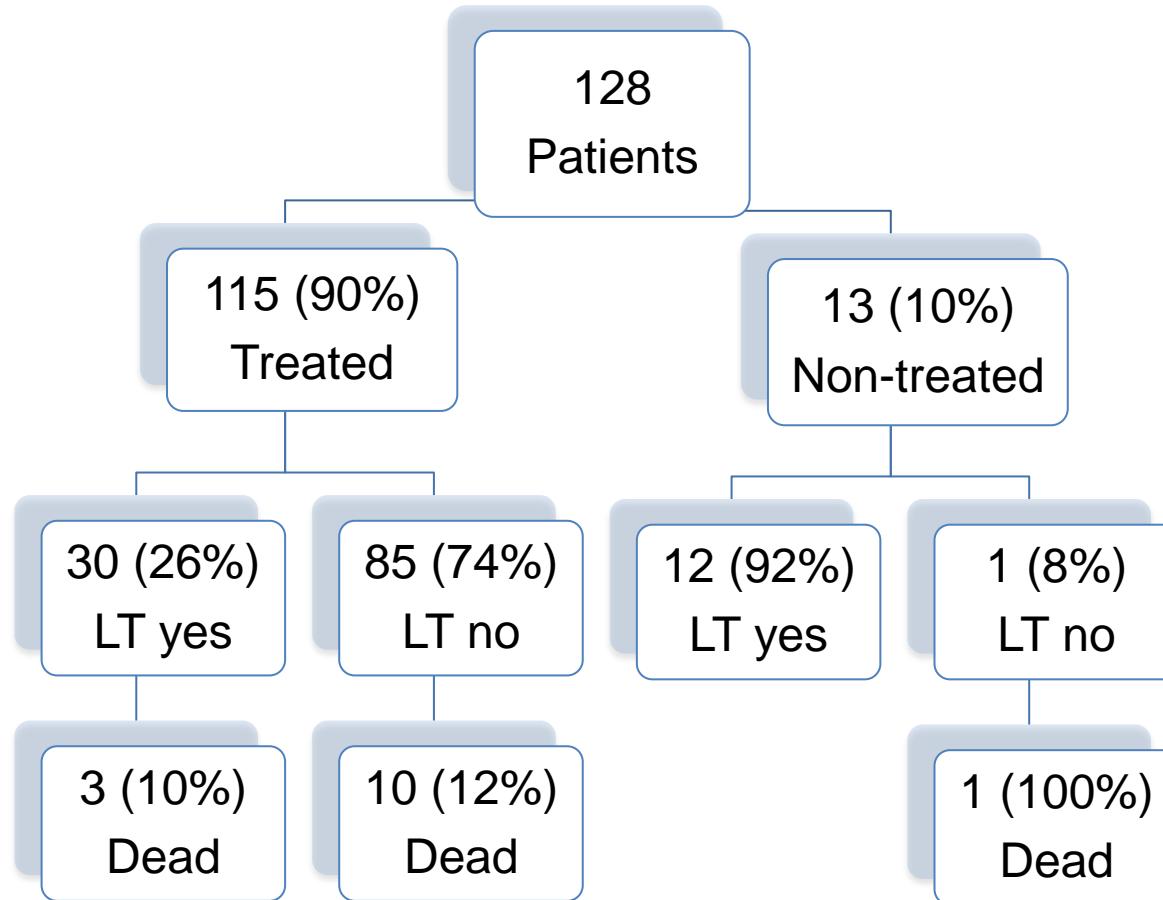
Overall survival at 90 days

Liver Transplantation free Survival
Overall patients

De Martin et al, AASLD 2017
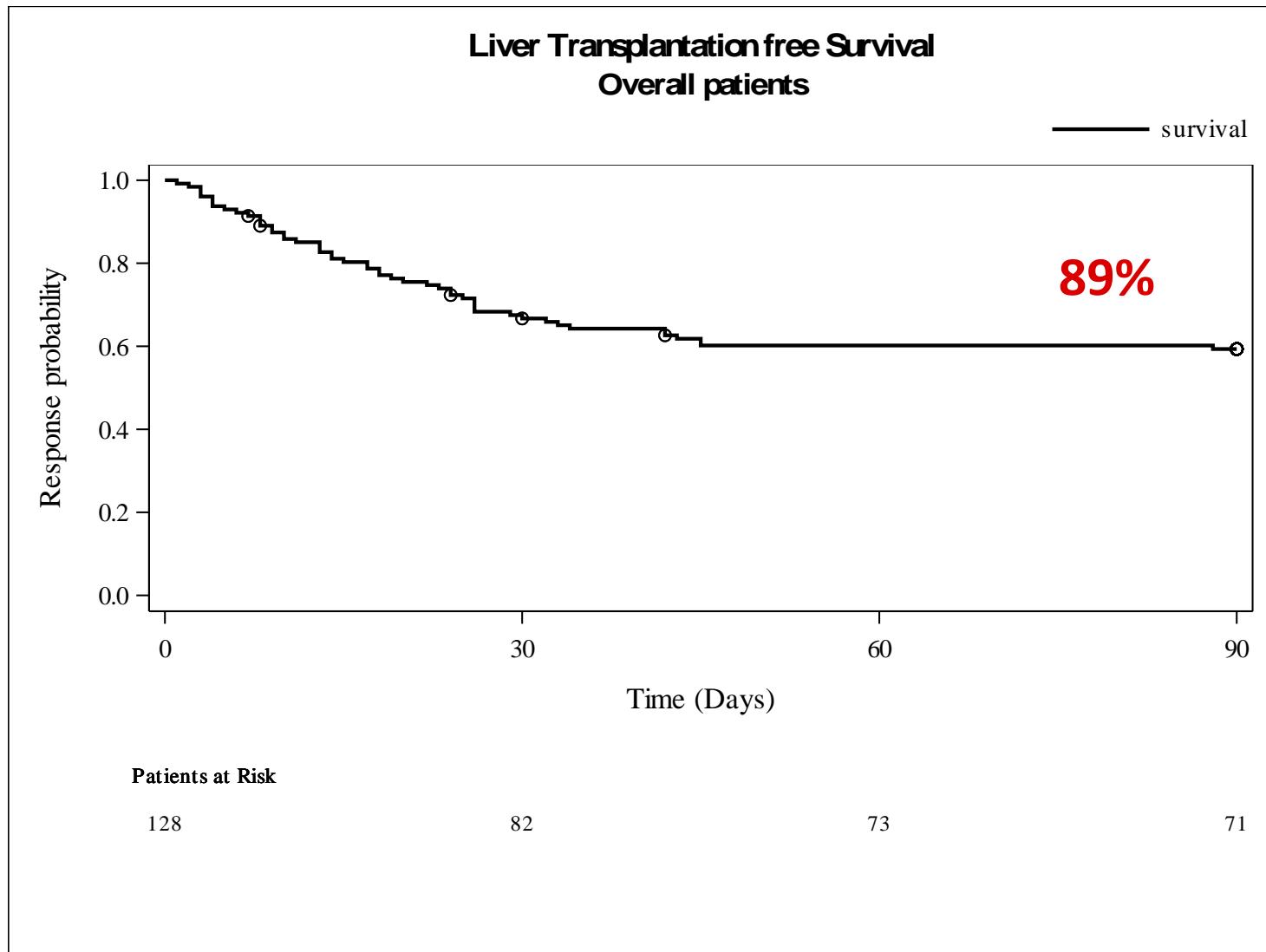
Which are the predictive factors for corticosteroid response defined by the LT-free survival ?

De Martin et al, AASLD 2017
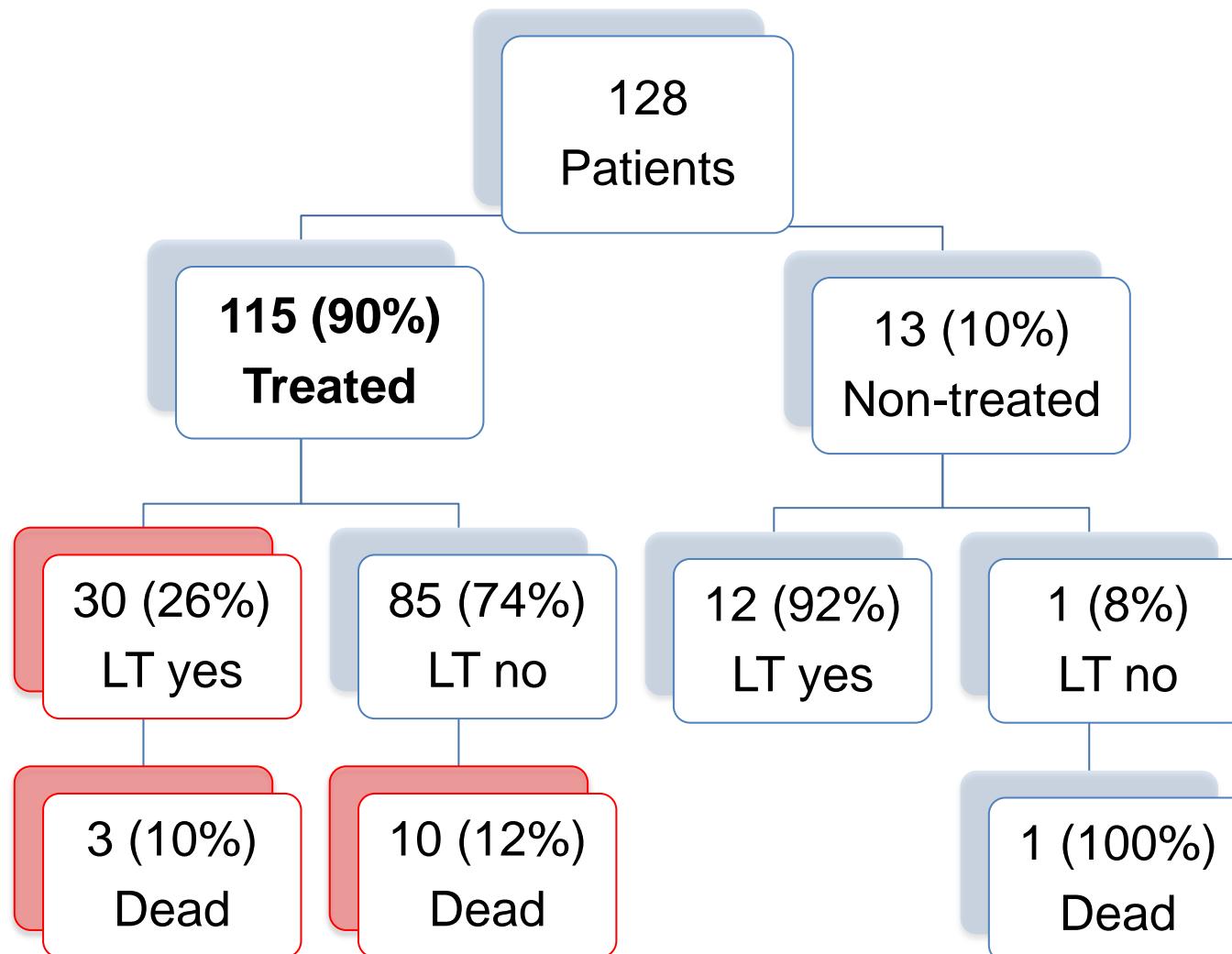
Predictive factors of corticosteroid response

Model retained at multivariate analysis

	p	OR	CI 95%
Day 0-7		0.90	0.84-0.97
PT 0	0.0021		
Δ%7-bilirubin*	0.0431		

* (D7-D0)/D0-bilirubin

X – coeff (PT 0) + coeff (Δ%7-bilirubin)

De Martin et al, AASLD 2017

Miss M : Biological evolution
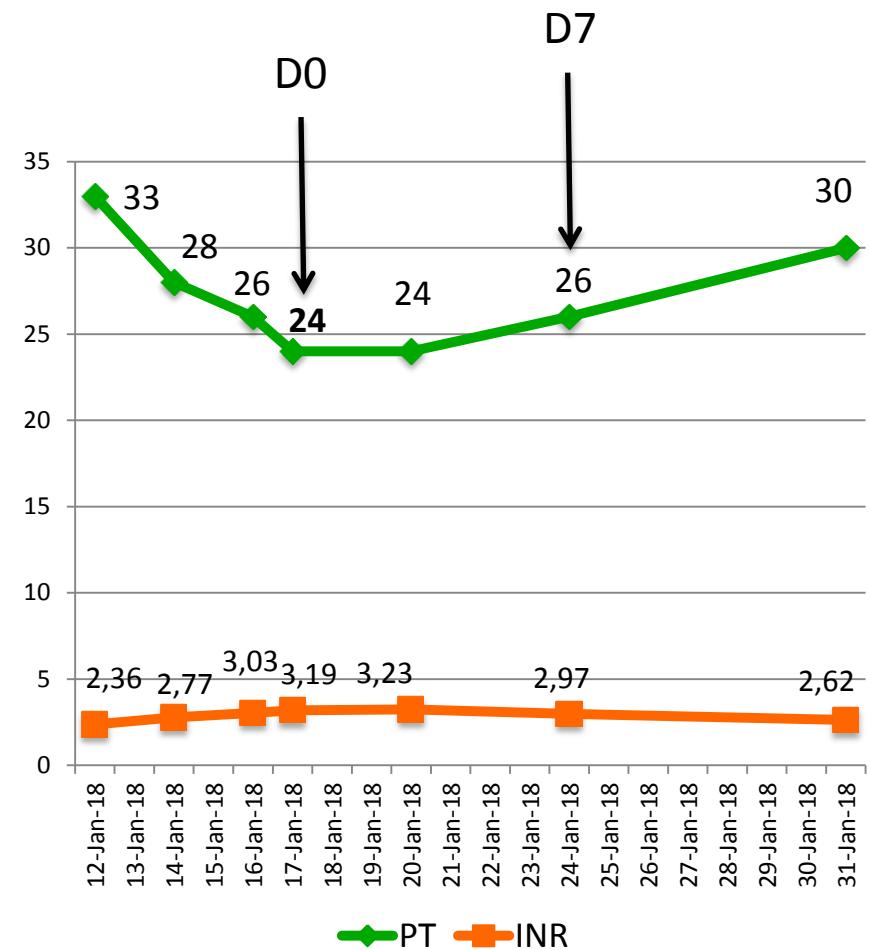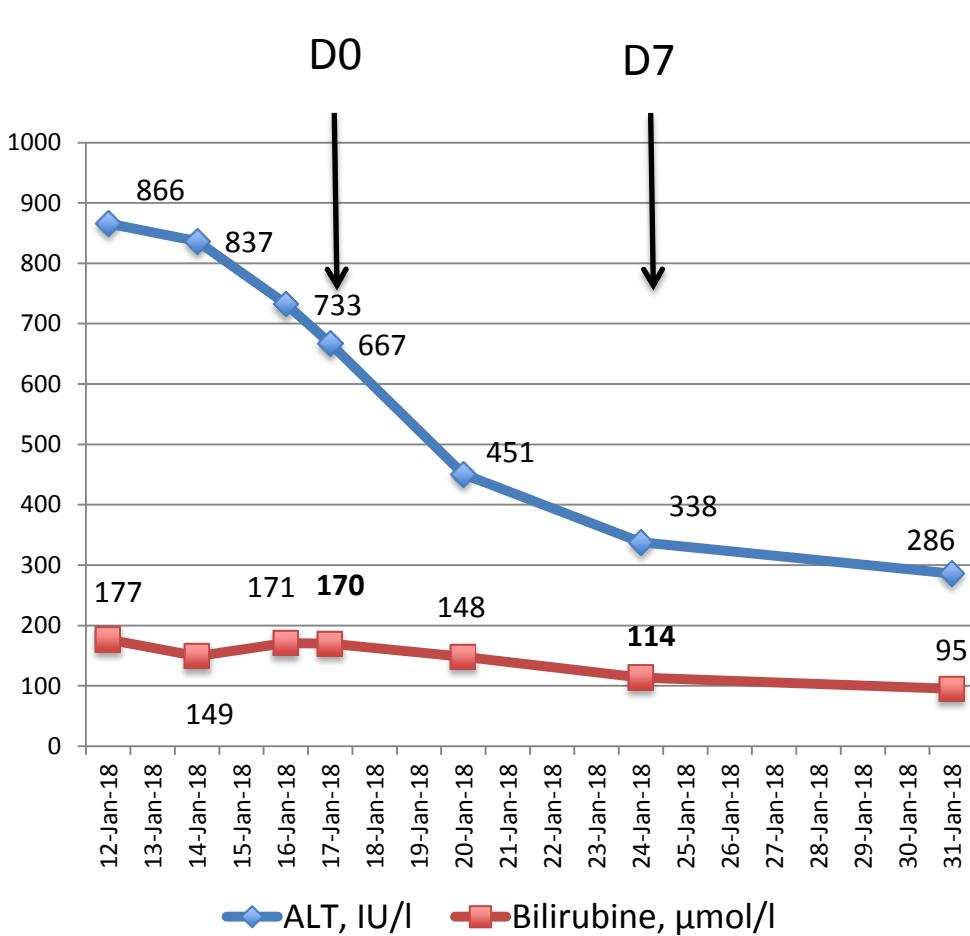
Corticosteroid response → continuation of therapy

Conclusion

- The diagnosis of AS-AIH is challenging as the main features of AIH may be absent.

- The liver biopsy is mandatory for the diagnosis and the assessment of a chronic disease. However the interpretation remains difficult.

- Corticosteroids are the therapy of choice.

- PT at day 0 and the improvement of bilirubin at day 7 since therapy introduction are associated with corticosteroid response

- The SURFASA score combining these variables predict whether corticosteroids should be continued or stopped and the patient rapidly evaluated for liver transplantation.

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