Supplementary Data.

Supplementary Methods:

1. Details of Histological Assessment

Certain points about histological assessment technique, histological diagnosis and interpretation have to be clarified. Regarding the optimal magnification we propose that pathologists use a low magnification (20-40x) for evaluating the distribution of fibrosis in the Masson's trichrome staining and higher magnifications (400x) to evaluate the cytopatic lesions such as ballooning, Mallory-Denk hyaline and PMN infiltration. Ideally, a 600x magnification should be used to assess the presence of megamitochondria. We strongly recommend to examine the whole liver biopsy and not only few fields.

The minimum diagnostic criteria for alcoholic steatohepatitis was the presence of any degree of ballooning and Mallory-Denk hyaline (MDH) and any degree of associated lobular inflammation (in some cases very mild or focal, in a context of steatosis [any degree]).

We consider as "mild" PMN infiltration the presence of isolated or a row of few PMNs around one or around a small cluster of 3-4 hepatocytes. Usually the number of PMNs is less than 15 per focus, and they are difficult to find at low magnification. We consider as "marked PMN infiltration" the presence of PMNs when they are easily recognized at low magnification, and numerous PMN around damaged hepatocytes (with ballooning or Mallory-Denk bodies)

Concerning to the ballooning, mild was considered when their presence is focal and dispersed, affecting isolated hepatocytes, not in groups. They usually should be searched intently. In contrast, marked ballooning was considered when groups of hepatocytes showed this change, and they are found easily at low magnification. The presence of only one focus of marked ballooning is enough to label the item as marked.

Finally, we have combined the presence of ductular and canalicular bilirubinostasis in as a category of the proposed histological scoring system. We agree that canalicular cholestasis is observed in many situations, from acute obstruction to sepsis to drug/cytokine injury, while ductular cholestasis has a much more limited differential diagnosis, mainly limited to sepsis. The only reason to combine them in the scoring system is that both types of cholestasis (i.e. canalicular and ductular) had the same impact on prognosis at the initial mortality analyses.

2.Detailed Description of Model Building

We used a training set/test set approach to build the histological model. The training set was the Hospital Clinic cohort (121 patients). For the test set two of the external cohorts were randomly selected (96 patients).

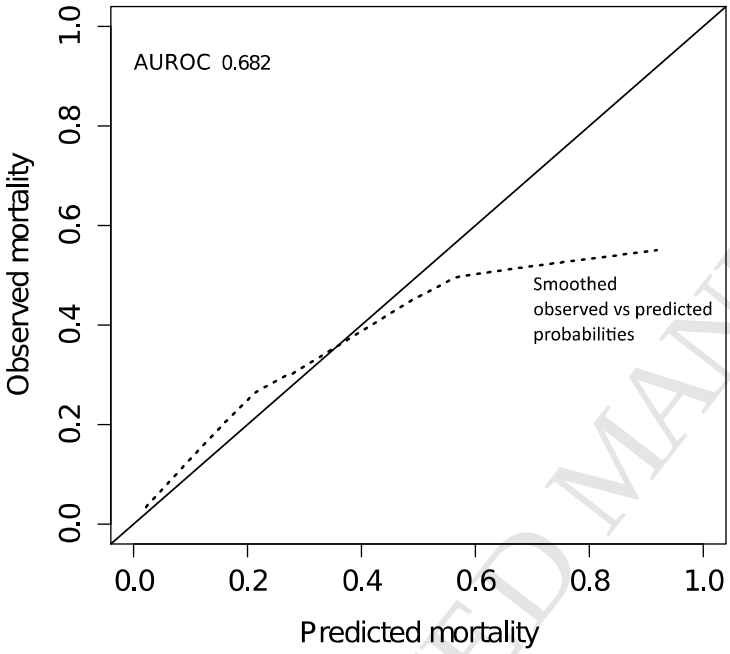
The initial model was developed in the training set. All histological data were included in the univariate analysis. A logistic regression univariate analysis was used to identify histological features associated with 90-day mortality. After an inspection of the data, categorical variables were simplified as follows: fibrosis stage was dichotomized (bridging fibrosis or cirrhosis vs absence of these features). The variable bilirubinostasis was divided in 3 categories: A: absence or hepatocellular only, B: canalicular or ductular, C: canalicular or ductular + hepatocellular. Variables that were statistically significant in the univariate model were entered into a backward stepwise elimination variable selection procedure (multivariate logistic regression). The criterion for retaining predictors was a p value $\leq$ 0.10.

The following logistic regression model was developed:

Logit = -5.97 + 2.47(Bridging fibrosis or cirrhosis) + 0.38*(Bilirrubinostasis canalicular or ductular) + 1.63* (Bilirrubinostasis canalicular or ductular + hepatocellular) + 2.16*(Megamitochondria) + 2.14*(severe PMN infiltration).*

R2: 0.404 and C-statistic: 0.829

The performance of this model (discrimination and calibration) was the evaluated in the test set. Discrimination decreased, as shown by a c-statistic of 0.682. Calibration (agreement between predicted and observed probabilities) was assessed by plotting smoothed predicted vs observed mortality rates.



As shown by the figure, calibration was excellent up to a predicted risk of 50%. Beyond this level, the model substantially over-predicted mortality. Therefore, we updated our logistic regression model by re-estimating the regression coefficients in the training and test set together. Of note, no further variable selection was performed at this stage. The final coefficients were corrected for optimism with bootstrapping (200 replications).

Final logistic regression model:

Logit= 4.20 + 1.96(Bridging fibrosis or cirrhosis) + 0.40*(Bilirrubinostasis canalicular or ductular) + 1.02* (Bilirrubinostasis canalicular or ductular + hepatocellular) + 0.90*(Megamitochondria) + 1.25*(severe PMN infiltration).*

Since all variables included in the model were categorical, we decided to simplify the model to a semiquantitative score (from 0-9 points):

	Points	
Fibrosis stage		AHHS categories (0-9 points)
None Fibrosis or Portal fibrosis	0	Mild : 0-3
Expansive fibrosis	0	Intermediate: 4-5
Bridging fibrosis or Cirrhosis	+3	Severe: 6-9
Bilirubinostasis		
None	0	
Hepatocellular only	0	
Canalicular or ductular	+1	
Canalicular or ductular plus Hepatocellular	+2	
PMN infiltration		
Mild PMN Infiltration	+2	
Severe PMN Infiltration	0	
Megamitochondria		
No Megamitochondria	+2	
Megamitochondria	0	

Furthermore, three categories of risk were defined:

Category	Score points	Predicted risk of 90-day mortality
Low risk	1 to 3	3 %
Intermediate risk	4 and 5	19 %
High risk	6 to 9	51 %

Supplementary Tables.

Supplementary Table 1. Histological Features and No Response to Corticosteroids in Patients with Alcoholic Hepatitis in the Training Cohort.

	Univariate logistic regression (events n=19)		
Histological Features	**OR**	**95% CI**	**p**
Fibrosis Stage (bridging fibrosis or cirrhosis)	0.84	0.12-5.83	.86
PMN Infiltration (severe/mild)	1.61	0.42-6.10	.47
Bilirubinostasis (type)	2.04	0.94-4.45	.07
Megamitochondria (y/n)	1.03	0.27-3.91	.96

Abbreviations: PMN, polymorphonuclears

Supplementary Table 2. Clinical and Hemodynamic Characteristics of Patients with Alcoholic Hepatitis in the Training and External Cohorts.

Characteristics	Training Cohort (n=121) Median (25-75 IQR)	External Cohorts (n=205) Median (25-75 IQR)	p
Age (years)	49 (41-54)	48 (43-54)	.8
Male n (%)	78 (67)	134 (65)	.9
Corticosteroids n (%)	54 (45)	88 (43)	.8
Laboratory and hemodynamic parameters			
Leukocyte count $x10^9$ /L	8.9 (6.3-13.9)	11.5 (7.9-17)	.002
AST (U/L)	125 (82-188)	130 (94-203)	.6
ALT (U/L)	51 (35-71)	51 (34-77)	.6
Serum albumin (g/dL)	2.7 (2.3-3.0)	2.8 (2.5-3.2)	.008
Serum creatinine (mg/dL)	0.8 (0.60-1.0)	1 (0.7-1.3)	.4
Serum bilirubin (mg/dL)	9.7 (4.3-17.7)	15.5 (9.4-26.6)	<.0001
International normalized ratio	1.6 (1.4-1.9)	1.7 (1.4-2.1)	.1
HVPG (mmHg)*	20 (15-24)	18 (14-23)	.3
Severity scores at admission			
MELD score	18 (12-22)	22 (17-29)	<.0001
ABIC score	7.3 (6.6-8.4)	7.9 (6.9-9.3)	.001
ABIC class n (%)			
A (<6.71)	33 (27)	40 (20)	.02
B (6.71-8.99)	68 (56)	105 (51)	
C (>9)	20 (17)	60 (29)	

Abbreviations: IQR, interquartile range; AST, aspartate aminotransferase level; ALT, alanine aminotransferase level; HVPG, hepatic venous pressure gradient; MELD, model for end-stage liver disease; ABIC, age, bilirubin, INR, creatinine score.

*Data from 112 patients in the study cohort and 142 patients in the validation cohort.

Supplementary Table 3. Histological Features Associated with Infections During Hospitalization in Patients with Alcoholic Hepatitis in the Training Cohort.

	Univariate logistic regression (events n=47)			Multivariate logistic regression (events n=47)		
Histological features	**OR**	**95% CI**	**p**	**OR**	**95% CI**	**p**
Fibrosis Stage (bridging fibrosis or cirrhosis)	0.87	0.33-2.29	.79	0.92	0.34-2.48	.87
PMN Infiltration (mild/severe)	0.91	0.42-2.00	.83	0.75	0.33-1.71	.52
Bilirubinostasis (type)	1.55	1.00-2.40	.04	1.57	1.00-2.47	.04
Megamitochondria (y/n)	0.65	0.28-1.49	.31	0.66	0.27-1.57	.35

Abbreviations: PMN, polymorphonuclears

Supplementary Table 4. Bivariate Survival Analysis Including Clinical Scoring Systems and Alcoholic Hepatitis Histological Score (AHHS) in Patients with Alcoholic Hepatitis

	Training cohort Multivariate logistic regression (events n=35)				External cohorts Multivariate logistic regression (events n=64)		
	OR	**95% CI**	**p**		**OR**	**95% CI**	**p**
AHHS	2.10	1.34-3.28	.001	AHHS	1.34	1.11-1.62	.002
ABIC score	2.43	1.56-3.77	<.0001	ABIC score	1.97	1.53-2.53	<.0001
AHHS	2.69	1.71-4.24	<.0001	AHHS	1.32	1.11-1.58	<.0001
MELD score	1.04	0.98-1.10	.18	MELD score	1.08	1.03-1.12	.002

Abbreviations: MELD, model for end-stage liver disease; ABIC, age, bilirubin, INR, creatinine score; CI, confidence interval; AHHS, alcoholic hepatitis histological score.

Supplementary Table 5. Backward stepwise multivariate logistic regression analysis according to 90-day mortality including AHHS plus clinical and analytical variables at admission.

Variables	Training Cohort (events n=35)		
	OR	**95%IC**	**p**
AHHS (points)	2.27	1.53-3.37	*<.0001*
Age	1.11	1.03-1.19	*.003*
Bilirubin	1.06	1.00-1.12	*.04*
INR	2.91	1.11-7.58	*.02*

Supplementary Figure Legends

Supplementary Figure 1. Three-month survival probability in patients with alcoholic hepatitis treated with corticosteroids according to the Alcoholic Hepatitis Histological Score (AHHS).

Supplementary Figure 2. Predicted vs observed mortality in the validation set according to the AHHS.

Supplementary Figure 3. Type of bilirubinostasis and Infections During Hospitalizations in Patients wih Alcoholic Hepatitis.

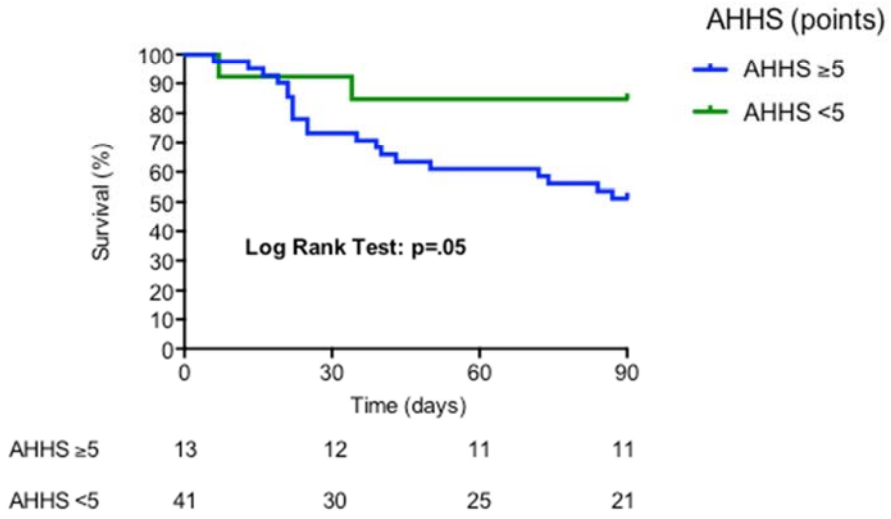
Supplementary Figure 4. Type of bilirubinostasis and baseline bilirubin serum levels.

Supplementary Figure 5. Side-by-side comparison of AHHS, ABIC score and MELD for predicting 90-day mortality in the complete cohort.

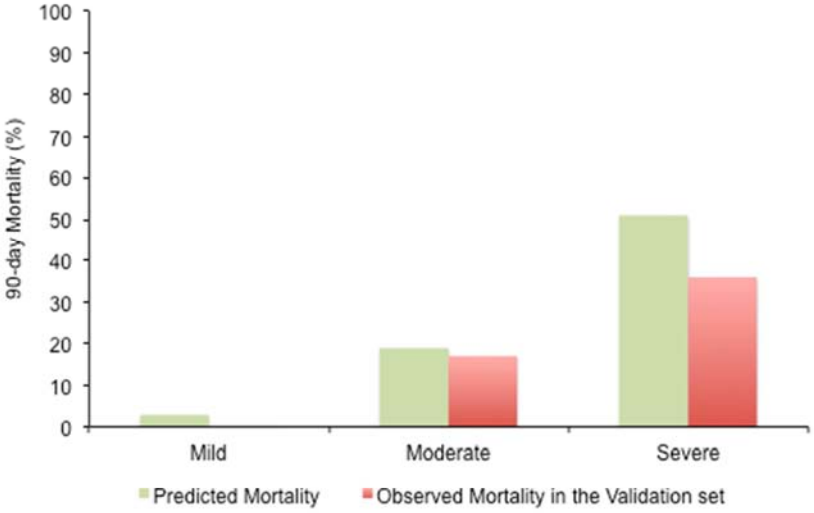
Supplementary Figure 6. Differences in MELD score between patients with AHHS ≥5 and AHHS <5 points.

Supplementary Figure 7. HVPG measurement in patients with AHHS ≥5 and AHHS <5 points in the complete cohort.

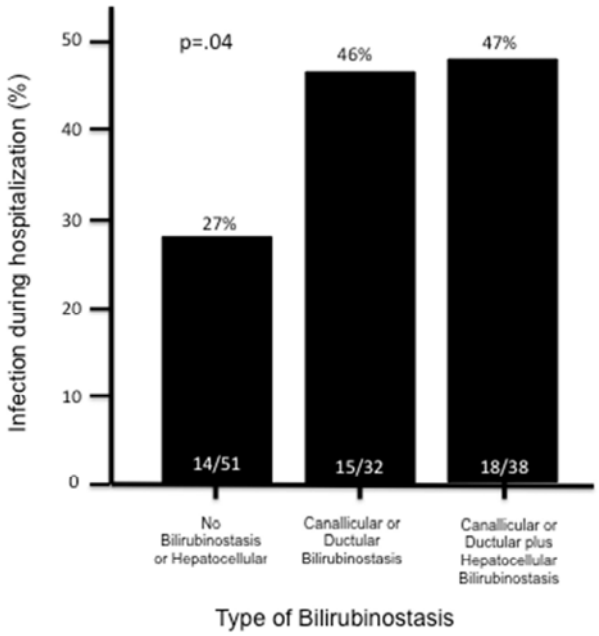
Supplementary Figure 1.



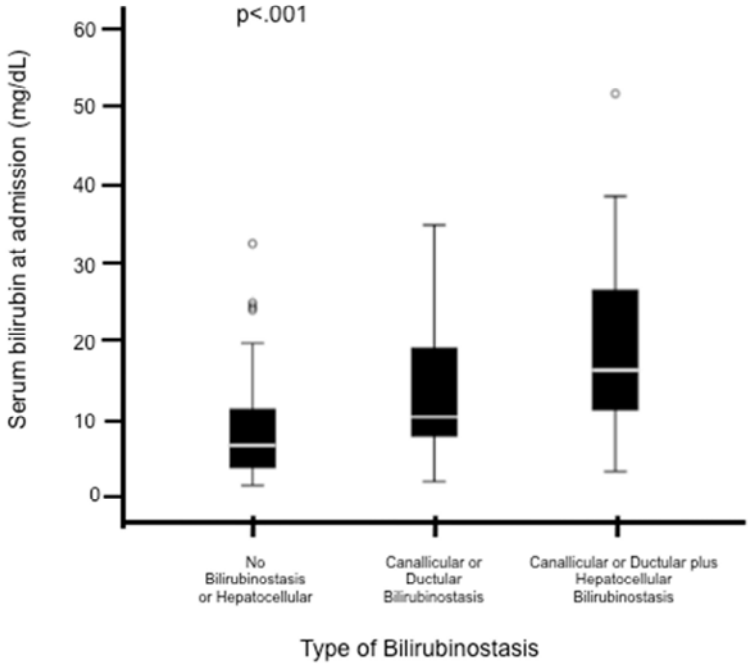
Supplementary Figure 2.



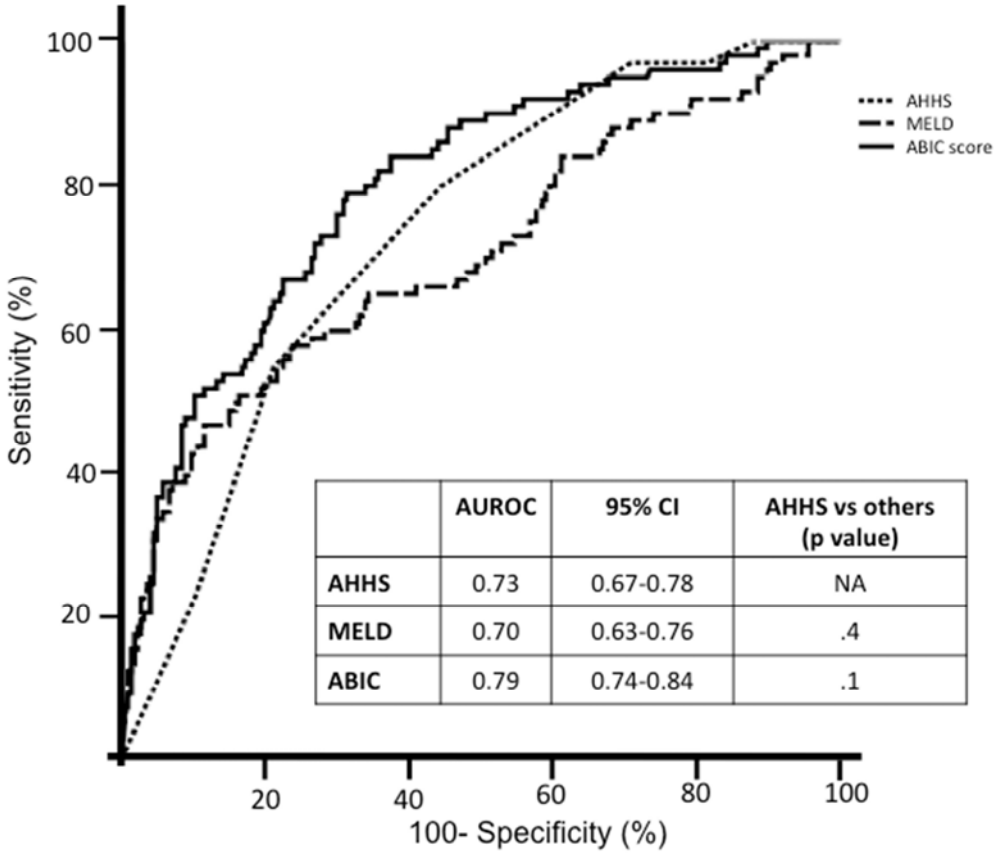
Supplementary Figure 3.



Supplementary Figure 4.

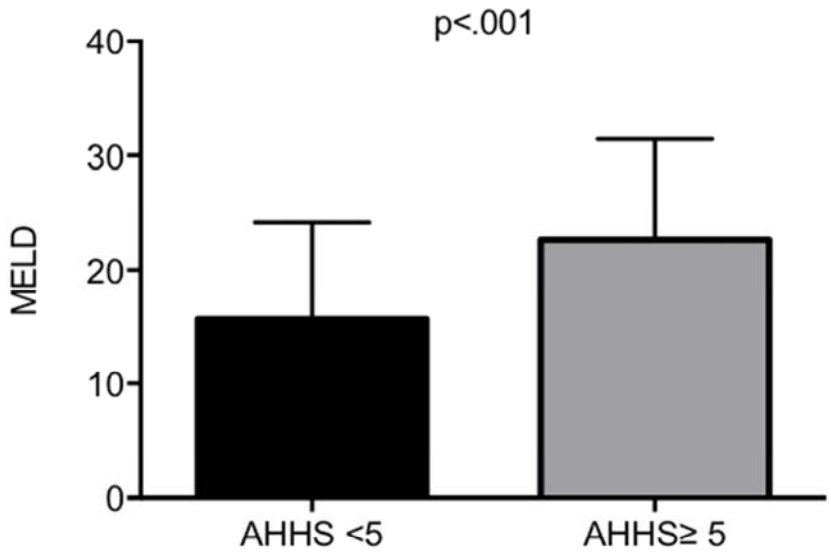


Supplementary Figure 5.



	AUROC	95% CI	AHHS vs others (p value)
AHHS	0.73	0.67-0.78	NA
MELD	0.70	0.63-0.76	.4
ABIC	0.79	0.74-0.84	.1

Supplementary Figure 6.



Supplementary Figure 7.