EASL The Home of Hepatology | 50th THE INTERNATIONAL LIVER CONGRESS™ 2015
APRIL 22-26, VIENNA, AUSTRIA

Risk stratification in PBC

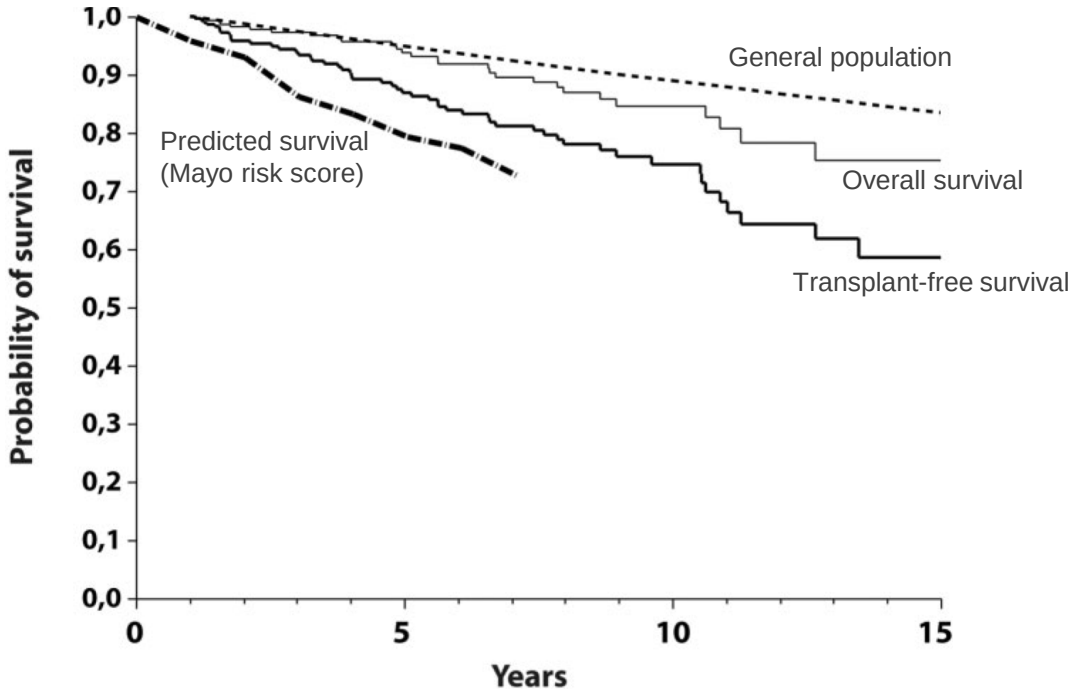
Christophe Corpechot

Reference Center for Inflammatory Biliary Diseases
Saint-Antoine hospital, Paris , France

What is currently known (background)

- PBC : chronic, progressive cholestatic disease
- Significant risk of cirrhosis, liver failure, and death
- Only one drug approved : UDCA (13-15 mg/kg/d)
- Variable response from patient to patient
- Still persistent risk of death or liver transplantation

Long-term prognosis under UDCA



(Corpechot et al. Hepatology 2008)

Main issues of clinical trials

- **Small-sized targeted population**
  - *International multicenter recruitment*
- **Slow disease progression**
  - *Use of surrogate markers*
- **Variable disease prognosis**
  - *Patient selection and risk stratification*

Selection/stratification & endpoints

Selection/stratification

- Demographics & symptoms
- Blood tests
- Imaging techniques
- Histology

Endpoints

- Death or LT
- Liver-related complications
- Histological progression
- Fibrosis markers
- Biochemical response

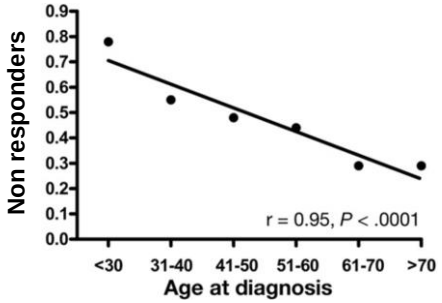
Demographics & symptoms

- Age
- Gender
- Symptoms

Demographics & symptoms

- **Age**
- Gender
- Symptoms

- **The younger, the poorer response to UDCA**
  (Carbone et al. Gastroenterology 2013)



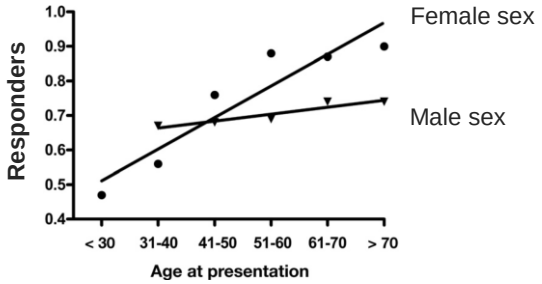
- **…and the higher mortality ratio**
  (Kubota et al. J Gastroenterol 2009)

SMR	Young (< 55 yr)	Old (≥ 55 yr)
Overall deaths	7.4 (3.0 - 15.2)	1.1 (0.6 - 1.7)
Liver-related deaths	218 (71- 509)	23 (7.3 - 53)

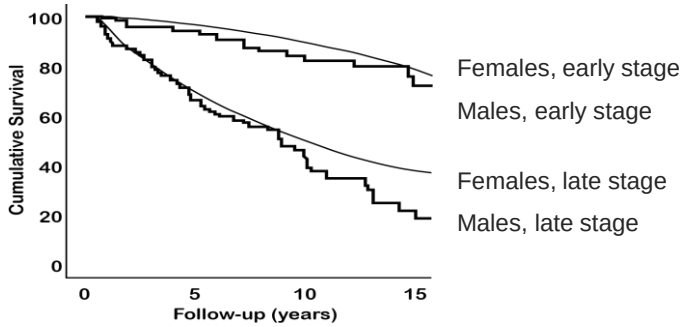
Demographics & symptoms

- Age
- **Gender**
- Symptoms

- **Are men less responsive to UDCA?**
  (Carbone et al. Gastroenterology 2013)



- **Probably not...**
  (Cheung et al. EASL meeting 2015, abstract P1184)



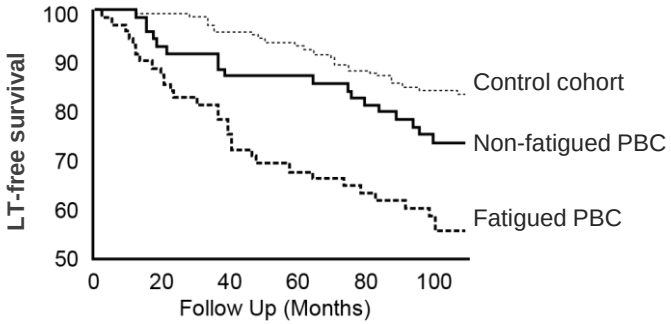
Demographics & symptoms

- Age
- Gender
- **Symptoms**

- **Pruritus or fatigue are predictive of poor response and outcomes**
  (Quarneti et al. Liver Int 2015)

	With	Without	*P*
Response (Paris I)	47 (63%)	114 (81%)	0.005
Adverse outcomes	23 (31%)	19 (13%)	0.004

- **Fatigue by itself may be of prognostic significance**
  (Jones et al. J Hepatol 2010)



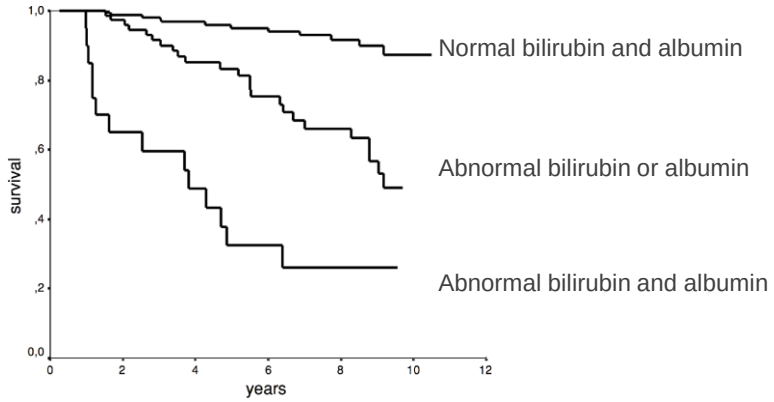
Blood tests

- Baseline parameters
  - Bilirubin & Albumin
  - ELF test
  - AST/platelet ratio
  - PBC-specific ANA
- Response to UDCA
  - Definitions
  - Paris criteria
  - Optimized criteria
  - New scores

Blood tests

- **Baseline parameters**
  - **Bilirubin & Albumin**
  - ELF test
  - AST/platelet ratio
  - PBC-specific ANA
- Response to UDCA
  - Definitions
  - Paris criteria
  - Optimized criteria
  - New scores

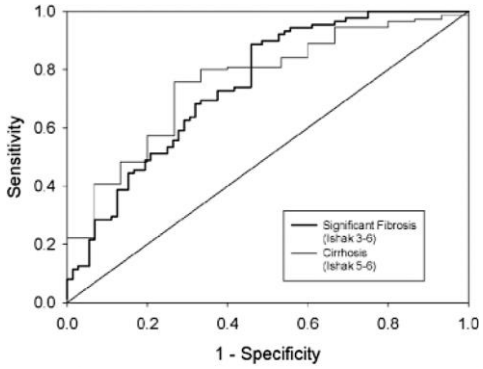
- **Simple, efficient risk stratifiers at baseline**
  (ter Borg et al. Am J Gastroenterol 2006)

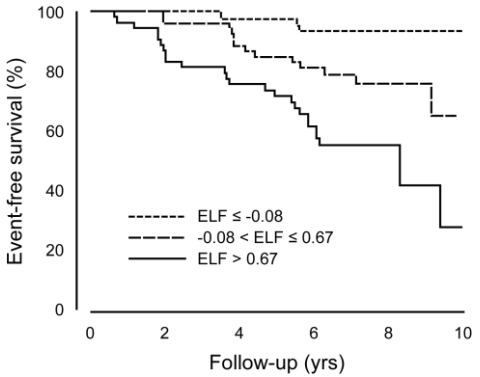


Blood tests

- **Baseline parameters**
  - Bilirubin & Albumin
  - **ELF test**
  - AST/platelet ratio
  - PBC-specific ANA
- Response to UDCA
  - Definitions
  - Paris criteria
  - Optimized criteria
  - New scores

- **Enhanced Liver Fibrosis (ELF) test competes with histological stage in predicting outcomes**
  (Mayo et al. Hepatology 2008)

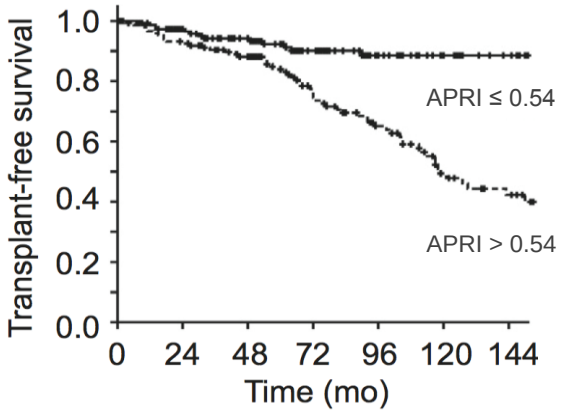




Blood tests

- **Baseline parameters**
  - Bilirubin & Albumin
  - ELF test
  - **AST/platelet ratio**
  - PBC-specific ANA
- Response to UDCA
  - Definitions
  - Paris criteria
  - Optimized criteria
  - New scores

- **Baseline APRI is predictive of death or liver transplantation**
  (Trivedi et al. J Hepatol 2014)

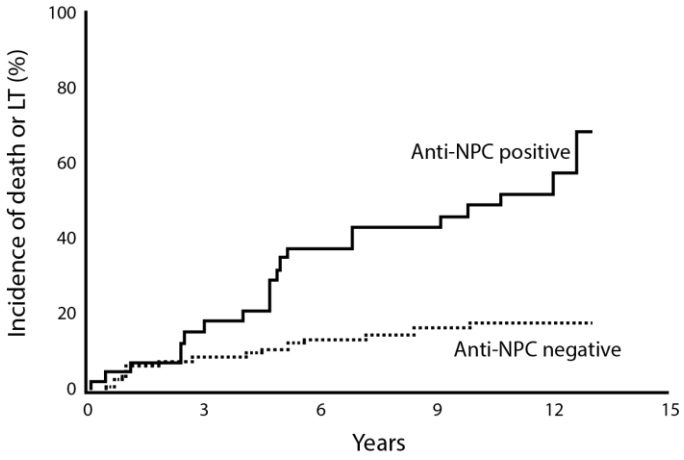


Blood tests

- **Baseline parameters**
  - Bilirubin & Albumin
  - ELF test
  - AST/platelet ratio
  - **PBC-specific ANA**
- Response to UDCA
  - Definitions
  - Paris criteria
  - Optimized criteria
  - New scores

- **Anti-nuclear pore complex (NPC) antibodies may identify high-risk patients for death or LT**

(Wesierska-Gadek et al. Hepatology 2006)



Blood tests

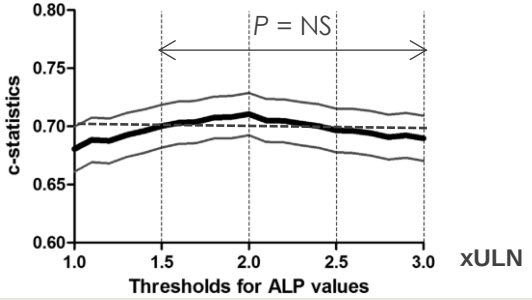
- Baseline parameters
  - Bilirubin & Albumin
  - ELF test
  - AST/platelet ratio
  - PBC-specific ANA
- **Response to UDCA**
  - **Definitions**
  - Paris criteria
  - Optimized criteria
  - New scores

- **Biochemical response to UDCA is a major predictor of death or LT**

Definition	Parameters	Time point
Barcelona	Δ(ALP) ≥ 40% ou ALP ≤ N	12 mo.
Paris-I	ALP ≤ 3N, AST ≤ 2N, BILI ≤ N	12 mo.
Toronto	ALP ≤ 1.67N	24 mo.
Rotterdam	BILI ≤ N, ALB ≤ N	12 mo.
Paris-II	ALP≤ 1.5N, AST≤ 1.5N, BILI ≤ N	12 mo.
Global PBC	ALP ≤ 2N, BILI ≤ N	12 mo.

- **Which optimal ALP cutoff ?**

(Lammers et al. Gastroenterology 2014)

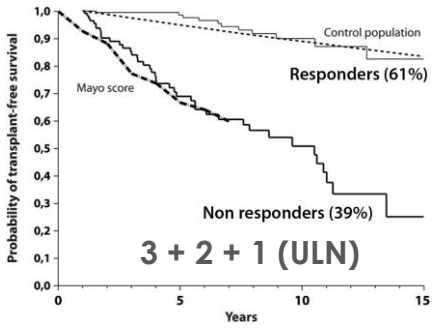


Blood tests

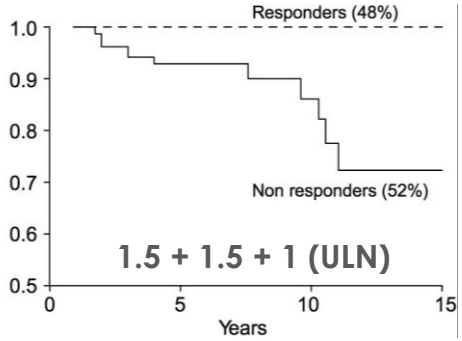
- Baseline parameters
  - Bilirubin & Albumin
  - ELF test
  - AST/platelet ratio
  - PBC-specific ANA
- **Response to UDCA**
  - Definitions
  - **Paris criteria**
  - Optimized criteria
  - New scores

- **ALP + AST + Bilirubin at 12 months**
  (Corpechot et al. Hepatology 2008; J Hepatol 2011)

All stages (Paris I)



Early stages (Paris II)



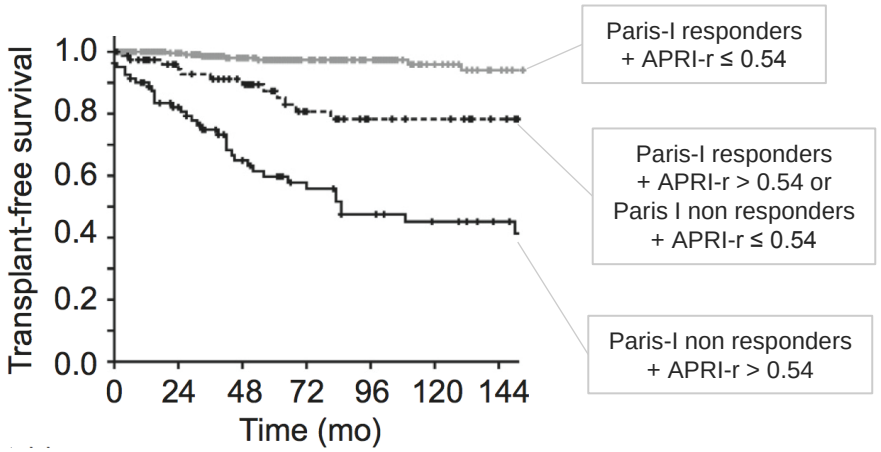
- **Extensive validation (>1,000 pts)**
  (Carbone et al. Gastroenterology 2013)

Criteria	Logrank	P-value
Paris I	106	< 1E-16
Paris II	46	1.4E-11
Toronto	24	8.8E-7
Barcelona	7	6.7E-3

Blood tests

- Baseline parameters
  - Bilirubin & Albumin
  - ELF test
  - AST/platelet ratio
  - PBC-specific ANA
- **Response to UDCA**
  - Definitions
  - Paris criteria
  - **Optimized criteria**
  - New scores

- **APRI at 1 year improves Paris I criteria prediction**
  (Trivedi et al. J Hepatol 2014)



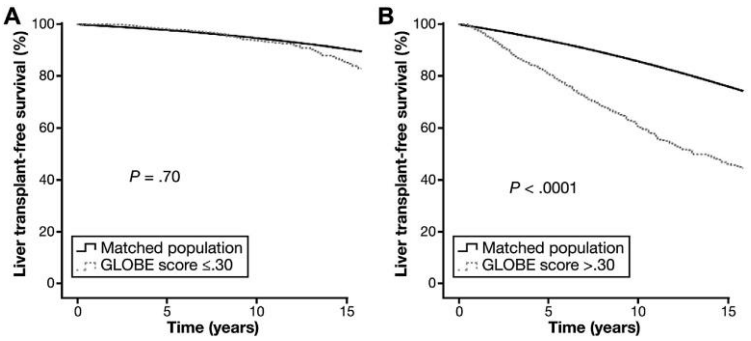
Blood tests

- Baseline parameters
  - Bilirubin & Albumin
  - ELF test
  - AST/platelet ratio
  - PBC-specific ANA
- **Response to UDCA**
  - Definitions
  - Paris criteria
  - Optimized criteria
  - **New scores**

- **Globe score**
  (Lammers et al. Gastroenterology 2015)

  Age at baseline, Bilirubin, ALP, Albumin at 12 mo.

  Predictive performance: 0.81



- **UK-PBC score**
  (Carbone et al. Hepatology 2015)

  Albumin and platelets at baseline, Bilirubin, ALP and Transaminase at 12 mo.

  Predictive performance: 0.95

Transient elastography

- Evaluating severity
- Predicting outcome
- Limitations

Transient elastography

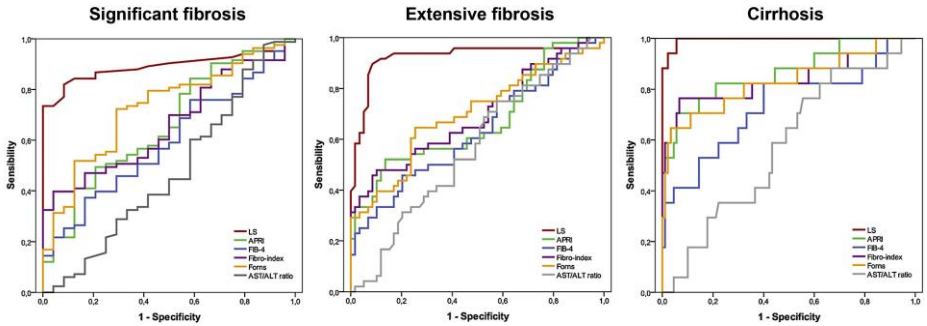
- **Evaluating severity**
- Predicting outcome
- Limitations

- **Liver stiffness *vs.* fibrosis stage**

	Patients	Extensive fibrosis*	Cirrhosis*
Gomez et al.	80	0.86	0.96
Floreani et al.	120	0.92	0.99
Corpechot et al.	146	0.95	0.99

*AUC for the specified stage

- **The best fibrosis marker of PBC?**

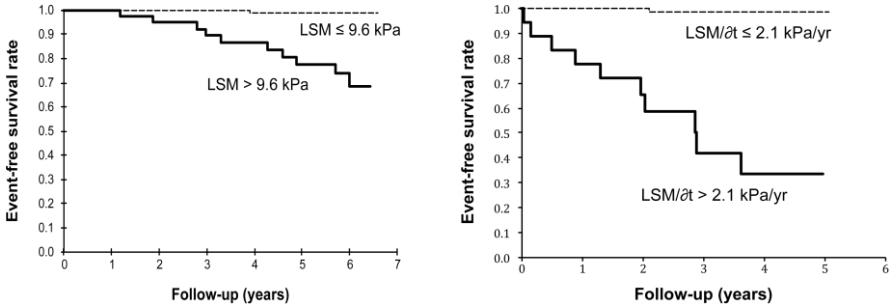


(Floreani et al. Dig Liver Dis 2011; Corpechot et al. Hepatology 2012)

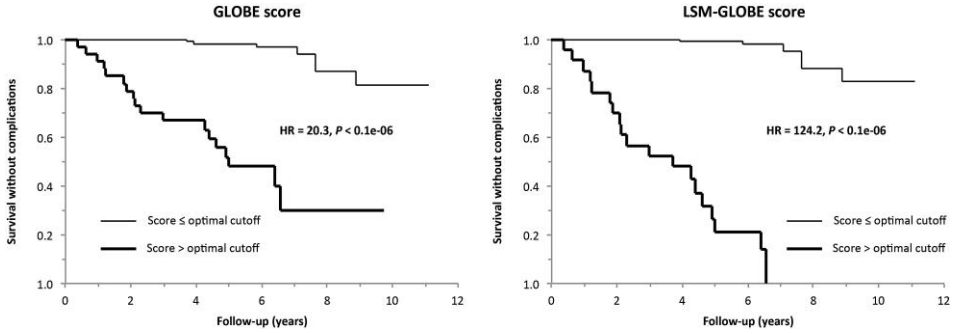
Transient elastography

- Evaluating severity
- **Predicting outcome**
- Limitations

- **LSM predicts clinical outcomes**
  (Corpechot et al. Hepatology 2012)



- **LSM improves the new risk scores' prediction**
  (Corpechot et al. EASL 2016, Barcelona)



Transient elastography

- Evaluating severity
- Predicting outcome
- **Limitations**

- **5% failure rate**
- **Up to 20% of unreliable results (IQR/median > 0.3)**
- **Influenced by cholestasis and inflammation**

Histology

- Histological (fibrosis) stage
- Interface hepatitis
- Ductopenia
- New staging systems

Histology

- **Histological (fibrosis) stage**
- Interface hepatitis
- Ductopenia
- New staging systems

- **Histological stage is a major independent prognostic factor**
  (Corpechot et al. Hepatology 2008)

	HR (95% CI)	P-value
Histological stage 3-4	1.5 (1.0 – 2.2)	0.04
Bilirubin > 1 mg/dl	1.7 (1.1 – 2.6)	0.01
Non response (Paris I)	2.3 (1.5 – 3.7)	< 0.001

- **Histological stage adds to the predictive ability of biochemical response**

  (Carbone et al. EASL meeting 2015, abstract P1198)

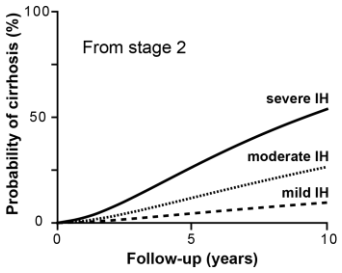
- **Elastography or ELF test are convenient alternative options**

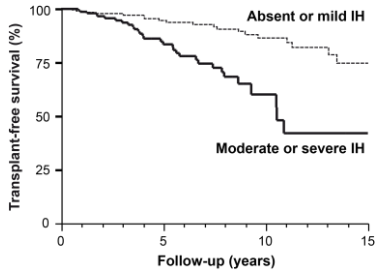
Histology

- Histological (fibrosis) stage
- **Interface hepatitis**
- Ductopenia
- New staging systems

- **Interface hepatitis is associated with a more progressive disease**
  (Corpechot et al. Gy 2002 & Hepatology 2008)

	HR (95% CI)	P-value
Histological stage 3-4	1.5 (1.0 – 2.2)	0.04
Interface hepatitis	1.9 (1.2 – 2.9)	0.002
Non response (Paris I)	2.3 (1.5 – 3.7)	< 0.001



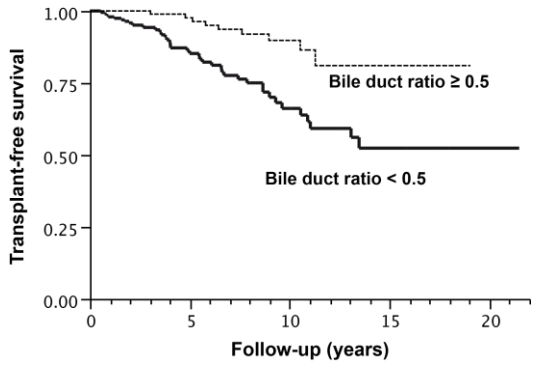


- **Recent large-scale validation from a UK cohort**
  (Carbone et al. EASL meeting 2015, abstract P1198)

Histology

- Histological (fibrosis) stage
- Interface hepatitis
- **Ductopenia**
- New staging systems

- **Ductopenia is predictive of poor response to UDCA and of histological progression**
  (Kumagi et al. Am J Gastroenterol 2010)
- **It may also be predictive of death or liver transplantation**
  (Personal data, Saint-Antoine hospital)



Histology

- Histological (fibrosis) stage
- Interface hepatitis
- Ductopenia
- **New staging systems**

- **The Japanese staging system**
  (Nakanuma et al. Pathol Int 2010; Kakuda et al. Human Pathol 2013)

Staging (combined score)	Grading (separate features)
Fibrosis (0 – 3)	Cholangitis activity
Bile duct loss (0 – 3)	Hepatitis activity
Cholestasis (0 – 3)	

- **The FBI French score**
  (Wendum et al. Liver Int 2015)

Fibrosis	5 stages (0 – 4)
Bile duct ratio	PT with duct/total PT
Interface hepatitis	4 grades (0 – 3)

In summary

Confidence level	Predictors
High (robust, extensively validated)	▪ Baseline bilirubin and albumin levels ▪ Histological stage (or its noninvasive evaluation) ▪ Response to UDCA based on ALP and bilirubin ▪ New PBC risk scores
Moderate (promising, awaiting large scale validation)	▪ Liver stiffness and its changes ▪ AST/platelet ratio ▪ ELF test
Insufficient (still limited data or poor expected applicability)	▪ Age category and symptoms ▪ PBC-specific ANAs ▪ Interface hepatitis and bile duct ratio ▪ New histological scoring systems

Conclusion

- Many prognostic tools are now available and should improve the design of trials
- My proposals for new RCTs would be :
  - **For patient selection :**
    - **Biochemical response to UDCA based on ALP and bilirubin**
    - Alternative options: new PBC risk scores
  - **For risk stratification :**
    - **Histological stage or its noninvasive evaluation (TE ++)**
    - Alternative options: bilirubin/albumin, new PBC risk scores
- Key remaining issue : what optimal endpoint?