The Lille Model: A New Tool for Therapeutic Strategy in Patients with Severe Alcoholic Hepatitis Treated with Steroids

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Early identification of patients with severe (discriminant function ≥ 32) alcoholic hepatitis (AH) not responding to corticosteroids is crucial. We generated a specific prognostic model (Lille model) to identify candidates early on for alternative therapies. Three hundred twenty patients with AH prospectively treated by corticosteroids were included in the development cohort and 118 in its validation. Baseline data and a change in bilirubin at day 7 were tested. The model was generated by logistic regression. The model combining six reproducible variables (age, renal insufficiency, albumin, prothrombin time, bilirubin, and evolution of bilirubin at day 7) was highly predictive of death at 6 months ($P < 0.000001$). The area under the receiver operating characteristic (AUROC) curve of the Lille model was 0.89 ± 0.02, higher than the Child-Pugh (0.62 ± 0.04, $P < 0.00001$) or Maddrey scores (0.66 ± 0.04, $P < 0.00001$). In the validation cohort, its AUROC was 0.85 ± 0.04, still higher than the other models, including MELD (0.72 ± 0.05, $P = 0.01$) and Glasgow scores (0.67 ± 0.05, $P = 0.0008$). Patients above the ideal cutoff of 0.45 showed a marked decrease in 6-month survival as compared with others: 25% ± 3.8% versus 85% ± 2.5%, $P < 0.0001$. This cutoff was able to identify approximately 75% of the observed deaths. *Conclusion:* In the largest cohort to date of patients with severe AH, we demonstrate that the term "nonresponder" can now be extended to patients with a Lille score above 0.45, which corresponds to 40% of cases. Early identification of subjects with substantial risk of death according to the Lille model will improve management of patients suffering from severe AH and will aid in the design of future studies for alternative therapies. (HEPATOLOGY 2007;45:1348-1354.)

The treatment of severe forms of alcoholic hepatitis (AH) constitutes a major challenge in management of severe alcoholic liver disease. Before the era of the Maddrey function (DF),[1,2] clinicians faced substantial difficulties in identifying subgroups of patients with high risk of death over a short term; as a consequence, survival of untreated patients enrolled in randomized controlled trials (RCTs) ranged from 0 to 81%.[3] Since the use of DF (DF ≥ 32) in several RCTs,[1,4-6] spontaneous 2-month survival has been approximately 50%. The DF clearly demonstrates the tremendous progress provided by elaborating specific prognostic functions for AH. The advantage of accurate models has been confirmed by the growing importance of the MELD score in the selection of candidates for liver transplantation.[7-9]

In patients with DF ≥ 32, several RCTs and a recent meta-analysis showed that corticosteroids improve short-term survival.[1,5,10-14] However, novel strategies or molecules are required, in light of the fact that approximately 40% of patients die at 6 months.[15] Therefore, improvement in the prediction of mortality in severe AH is warranted. However, we lack evidence supporting the higher efficacy of new models such as MELD and Glasgow scores compared with the DF.[16-18] In the particular setting of

Abbreviations: AH, alcoholic hepatitis; AUROC, area under the receiver operating characteristic; DF, Maddrey function; INR, international normalized ratio; RCT, randomized controlled trial.

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patients treated by corticosteroids, new specific models could pose a challenge to clinical practitioners by inciting them to consider all available options in targeted patients after a short period of evaluation.[15,19,20]

The aims of the current study on a large cohort of patients with severe AH prospectively treated with corticosteroids were: (1) to generate a specific prognostic model, the so-called Lille model, enabling clinicians to identify subjects early on who are unlikely to survive; and (2) to propose new management based on this specific model.

Patients and Methods

Patients

Inclusion Criteria and Corticosteroid Protocol. All patients with a DF $\geq$ 32 or encephalopathy at admission were treated by corticosteroids if they fulfilled the following criteria: (1) a history of alcoholism; (2) liver chemistry suggestive of AH; (3) the absence of uncontrolled infection or recent gastrointestinal hemorrhage (<15 days); (4) transjugular liver biopsy, which was carried out for all patients. Histological diagnosis of AH was based on the presence of hepatocellular necrosis and infiltration of polymorphonuclear leukocytes.[21] We excluded patients with active peptic ulcers, neoplasms, positive test for hepatitis B surface antigen, and human immunodeficiency virus antibodies. Patients were treated in all centers using the same treatment protocol.[6] Prednisolone was given in a single dose of 40 mg each morning for 28 days. Patients unable to take oral medication received intravenous infusions of 32 mg methylprednisolone. In the validating cohort, only patients with a DF $\geq$ 32 were treated.

Exploratory Cohort of Severe AH. For development of the model, 320 patients were included from July 1990 to October 2001 in Beaujon, Beclere, and Saint-Antoine Hospitals and from October 2001 to October 2003 in the Lille Hospital.

Validating Cohort of Severe AH. We validated the performance of the Lille model in an independent prospective cohort of patients hospitalized in Lille and Bethune Hospitals for severe AH treated by corticosteroids. Validation and comparison of models were performed prospectively from November 2003 to April 2005 in all patients (n = 118) admitted. International normalized ratio (INR) was measured in this validating cohort to compare the Lille model with the MELD score calculated using the formula described by Dunn et al.[16]

Clinical and Biological Data

The following clinical and biological variables were recorded at admission, and biological data were prospectively determined during the treatment period (7, 14, 21, and 28 days): center, age, sex, alcohol intake, presence of encephalopathy, ascites, survival, bilirubin, prothrombin time, albumin, AST, creatinine, white blood cell count, polymorphonuclear count, and DF. All patients were followed for at least 6 months. For patients lost to follow-up before 6 months, data were censored at the last follow-up.

Statistical Analysis

The primary end-point was 6-month survival. As a first step, clinical and biological baseline variables that differed significantly between living and deceased patients were identified by univariate analysis using chi-square, Student *t* test, and the Mann-Whitney test. All *P* values were two-tailed. In the second step, the independent discriminative values of variables reaching a univariate $P \leq 0.05$ were then assessed by logistic regression analysis. The logistic regression method was used because our objective was to predict, in a binary fashion, whether a patient would be alive after 6 months regardless of the time of death. The third step was to construct a model that combined predictive factors of survival at 6 months. To construct a reproducible model, we included only objective criteria; thus, subjective and fluctuating criteria such as encephalopathy were not used. The best index for discrimination was the R function obtained by the forward logistic regression function combining the most discriminatory independent factors. The score probability of death ranged from 0 to 1 using the following formula: $\text{Exp}(-R)/[1 + \text{Exp}(-R)]$. The prediction of the model was expressed by the area under the receiver operating characteristic (AUROC) curves. The differences in terms of diagnostic accuracy between the models were assessed by comparison of AUROC curves using the *z* test described in Zhou et al.[22] Sample size calculation of the validating cohort was determined to show a significant difference between the Lille model and MELD and Maddrey scores. We hypothesized that the AUROC of MELD and Maddrey scores would not be significantly different, according to two previous studies comparing both scores.[16,18] With an α risk of 0.05 and a β risk of 0.2, a prevalence of death at 0.4, and a bilateral test, the sample size was calculated for the following hypotheses of AUROC curves: 0.85 for the Lille model and 0.7 for the Maddrey or MELD. Thus, the sample size of the validating cohort was calculated to be at least 100 patients.

In the final step, we determined the best cutoff of the Lille model capable of identifying patients at high risk of death. In a final step, we evaluated the accuracy of the model and its defined cutoff in nontreated patients using individual data from the last three RCTs. For this purpose, data from 102 placebo-randomized patients and 113 randomized corticosteroid patients were used.[11] All statistical analyses were performed using NCSS 2004 software.

Table 1. Clinical and Biochemical Features of Patients Included in the Exploratory Cohort

Number of patients	295
Male sex, no (%)	149 (50.5%)
Age (y), median (range)	49.7 (28.2–78)
Presence of ascites, no. (%)	203 (78%)
Encephalopathy, no. (%)	78 (26.6%)
Bilirubin (μmol/l), median (range)	210 (32–877)
Prothrombin time (s), median (range)	19.5 (13.5–32)
Albumin (g/l), median (range)	27 (11–49)
Serum creatinine (mg/dl), median (range)	0.8 (0.32–6.7)
AST (IU/l), median (range)	95 (15–504)
White blood cells (no/mm^3), median (range)	10,800 (2,200–64,000)
Daily alcohol intake (g/day), median (range)	120 (30–400)
Evolution of bilirubin between day 0 and day 7 (μmol/l), median (range)	32.2 (355–403)
Child-Pugh score, median (range)	10 (7–15)
Maddrey function (DF), median (range)	47.5 (23.2–144.6)

The data "presence of ascites" were not available for 37 patients.

Results

General Characteristics of the Exploratory Cohort of Patients with Severe AH

Three-hundred twenty patients were prospectively treated by corticosteroids. Before inclusion, DF was recalculated for all patients. AH was biopsy-proven in 94% of cases. In the remaining cases, the size of biopsy sample or failure of the transjugular procedure did not permit histological diagnosis of AH. We retrospectively identified and excluded 25 patients who did not fulfill the inclusion criteria of severity (DF $<$ 32 and absence of encephalopathy). Thus, a total of 295 patients with severe AH assessed by a DF $\geq$ 32, or encephalopathy at admission, constituted the exploratory cohort for the development of the Lille model (Table 1). Survival of these patients was 86.5% $\pm$ 2%, 77% $\pm$ 2.5%, 65.4% $\pm$ 2.9% at 1, 2, and 6 months, respectively.

Development of the Lille Model in the Exploratory Cohort

In a first step, we tested, in univariate analysis, the prognostic values of clinical and biological variables for survival at 6 months (Table 2). Ten variables reached a P value $\leq$ 0.05 in univariate analysis: age (P = 0.03), albumin (P = 0.01), renal insufficiency (P = 0.000001), difference in bilirubin levels between day 0 and day 7 ($P <$ 0.000001), serum bilirubin (P = 0.000003), prothrombin time (P = 0.02), DF (P = 0.00001), Child-Pugh score (P = 0.02), presence of encephalopathy (P =

Table 2. Prognostic Significance at 6 Months According to the Log-Rank Test in Baseline Variables Included in Univariate Analysis

	6-Month Survival $\pm$ SE	P Value of Log-Rank Test
Male	61% $\pm$ 4%	P = 0.11
Female	69.9% $\pm$ 4%	
Age $<$ 49.7 years	74.1% $\pm$ 3.7%	P = 0.003
Age $\geq$ 49.7 years	56.9% $\pm$ 4.2%	
Serum bilirubin $<$ 237 μmol/l	77% $\pm$ 3.3%	P = 0.000003
Serum bilirubin $\geq$ 237μmol/l	54.3% $\pm$ 4.4%	
Prothrombin time $<$ 19.7 s	72.9% $\pm$ 3.6%	P = 0.02
Prothrombin time $\geq$ 19.7 s	62.1% $\pm$ 4%	
DF $<$ 47.5	77.3% $\pm$ 3.6%	P = 0.00001
DF $\geq$ 47,5	54.1% $\pm$ 4.3%	
Serum albumin $<$ 27 g/l	60.5% $\pm$ 4.4%	P = 0.01
Serum albumin $\geq$ 27 g/l	75.5% $\pm$ 4%	
Child-Pugh score $<$ 10	78.2% $\pm$ 5.2%	P = 0.02
Child-Pugh score $\geq$ 10	63.8% $\pm$ 4.6%	
Renal insufficiency	33.3% $\pm$ 6.8%	P = 0.000001
Absence of renal insufficiency	69.2% $\pm$ 3.3%	
Difference in bilirubin between day 0 and day 7 $<$ 32 μmol/l	43.4% $\pm$ 4.7%	$P <$ 0.000001
Difference in bilirubin between day 0 and day 7 $\geq$ 32 μmol/l	85% $\pm$ 3.3%	
AST $<$ 93 IU/l	66.1% $\pm$ 4.3%	P = 0.4
AST $\geq$ 93 IU/l	66.7% $\pm$ 4.3%	
Daily alcohol intake $\geq$ 120 gram/day	60.8% $\pm$ 5.3%	P = 0.13
Daily alcohol intake $<$ 120 gram/day	70.9% $\pm$ 4.4%	
White blood cells $<$ 10,800/mm^3	64% $\pm$ 4.5%	P = 0.8
White blood cells $\geq$ 10,800 cells/mm^3	64.7% $\pm$ 4.5%	
Absence of ascites	82.4% $\pm$ 5.3%	P = 0.003
Presence of ascites	61.7% $\pm$ 3.5%	
Absence of encephalopathy	71.8% $\pm$ 3.2%	P = 0.0002
Presence of encephalopathy	48.4% $\pm$ 5.9%	

NOTE. The cutoff level for values was the median value. Renal insufficiency was defined by serum creatinine above 1.3 mg/dl (115 μmol/l) or creatinine clearance of less than 40 ml/min.

Table 3. Multivariate Analysis

	Age	Albumin Day 0	Evolution of Bilirubin at Day 7	Renal Insufficiency	DF Day 0
Odds ratio (95 % CI)	0.93 [(0.89)-(0.97)]	1.13 [1.05-1.23]	1.01 [1.01-1.02]	0.33 [(0.13)-(0.86)]	0.98 [(0.97)-(0.999)]
P	0.0004	0.002	<0.000001	0.02	0.04

0.0002), and ascites ($P = 0.003$). Because our objective was to develop a reproducible function for predicting death at 6 months, only objective variables were considered. Multivariate analysis was performed using logistic regression (Table 3). Because the DF combines bilirubin and prothrombin time, those two functions were included individually in the definitive formula of the Lille model. The final logistic regression function (R Lille model) combining six variables (P logistic function $<$ 0.000001) was: 3.19 − 0.101 * (age in years) + 0.147 * (albumin day 0 in g/L) + 0.0165 * (evolution in bilirubin level in μM) − 0.206 * (renal insufficiency) − 0.0065 * (bilirubin day 0 in μM) − 0.0096 * (prothrombin time in seconds). Renal insufficiency was rated 0 if absent and 1 if present (below or above 115 μM [1.3 mg/dl]). The final Lille model score fluctuated from 0 to 1 (see Materials and Methods for more details). The AUROC curve for survival at 6 months of the derived score probability (Lille model, Fig. 1) was 0.89 ± 0.02 (95%CI: 0.83-0.93). In a second step, we compared the AUROC curve of the Lille model with the AUROC of the Child-Pugh and DFs, the other two models prospectively calculated in the exploratory cohort. The AUROC curve of the Lille model was significantly higher than that of the Child-Pugh (0.62 ± 0.04, $P < 0.00001$) and Maddrey scores (0.66 ± 0.04, $P < 0.00001$). The AUROC curve of the Lille model was significantly higher than that of the evolution of DF between day 0 and day 7: 0.88 ± 0.03 versus 0.70 ± 0.04, $P = 0.0001$. In terms of prediction of mortality, the evolution of DF between day 0 and day 7 did not add any advantage to the DF at day 0, as shown by comparison of their AUROC curves: 0.70 ± 0.04 versus 0.66 ± 0.04 ($P = 0.6$).

Validation of the Lille Model and Comparison with All Available Models in the Validating Cohort

One hundred eighteen patients with severe AH were prospectively included in the validating cohort (Table 4). In addition, MELD and Glasgow scores were calculated. The AUROC curve of the Lille model in the validation cohort was: 0.85 ± 0.04 (95% CI: 0.76-0.91). The AUROC curve of the Lille model was significantly higher than that of all other prognostic models: Child-Pugh (0.67 ± 0.05, 95% CI: 0.56-0.76, $P = 0.003$), DF (0.73 ± 0.05, 95% CI: 0.62-0.81, $P = 0.03$), MELD (0.72 ± 0.05, 95% CI: 0.61-0.8, $P = 0.01$), and Glasgow scores (0.67 ± 0.05, 95% CI: 0.56-0.76, $P = 0.0008$) (Fig. 2). The AUROC curve of the Lille model was also significantly higher than the AUROC curves of changes

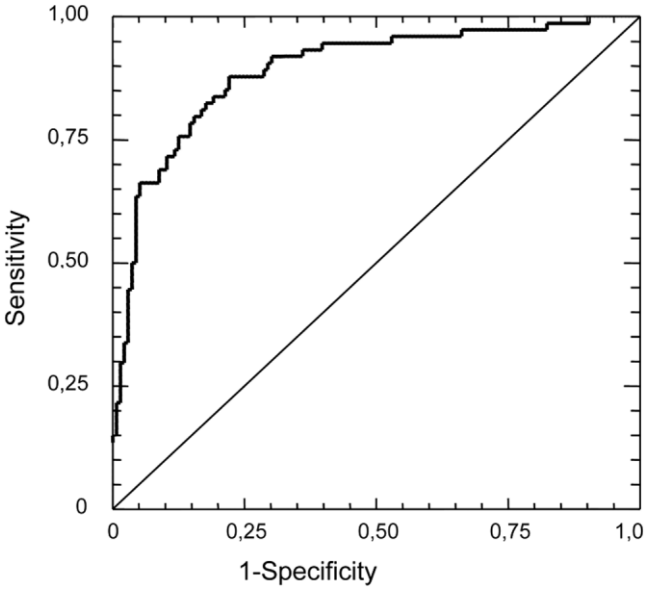

Fig. 1. Receiver operating characteristic curve for survival at 6 months in the exploratory cohort using the Lille model.

Table 4. Clinical and Biochemical Features of Patients Included in the Validating Cohort

Number of patients	118
Male sex, no. (%)	55 (48.3%)
Age (year), median (range)	53 (32.4-70.2)
Presence of ascites, no (%)	83 (72.8%)
Encephalopathy, no (%)	37 (32.5%)
Bilirubin (μmol/l), median (range)	261.7 (42.5-1102)
Prothrombin time (sec), median (range)	21.6 (15.2-51.5)
INR, median (range)	2.06 (1.28-6.35)
Albumin (g/l), median (range)	23.3 (13-44.2)
Serum urea (mmol/l), median (range)	3.8 (0.7-32.9)
Serum creatinine (mg/dl), median (range)	0.9 (0.4-5.5)
AST (IU/l), median (range)	118 (38-471)
White blood cells (no/mm^3), median (range)	9450 (3600-35200)
Evolution of bilirubin between day 0 and day 7 (μmol/l), median (range)	32.3 (394-543)
Child-Pugh score, median (range)	12 (8-15)
DF, median (range)	61.6 (33.1-176)
Glasgow alcoholic hepatitis score, median (range)	9 (6-12)
MELD, median (range)	23.6 (10.4-53.5)
Lille model, median (range)	0.46 (0.0008-0.998)

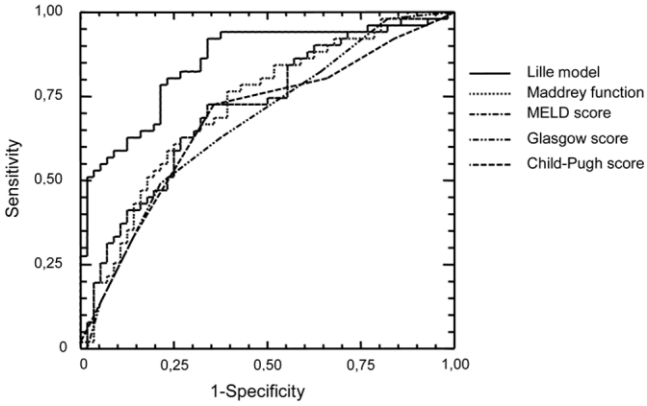

Fig. 2. Receiver operating characteristic curves for survival at 6 months in the validation cohort as determined by the Lille model versus the evolution of the Maddrey function ($P = 0.03$), the MELD score ($P = 0.01$), the Glasgow score ($P = 0.0008$) and the Child-Pugh score ($P = 0.003$).

between day 0 and day 7 of the DF score (0.72 ± 0.05, $P = 0.02$), MELD score (0.67 ± 0.07, $P = 0.0003$) and Glasgow score (0.61 ± 0.06, $P = 0.002$) (Fig. 3). The AUROC curves of the Maddrey, MELD, and Glasgow scores at day 0 were not significantly different from the AUROC of their change between day 0 and day 7 (data not shown).

New Management Based on the Lille Model

Because our main objective was to propose a new therapeutic strategy, we tested the cutoff of the Lille model with the highest prediction value in the validation cohort. The 0.45 cutoff fulfilled this ideal criterion with sensitivity and specificity at 81% and 76%, respectively, in the validation cohort and 76% and at 85% on overall patients. After 7 days of treatment, 62% of patients had a score less than 0.45 and 38% of patients had a score of 0.45 or greater. As expected, the group of patients with a score 0.45 or better were shown to have a higher median

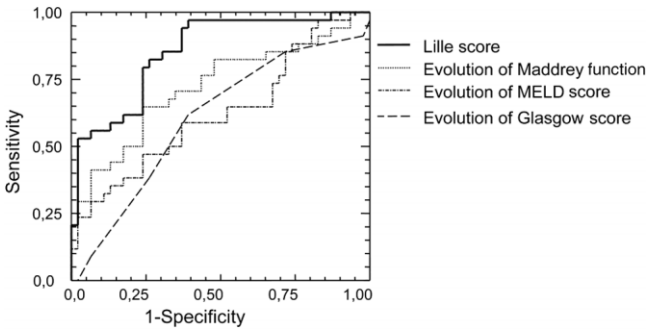

Fig. 3. Receiver operating characteristic curves for survival at 6 months in the validation cohort as determined by the Lille model versus the evaluation of the Maddrey function ($P = 0.02$), the MELD score ($P = 0.0003$) and the Glasgow score ($P = 0.002$).

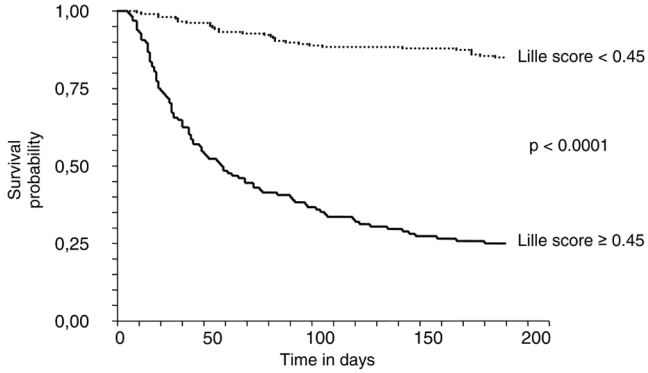

Fig. 4. Kaplan-Meier survival analysis according to 0.45 cutoff of the Lille model.

Lille score than the group with a score below 0.45: 0.75 (95% CI: 0.7-0.83; range: 0.451-0.999) versus 0.11 (95% CI: 0.1-0.16; range, 0.00008–0.44), $P < 0.0001$. Using this cutoff, patients with a Lille score ≥0.45 had a drastic decrease in 6-month survival as compared with patients with a Lille score <0.45: 25% ± 3.8% versus 85 ± 2.5%, $P < 0.0001$ (Fig. 4). In terms of diagnostic accuracy for prediction of death, the 0.45 Lille score cutoff was more efficient than our previous simple criterion referred to as ECBL[12] ($P = 0.001$) and the proposed cutoff of 9 for the Glasgow score[17] ($P < 0.01$). In terms of number of predicted deaths, the 0.45 cutoff of the Lille model was able to identify 75.6% of the observed deaths, whereas ECBL and the cutoff of 9 for the Glasgow score were able to identify 62.5% and 64.5%, respectively. The comparisons between Lille and Glasgow scores were performed only in the subgroup of patients in whom the Glasgow score was available (n = 167).

In placebo patients from the last three RCTs,[1,6,11,23] the AUROC curve of the Lille model was 0.76 ± 0.05, $P < 0.00001$ (in comparison with 0.5, because the AUC of a "useless" criterion is 0.5). In the placebo group, 6-month survival of patients with a Lille score of at least 0.45 was significantly lower than that of patients with a Lille score < 0.45: 25.7 ± 7.2% versus 63.9% ± 8.3%, $P = 0.0003$. The usefulness of the 0.45 cutoff was confirmed in randomized corticosteroid patients: 6-month survival of patients with a Lille score of at least 0.45 (27.8 ± 10%) was significantly lower than that of patients with a Lille score < 0.45 (84.6% ± 5.1%, $P < 0.00001$). The percentage of patients who may be considered as responders to the assigned treatment (with a Lille score < 0.45) was higher in the randomized corticosteroid group than in the randomized placebo group: 74.3% versus 53.8%, $P = 0.003$. Before initiation of treatment, the placebo and corticosteroid groups had similar DF: 45 (95% CI 42-48.3) versus 45.1 (95% CI: 41.4-47), NS.

Randomized corticosteroid patients with a Lille score <0.45 had a significantly higher 6-month survival than placebo patients with a Lille score <0.45: 84.6 ± 5.1% versus 63.8 ± 8.3%, $P = 0.005$. Twenty-eight-day survival (end of treatment period) was still significantly higher in corticosteroid patients: 97.3% ± 1.9% versus 81.6% ± 5.5%, $P = 0.003$. Before initiation of therapy, randomized placebo and corticosteroid patients with a Lille score <0.45 were similar in terms of AH severity as assessed by the Maddrey function: 43 (95% CI: 38.6-45.2) versus 41.4 (95% CI: 39.9-45.2), NS. Conversely, in patients with a Lille score ≥0.45, there was no significant survival difference at 6 months between the corticosteroid and placebo groups: 27.8 ± 10% versus 25.7 ± 7.2%, NS. The formula is available online at http://www.lillemodel. com.

Discussion

Our study demonstrates that the Lille model, a combination of six reproducible variables, has high sensitivity and specificity for early identification of patients at high risk of death at 6 months. Indeed, its accuracy with the AUROC curve is excellent, 0.89. Although its accuracy is significantly higher than that of Child, Maddrey, Glasgow, or MELD scores, the Lille model is not designed to compete with such models but rather to predict poor survival in subjects with AH treated with corticosteroids. Above the ideal cutoff of 0.45, the Lille model is able to predict 76% of the observed 6-month deaths. The absence of differences in survival among patients with a Lille score ≥0.45 who were treated with either corticosteroids or placebo suggests that continuing corticosteroids after 7 days may be futile. Thus, alternative treatments should be tested in these subjects.[15,20]

The current study was performed using a large sample size of over 650 patients carefully selected and prospectively treated or not for severe AH. To ensure the reproducibility of the model, subjective and fluctuating criteria likely to be affected by standard medical therapies, such as encephalopathy and ascites, were not considered. In the exploratory and validating cohorts, the Lille model was constantly and significantly more effective than other tested models when comparing AUROC curves.

At first glance, the Lille model might not necessarily appear to constitute a novel approach, because its formula does include some well-known variables. However, our objective was not to develop a completely innovative model but rather to improve the current management of severe AH using a model that includes the most informative and reproducible variables for early prediction of mortality.

The superiority of the Lille score when compared with all other prognostic models cannot be attributed simply to the incorporation of a dynamic variable, for at least three reasons: (1) the AUROC curve of the Lille score is higher than the AUROC curves of the dynamic evolution of Maddrey, MELD, and Glasgow scores between day 0 and day 7; (2) the evolution of Maddrey, MELD, and Glasgow scores did not add any advantage to their respective diagnostic accuracy at baseline; (3) the Lille model has better diagnostic accuracy than the previous dynamic criterion, ECBL. For centers using INR instead of prothrombin time in seconds, we provided a formula using INR instead of prothrombin time: $3.19 - 0.101 * (\text{age in years}) + 0.147 * (\text{albumin day 0 in g/L}) + 0.0165 * (\text{evolution in bilirubin level in } \mu\text{M}) - (0.206 * \text{renal insufficiency}) - 0.0065 * (\text{bilirubin day 0 in } \mu\text{M}) - 0.0096 * (\text{INR})$. We showed that the two formulas of the Lille model were similar, as indicated by comparison of AUCs: 0.85 ± 0.038 (Lille model with prothrombin time) versus 0.85 ± 0.037 (Lille model with INR), NS. Therefore, both formulas may be used.

The term "nonresponder to corticosteroids" is not restricted simply to patients without ECBL, but should now be extended to all patients with a Lille score above 0.45. Using the 0.45 Lille model cutoff, close to 40% of patients do not benefit from corticosteroids, a percentage higher than the 25% previously identified by ECBL.[12] Clinicians need to improve the management of poor responders to corticosteroids, that is, patients with a Lille score ≥0.45.

The current study highlights the benefits obtained from studies focusing on a strategy integrating the impact of treatment on the evaluated endpoint. As an example, in patients with hepatitis C, therapeutic strategy is now based on pretreatment variables (*e.g.,* genotype, viral load) and response to treatment, as assessed by a decline in viral load at week 12. Thus, the Lille model, developed using a similar approach that included both pretreatment and "on treatment" variables, is the first model to propose guidelines for adapting patient therapeutic strategy to alcoholic liver disease. Using this model, the percentage of patients considered to be responders to the assigned treatment was higher among those treated with corticosteroids than those given a placebo. This suggests that corticosteroid treatment produces 20% more responders, thereby reducing the risk of death in comparison with the absence of therapy.

Whereas 25% of patients with a Lille score ≥0.45 do not die at 6 months and thus cannot be considered "true" nonresponders, the persistence of severe liver insufficiency at 6 months in such "non-responders" is of utmost importance. Although data on the evolution of liver func-

tion at 6 months were available for only a small number of such patients, we observed that approximately half of them still had severe liver insufficiency, with a median Child score of 8.5 (range, 6-14) and a median MELD score of 21.5 (range, 12-31) (data not shown). This suggests that, among live non-responders with a Lille score $\geq$ 0.45, only half are no longer at risk of liver-induced death.

In conclusion, we have developed a model for predicting survival at 6 months in patients with AH being treated with prednisolone. This model uses five routine pretreatment variables and change in bilirubin level at day 7. It is significantly more accurate than DF, MELD, or Glasgow scores in predicting short-term mortality, and is better than ECBL at predicting subjects likely to die. The Lille model is able to identify 40% of subjects receiving prednisolone treatment who have a poor survival prognosis and who thus may be candidates for alternative treatments. The formula is available online at http://www.lillemodel.com.

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