A Day-4 Lille Model Predicts Response to Corticosteroids and Mortality in Severe Alcoholic Hepatitis

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- OBJECTIVES:** Prednisolone therapy increases the risk of infections in patients with severe alcoholic hepatitis (SAH). We evaluated whether the use of the Lille Model at day 4 (LM4) is useful to predict response to prednisolone compared with the classic day 7 (LM7) in order to limit a futile exposure to corticosteroids.
- METHODS:** We performed a retrospective analysis of a large multinational cohort of patients with SAH with Maddrey's discriminant function (DF) ≥ 32 . Response to corticosteroids was assessed with LM4 and LM7, according to the validated cutoff value (CUV > 0.45). Receiver operating characteristics (ROC) curves were constructed to determine the optimal CUV for LM4 and to compare accuracy between LM4, LM7, MELD (Model for End-Stage Liver Disease), and ABIC (age, bilirubin, international normalized ratio, and creatinine). Logistic regression models were constructed to predict 28- and 90-day mortality. Cox regression analysis was performed to assess long-term survival.
- RESULTS:** A total of 163 (62.7%) out of 260 patients received corticosteroids. The median DF for the patients treated with corticosteroids was 64.1 (47.9–81.3). Overall 90-day mortality was 35.9%. The median LM4 and LM7 for the patients who received treatment was 0.39 (0.19–0.83) and 0.36 (0.13–0.77). LM4 was a strong independent predictor of 28-day mortality (OR 25.4, (95% confidence interval (CI) 5.1–126.8), $P < 0.001$). By using LM4 with a CUV > 0.45 , 28- and 90-day survival was significantly higher for responders (90% and 76%) than non-responders (66% and 40%), $P < 0.001$. Importantly, the area under the ROC curve for predicting mortality for LM4 was similar than the classic LM7 (0.77 vs. 0.75, respectively; $P = 0.558$).
- CONCLUSIONS:** LM4 is as accurate as LM7 in predicting response to corticosteroids, as well as 28- and 90-day mortality. Assessing the efficacy of prednisolone at an earlier time point can avoid a more prolonged futile use of this therapy.

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INTRODUCTION

Severe alcoholic hepatitis (SAH) presents within a spectrum ranging from decompensated liver disease with jaundice to life-threatening liver failure associated with a significant morbidity

and early mortality that can attain 50–75% (1,2). It ranks among the most costly diseases during hospitalization (3). Thus the early detection of high-risk patients, prompt intervention, and accurate prognostic stratification is crucial.

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Various prognostic models have been developed with the goal of determining which patients are at high risk of death. Maddrey's discriminant function (DF) has been the standard surrogate for the assessment of disease severity and to guide treatment in AH. A cutoff value (CUV) ≥ 32 identifies subjects with an adverse prognosis, with a mortality of 20–30% during the first month after AH onset and up to 40% at 6 months (4). Other prognostic models that evaluate the severity of the disease at baseline, such as the MELD (Model for end-stage liver disease), ABIC (age, bilirubin, international normalized ratio, and creatinine), and Glasgow alcoholic hepatitis score (GAHS), are all useful tools to determine the patient's outcome (5–7). However, the time necessary to prognosticate a therapeutic strategy and response is crucial in order to avoid damage from intervening too early or too late and to guide therapy in patients at high risks of short-term mortality (8).

Prednisolone continues to be the mainstay of treatment for patients with SAH, being the only treatment demonstrating modest improvement in survival at 28 days (9). Early improvement in liver function with corticosteroid therapy is strongly associated with a marked decrease in short-term mortality. This improvement can be assessed by using the Lille Model (LM), which includes a measurement of response to treatment on day 7 of corticosteroid therapy (10). Almost 40% of patients with SAH are classified as non-responders to corticosteroids according to the originally validated $\text{CUV} > 0.45$, which is associated with a 6-month survival as low as 25% and dictates discontinuation of prednisolone owing to lack of therapeutic benefit (11). However, this means that LM assessment requires at least 7 days of high-dose corticosteroids, increasing length of stay and related health-care costs. Also, non-response to corticosteroids is highly predictive of sepsis, and it is tempting to hypothesize that prednisolone treatment further increases the risk of infection (2,12). This indicates the need for a prediction tool that identifies patients at high risk for complications or mortality at an earlier stage from the start of corticosteroids.

Early identification of response to corticosteroid treatment is utterly important, allowing prediction of a complicated SAH course and survival and avoiding unnecessary treatment that might further aggravate prognosis. Therefore, we aimed to evaluate LM performance at day 4 (LM4) in comparison with LM at day 7 (LM7) as an earlier predictor of response to corticosteroid therapy and its performance to predict survival in patients with SAH.

METHODS

The present study is a retrospective analysis of a multinational cohort of patients admitted with clinically SAH from January 2010 to May 2015 at the University of Arkansas for Medical Sciences (United States); Liver Unit, Hospital Clinic, Barcelona (Spain); and Hospital das Clinicas, Faculty of Medicine University of São Paulo (Brazil). The study protocol received prior approval from the corresponding Institutional Review Board. All consecutive patients aged > 18 years admitted with SAH based

on a (1) $\text{DF} \geq 32$ (2), recent onset of jaundice (< 12 weeks) (3), history of excessive alcohol consumption, and (4) suggestive liver chemistries were included. Data were obtained from the electronic medical records from each participating institution. Subjects without documentation of alcohol consumption of at least 40 g/day of alcohol prior to admission (13), patients with hepatocellular carcinoma, or other concomitant liver disorders were excluded.

Clinical and biological data

Demographic, clinical and biochemical data were recorded on admission: age, sex, alcohol intake (g/day), body mass index, white blood cell count, creatinine, aminotransferases (alanine aminotransferase and aspartate aminotransferase), bilirubin, albumin, prothrombin time, and international normalized ratio. Biochemical data corresponding to treatment days 4 and 7 in patients receiving corticosteroids were documented as well. Clinical complications present at admission or developing during hospitalization (hepatic encephalopathy, renal failure on admission, acute kidney injury [AKI] during hospitalization, bacterial infection or gastrointestinal bleeding [GIB] were recorded. Renal failure on admission was defined as a creatinine ≥ 1.5 mg/dl, as creatinine determination prior to hospitalization was not available in the majority of patients. Development of AKI during hospitalization was defined according to the recommendations of the International Club of Ascites, and we defined systemic inflammatory response syndrome (SIRS) according to the American College of Chest Physicians (14,15). We paid special attention to the treatment received during hospitalization and the final outcome at last follow-up visit available on electronic medical records.

Diagnosis of SAH was made in patients who fulfilled the following criteria (1): history of excessive alcohol consumption up until the onset of jaundice and prior to admission (2); liver chemistry suggestive of AH with a $\text{DF} \geq 32$. In 95 (58%) cases, histological confirmation was available, demonstrating hepatocellular damage (ballooning and Mallory bodies) and characteristic inflammatory infiltrate (16,17). Patients were treated in all centers as per current standards of care (18). In order to timely screen for possible subclinical infections, all centers routinely performed chest X-ray, urinalysis, urine culture, blood culture, and ascitic fluid cell count and culture (when clinically feasible) immediately after admission. Across, infection surveillance was performed on a case-by-case basis and driven by clinical manifestations. Treatment with corticosteroids was contraindicated in cases with uncontrolled infection, sepsis, or uncontrolled GIB. All patients receiving prednisolone were given 40 mg on a daily dose for up to 28 days, according to response assessed by LM7. LM was calculated for all patients by using the calculator at www.lillemodel.com. A patient with LM score > 0.45 at day 7 was considered a non-responder and prednisolone was discontinued on day 8. We calculated LM for all patients at day 4 with the same calculator, using day 4 bilirubin instead of day 7. Baseline severity scores (DF, MELD, ABIC, and GAHS) were calculated for all the patients by using the calculators provided at www.lillemodel.com.

Statistical analysis

The primary end point of our study was all-cause mortality at 90 days from hospital admission. Long-term survival was considered a secondary end point given the rate of patients expected to be lost during follow-up. Data were described as median (range) for continuous variables and number (%) for discrete variables. Mann–Whitney *U*-test was used to compare continuous variables, whereas χ^2 or Fisher was used to compare proportions, as appropriate. Correlation between LM4 and LM7 was assessed with Cohen's kappa coefficient. In patients treated with corticosteroids, baseline characteristics showing a *P* value <0.2 in 28- and 90-day mortality univariate analyses (or those with biological interest) were entered into backward stepwise multivariable logistic regression models in hierarchized manner to avoid over fitting. The utility of LM4 to predict 28-day and 90-day mortality was evaluated by calculating the area under the receiver operating characteristics curve (AUROC). A model with an AUROC ≥ 0.7 was considered clinically useful, showing at least good accuracy. Sensitivity, specificity, positive predictive values and negative predictive value of LM4 and LM7 at different CUV were calculated (including CUV from Youden method to maximize accuracy). The accuracy of LM4, LM7, MELD, ABIC, and GAHS to predict 28- and 90-day mortality was assessed by comparing AUROCs by the method of Hanley and McNeil. Survival estimations were performed using Kaplan–Meier curves and Cox proportional hazards models for both univariate and multivariable analyses. Patients lost to follow-up were censored at the time of their last visit. In all comparisons, a two-sided *P* < 0.05 was considered statistically significant. All analyses were performed using STATA version 12 (StataCorp, College Station, TX).

RESULTS

Patient characteristics

A total of 260 patients with a DF ≥ 32 on admission (43% with biopsy-proven AH) were included, out of which 163 (62.7%) were treated with corticosteroids, whereas the remaining 97 (37.3%) were deemed not optimal candidates for corticosteroid therapy and received pentoxifylline or supportive therapy (**Figure 1**). Among the patients who did not receive corticosteroids, 63% had uncontrolled sepsis on admission, 12.5% had active GIB, 2.5% presented multiorgan failure, and in 22.5% a clear cause could not be identified. The main baseline characteristics, severity scores, and in-hospital complications are shown in **Table 1**. The median age of the patients treated with corticosteroids was 48 (41–55) years, 67.5% were males, and median body mass index was 26.6 kg/m² (23.2–30.1). Apart from patients receiving corticosteroids being slightly older, reporting less alcohol abuse, and having higher total bilirubin levels, there were no statistical differences compared with those who did not. On admission, 45 (36.3%) subjects receiving prednisolone fulfilled criteria for SIRS, and GIB occurred in 34 (20.9%) during hospitalization, with no differences when compared with patients not treated with corticosteroids. Hepatic encephalopathy manifested in 66 (40%) during hospitalization, and it was more frequently seen among patients

receiving corticosteroids. Renal failure on admission was documented in 43 (26.4%) of the patients treated with corticosteroids, and AKI developed in 30/67 (44.8%) more as inpatients, with no differences between groups. Regarding severity scores at admission, only DF and ABIC were found to be higher in patients with corticosteroids, with no differences in MELD and GAHS when compared with patients without corticosteroids. LM4 and LM7 did not differ between patients treated or not with corticosteroids.

Predictors of 28- and 90-day mortality

The median follow-up for patients treated with corticosteroids was 119 days (25–474), and for patients without corticosteroids it was 60 days (11–416), *P* = 0.01. Overall 90-day mortality was 35.9% for patients receiving corticosteroids and 36.6% for those who did not (*P* = 0.916). Univariate predictors of 28- and 90-day mortality are summarized in **Table 2**. Among all demographic and clinical variables, only hepatic encephalopathy, GIB, and AKI predicted 28-day mortality. Older age, GIB, renal failure on admission and AKI were significantly associated with 90-day mortality. As for biochemical variables, elevated creatinine and international normalized ratio were significantly associated with both 28- and 90-day mortality; whereas elevated white blood cell count and bilirubin were significantly associated with 28- or 90-day mortality, respectively. Finally, all of the AH severity scores (including LM4) were associated with 28- and 90-day mortality in patients with SAH treated with corticosteroids.

In the multivariate model, LM4 remained an independent predictor of mortality at 28 days (odds ratio (OR) 25.4, (95% confidence interval (CI) 5.1–126.8)), *P* < 0.001 and 90 days (OR 16.9, (95% CI 4.5–64.3), *P* < 0.001). Among the remaining variables tested in the univariate analysis, only the presence of GIB (OR 4.7, (95% CI 1.8–13.3), *P* < 0.003) was an independent predictor of mortality at 28 days. GIB (OR 6.3, (95% CI 2.3–17.6), *P* < 0.001) and renal failure on admission (OR 2.5, (95% CI 1.0–6.3), *P* = 0.032) showed to be independent predictors of mortality at 90 days in multivariable analysis.

Performance of LM4 and LM7 in predicting 28- and 90-day mortality

We were able to evaluate LM4 in 153 (94%) and LM7 in 150 (92%) of the patients who received corticosteroids. There were 70 (45.8%) non-responders by LM4 and 68 (45.3%) by LM7. When classified as responders or non-responders according to LM4 and LM7 score >0.45, the 28-day mortality was 8% and 10% among the former and 34% and 32% among the latter, *P* < 0.001. At 90 days, mortality for responders according to LM4 and LM7 was 34% and 35% and for non-responders it was 60% and 58%, *P* < 0.001.

Overall, there was 91.1% of agreement between LM4 and LM7 to predict response (κ = 0.82, *P* < 0.001) in patients receiving prednisolone. The AUROCs for all severity scores as predictors of 28- and 90-day mortality are shown in **Table 3**. No significant differences were found in pairwise comparisons between AUROCs from different models, and particularly there were no differences between the AUROC from LM4 (0.77 (95% CI, 0.66–0.88)) as an earlier predictor of corticosteroid response and that of LM7 (0.74

Figure 1. Flow chart summarizing patient selection from the three participating centers. DF, discriminant function; PTX, pentoxifylline; SAH, severe alcoholic hepatitis.

(95% CI 0.63–0.85), $P=0.406$). Notably among 7 patients who were non-responder by day 4 and became responder by day 7, 71% died. On the other hand, of the 6 patients who were responders by day 4 but not by day 7, only 50% died. Operational characteristics of LM4 and LM7 to predict 28- and 90-day mortality are shown in **Table 4**. Apart from the original CUV of 0.45, we tested a more recently proposed CUV of 0.56 in both LM4 and LM7. Notably, Youden index identified 0.45 as the most accurate CUV, therefore, we kept the original 0.45 cutoff point for the remainder of analyses.

LM4 and LM7 and long-term survival

By using LM4, the 90 days and 1-year survival were significantly higher for responders (<0.45) compared with non-responders (76% and 63% vs. 40% and 32%, $P<0.001$), for patients receiving corticosteroids, **Figure 2a**. Also, LM7 showed significantly higher survival for responders at 90 days and 1-year (75 and 60% vs. 42 and 35%, $P<0.001$), **Figure 2b**.

On the multivariate Cox regression analysis, response by LM4 (<0.45) was associated with improved survival, with a hazard ratio (HR) 0.33 (95% CI; 0.19–0.56, $P<0.001$). GIB with an HR 4.3 (95% CI; 2.5–7.7, $P<0.001$) and renal failure on admission with an HR 1.9 (95% CI; 1.1–3.2, $P=0.19$) were the only covariables that independently predicted decreased long-term survival.

DISCUSSION

Research interest in AH has gained momentum over the past few years. As SAH has a high mortality in the short term, the rational use of existing therapies or identification of novel ones has become a priority. A recent randomized controlled trial by Thurz *et al.* (9) that included 1053 patients with SAH, prednisolone showed only a modest trend toward improved survival at 28 days. Its use might increase fungal and bacterial infections, increasing the mortality risk in subjects with already poor prognosis. In the case of corticosteroids, rules and scores to abide to the *primum non nocere* principle have taken great relevance. Among the available scores to identify and prognosticate SAH, only the LM proposed by Louvet *et al.* (10) takes into account the impact of treatment upon patient survival, allowing a timely termination of corticosteroids with the aim of preventing further complications that could negatively affect survival (10,19). However, calculation of the LM requires availability of biochemical data at day 7 of prednisolone therapy. Our study demonstrates that using LM4 is as accurate as the widespread LM that is currently applied on day 7 (LM7), with an agreement of 91%, and it has the potential of increasing safety through earlier termination of corticosteroids. Moreover, as shown in our AUROC analysis, LM4 can predict 28- and 90-day mortality in SAH patients receiving corticosteroids as accurately as LM7 and any of the other existing prognostic scores (i.e., Maddrey's DF, MELD, ABIC, and GAHS). Although re-calculation

Table 1. Demographic and baseline characteristics

Variables	Total cohort, <i>n</i> =260	Corticosteroids, <i>n</i> =163	Without corticosteroids, <i>n</i> =97	<i>P</i> value
Age (years) ^a	47 (40–55)	48 (41–55)	45 (35–51.5)	0.03
Gender, male ^b	184 (70.7)	110 (68)	74 (76.3)	0.131
BMI (kg/m ²) ^a	26.7 (24–30.1)	26.6 (23.2–30.1)	27.3 (25–30.1)	0.39
EtOH consumption (g/day) ^a	120 (100–180)	100 (90–165.7)	150 (100–308)	0.024
SIRS ^b	90 (41.1)	45 (36.3)	45 (47.4)	0.099
Follow-up days ^a	95 (19–435)	119 (25–474)	60 (11–416)	0.106
90-Day mortality ^a	90 (36.1)	56 (35.9)	34 (36.6)	0.916
Biochemical features^a				
WBC (K/μl)	9.88 (6.42–14.67)	9.76 (6.7–14.5)	10.0 (5.9–14.98)	0.917
Platelets (K/μl)	110 (77–177)	107 (77–163)	128 (77.5–189)	0.218
PT (s)	20.6 (17.6–24.7)	21.2 (18.8–26)	20.4 (17–24.1)	0.123
INR	1.76 (1.5–2.19)	1.78 (1.56–2.16)	1.7 (1.4–2.2)	0.131
Creatinine (mg/dl)	0.92 (0.7–1.79)	0.9 (0.69–1.6)	1.0 (0.7–1.98)	0.126
Bilirubin (mg/dl)	15.1 (7.7–25.7)	19.5 (9.9–27.1)	11.2 (5.6–21.3)	0.002
AST (IU/l)	152 (103–222)	146 (105–207)	172 (97.5–248)	0.207
ALT (IU/l)	49.5 (34–77)	51 (35–75)	48 (30–79)	0.839
Albumin (g/dl)	2.5 (2.1–3.0)	2.5 (2.2–3.0)	2.6 (2.0–3.0)	0.678
Complications^b				
Hepatic encephalopathy	124 (47.5)	66 (40.5)	58 (59.8)	0.003
Gastrointestinal bleeding	62 (23.9)	34 (20.9)	28 (28.9)	0.143
Severity scores^a				
Maddrey's DF	54.4 (42.7–78.7)	64.1 (47.9–81.3)	55 (35.4–74.9)	0.011
MELD	22.9 (18.6–29.4)	22.7 (18.8–29.3)	23.5 (18–30.3)	0.885
ABIC	7.92 (6.9–9.08)	8.02 (7.1–9.12)	7.43 (6.42–8.96)	0.016
GAHS	9 (8–10)	9 (8–10)	9 (8–10)	0.203
Lille Model 4	0.41 (0.19–0.85)	0.39 (0.19–0.83)	0.69 (0.17–0.91)	0.318
Lille Model 7	0.37 (0.12–0.77)	0.36 (0.13–0.77)	0.44 (0.11–0.87)	0.98

ABIC, age, bilirubin, international normalized ratio and creatinine; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; DF, discriminant function; EtOH, alcohol; GAHS, Glasgow alcoholic hepatitis score; INR, international normalized ratio; MELD, model for end-stage liver disease; PT, prothrombin time; SIRS, Systemic inflammatory response syndrome; WBC, white blood cell count.

^aData are presented as median and interquartile range 25–75.

^bData are presented as *n* (%).

of MELD and Maddrey's DF at day 7 were reported to have good predictive accuracies (AUROCs>0.80) (20), their dynamic evolution (Δ MELD and Δ DF) has been reported to have less prognostic power in comparison to LM7 and have not been validated as tools permitting early stopping of corticosteroids (10). Therefore, earlier application of LM would spare 3 days of corticosteroids to patients with an LM4>0.45, potentially increasing safety and decreasing health-care costs and allowing considering these subjects for alternative treatments, where available.

It has been proposed that the use of a single cutoff point in LM might be too restrictive and will not allow identification of subjects

with an intermediate risk of death. In a meta-analysis by Mathurin *et al.* (11), patients were classified according to the percentile distribution of their Lille score to avoid an arbitrary cutoff, identifying three patterns of response (complete, intermediate, and null) with significant differences in the risk of death. Results suggested that corticosteroids could positively impact survival in patients with complete (LM≤0.16) and intermediate response (LM>0.16–<0.56), although novel therapies might bring further benefit to the latter group. In contrast, null responders (LM≥0.56) have no benefit from corticosteroids and may be considered for liver transplantation in highly selected cases, depending on age,

Table 2. Univariate analysis on predictors of 28- and 90-day mortality in patients treated with corticosteroids

Variable	28-Day status		P value	90-Day status		P value
	Alive	Death		Alive	Death	
Age (years) ^a	47 (39–53)	50 (46–56)	0.07	46 (39–52)	49 (42–56)	0.031
Gender, male ^b	84 (70)	20 (67)	0.72	70 (65.4)	37 (34.6)	0.612
BMI (kg/m ²) ^a	26 (23.2–30.1)	27.3 (25–29.4)	0.34	26.1 (23.2–30)	27.5 (24.9–32.3)	0.144
SIRS ^b	36 (36)	7 (46)	0.44	13 (30.9)	29 (69)	0.325
Hepatic encephalopathy ^b	38 (32)	18 (60)	0.004	27 (44.3)	34 (55.7)	0.081
Gastrointestinal bleeding ^b	18 (15)	12 (40)	0.002	11 (33.3)	22 (66.7)	<0.001
Renal failure ^b	20 (17)	18 (60)	<0.001	15 (15)	23 (41.1)	<0.001
AKI ^b	20 (39)	7 (70)	0.07	13 (43.3)	17 (56.7)	0.030
Biochemical features^a						
WBC (K/μl)	9.4 (6.3–13.9)	13.0 (8.4–17.9)	0.003	9.2 (6.1–14.0)	11.0 (7.7–15.4)	0.215
Platelets (K/μl)	111 (77–183)	124 (82–192)	0.263	109 (77–175)	112 (78–182)	0.803
INR	1.7 (1.5–2.0)	2.0 (1.6–2.5)	0.004	1.7 (1.5–1.9)	1.9 (1.6–2.5)	0.002
Creatinine (mg/dl)	0.9 (0.7–1.3)	1.8 (0.9–3.7)	<0.001	0.8 (0.6–1.2)	1.4 (0.8–3.0)	0.003
Bilirubin (mg/dl)	13.9 (7.3–21.8)	22.5 (10.0–30.1)	0.08	12.7 (6.0–19.7)	22.5 (10.0–30.0)	0.045
AST (IU/l)	153 (107–208)	147 (99–234)	0.155	160 (110–216)	145 (96–241)	0.058
ALT (IU/l)	48 (34–69)	60 (38–92)	0.140	48 (32–70)	55 (36–83)	0.635
Albumin (g/dl)	2.6 (2.2–3.0)	2.5 (2.0–2.8)	0.736	2.6 (2.3–3.0)	2.3 (2.0–2.8)	0.082
Severity scores^a						
Maddrey's DF	53 (39–68)	75 (58–98)	0.002	52.8 (37.6–67)	77 (55.4–108)	<0.001
MELD	22 (18–25)	33 (25–40)	<0.001	21.6 (17.5–24.7)	29.2 (21–37)	<0.001
ABIC	7.6 (6.7–8.5)	9.6 (8.2–10.9)	<0.001	7.36 (6.56–8.37)	8.74 (7.81–10–1)	<0.001
GAHS	8 (8–10)	10 (8–11)	0.01	8 (7–10)	10 (9–10)	0.003
Lille Model 4	0.36 (0.15–0.72)	0.89 (0.52–0.96)	<0.001	0.28 (0.13–0.65)	0.80 (0.39–0.95)	<0.001
Lille Model 7	0.30 (0.09–0.62)	0.89 (0.37–0.98)	<0.001	0.21 (0.08–0.59)	0.75 (0.35–0.97)	<0.001

ABIC, age, bilirubin, international normalized ratio and creatinine; AKI, acute kidney injury; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; DF, discriminant function; GAHS, Glasgow alcoholic hepatitis score; INR, international normalized ratio; MELD, model for end-stage liver disease; SIRS, Systemic inflammatory response syndrome; WBC, white blood cell count.

^aData are presented as median and interquartile range 25–75.

^bData are presented as *n* (%).

comorbidities, and addiction/social profile (21–23). However, liver transplantation for patients with SAH is still controversial and, consequently, still far from gaining universal acceptance. In our study using the CUV>0.56 to define response showed an inferior agreement at 84% ($\kappa=0.68$, $P<0.001$) between LM4 and LM7. Such increase in the CUV did not translate into improved performance when compared with the standard 0.45 CUV, and it actually coincided with the CUV statistically obtained to maximize sensitivity and specificity. Thus our results support the use of 0.45 as the only CUV when applying LM4; however, it is not sensitive enough to identify subjects with SAH who will be in need for liver transplantation.

Patients with SAH developing infections have a higher mortality, and this has also been proven to be true among those treated with corticosteroids (12). Louvet *et al.* (2) demonstrated that the probability of infection was lower in responders (LM<0.45) than in no responders (LM>0.45): 11% vs. 43%, with a median time for infection development of 14 days. This suggests that earlier discontinuation of corticosteroids might contribute to improved outcomes in non-responders by limiting immunosuppression exposure. Although infections during index hospitalization and the presence of SIRS on admission were significant predictors of 90-day mortality in our univariate analysis, they were not independent risk factors in the

Table 3. Accuracy of severity scores to predict 28- and 90-day mortality

Variable	28-Day mortality			90-Day mortality		
	AUROC	95% CI	P value ^a	AUROC	95% CI	P value ^a
Lille Model 4	0.77	0.66–0.88	0.406	0.77	0.69–0.84	0.706
Lille Model 7	0.74	0.63–0.85		0.75	0.67–0.84	
Maddrey's DF	0.80	0.64–0.96	0.649	0.79	0.66–0.92	0.769
ABIC	0.80	0.72–0.89	0.307	0.73	0.67–0.80	0.51
MELD	0.76	0.65–0.88	0.863	0.67	0.57–0.77	0.106
GAHS	0.75	0.58–0.92	0.232	0.72	0.61–0.81	0.227

ABIC, age, bilirubin, international normalized ratio and creatinine; AUROC, area under receiver operational curve; CI, confidence interval; DF, discriminant function; GAHS, Glasgow alcoholic hepatitis score; MELD, model for end-stage liver disease.
^aRepresents comparison of LM4 with the other severity scores.

Table 4. Operational characteristics of Lille Model at days 4 and 7

Variable	Time	CUV	Sensitivity	Specificity	PPV	NPV
Lille Model 4	28 days	>0.45	79%	63%	34%	92%
		>0.56	71%	67%	33%	90%
Lille Model 7		>0.45	71%	62%	32%	90%
		>0.56	64%	68%	33%	88%
Lille Model 4	90 days	>0.45	70%	69%	56%	80%
		>0.56	60%	60%	72%	76%
Lille Model 7		>0.45	65%	68%	53%	78%
		>0.56	55%	29%	53%	74%

CUV, cutoff value; NPV, negative predictive value; PPV, positive predictive value.

multivariable analysis. Louvet *et al.* (2) had similar findings when prospectively evaluating 254 subjects with SAH, where at first glance, infection was considered a major factor contributing to death, but it ended up not being an independent prognostic factor, as early response to therapy was more important for predicting both survival and infection. As part of the standard of care in all patients with SAH, we routinely obtain blood and urine (±ascitic fluid) cultures, provide prophylactic antibiotics during bleeding, and have a low threshold to start antibiotics when early clinical signs of infection are noted (i.e., pathological urinalysis). Variations in the infections surveillance protocol during and after index admission among centers, as well as the lack of SIRS data during hospitalization, in our sample might explain discordant results.

European Association for the Study of Liver and American Association for the Study of Liver Disease guidelines specify that patients with SAH and recent episode of upper GIB or renal failure are not ideal candidates for prednisolone treatment (24,25). The reason for excluding patients with recent GIB is based on clinical trials performed in 1970s and 1980s where they were

initially excluded owing to higher rate of complications (renal failure and infections) and mortality. However, this was mainly based on the lack of effective therapies for GIB. Much has changed since the initial trials, now we have effective treatment for most cases of upper GIB, including endoscopic band ligation or transjugular intrahepatic porto-systemic shunt (26,27). However, the characteristics and outcomes of patients with GIB and SAH have not been well described. Rudler *et al.* (12) conducted a retrospective analysis of 105 patients of which 47 were admitted with SAH and GIB and compared with 58 with SAH without GIB. Survival was not significantly different (73.9% and 69.9%), and interestingly, subjects with GIB were less prone to develop infections. Development of infection after starting corticosteroids, LM>0.45, and high MELD score were independent risk factors of poor survival (12). The diagnosis of SAH might have been overestimated in that study as DF is not a diagnostic tool and liver biopsy findings are not specific. In our study, GIB was an independent risk factor for 28- and 90-day mortality and long-term survival together with response by day 4 as assessed by LM4. We did not differentiate between GIB present on

Figure 2. Kaplan-Meier survival analysis according to cutoff of the Lille Model, (a) LM4, Lille Model at day 4, (b) Lille Model at day 7.

admission or during hospitalization. These might suggest that the presence of GIB on admission as long as patients receive adequate treatment should not be contraindication for steroid therapy, and measures should be taken to prevent the development of GIB during hospitalization.

Presence of SIRS on admission has been shown in previous reports to be a major predictor of multiorgan failure and death in AH (28). Infections during hospitalization, especially after starting treatment with corticosteroids, but not on admission, are associated with higher mortality (2,28). Development of nosocomial infections is also associated with AKI and reduced survival; hence, the earlier application of LM will allow less exposure to corticosteroids in already high-risk population. Renal failure and

development of AKI has been linked to infections and to reduced survival in SAH (29). In our study, SIRS and infections were not associated directly with 90-day mortality. This might be in relation to the retrospective nature of the design. However, we demonstrated that the presence of renal failure on admission was an independent risk factor associated with increased 90-day mortality. In the present study, AKI was also a predictor of short-term mortality; however, it was not independently associated in the multivariable analysis owing to the small number of subjects with available information.

The present study has some limitations, including its retrospective nature. Only 95 (58%) of the patients treated with corticosteroids had a confirmatory liver biopsy. However, our study

represents a multinational cohort reflecting the experience of three referral centers. Given the few patients who responded between day 4 and 7, we were not able to prove that patients with an earlier response show further improvement in their prognosis. Our results need to be further investigated and validated prospectively.

Discovering an accurate biomarker capable of identifying high-risk patients who will fail to respond to corticosteroids is of utter importance. In the absence of such a biomarker, optimizing the use of current available predictive models is a priority in SAH. Our results showed that LM4 is as good as LM7 to determine response to corticosteroids and for prediction of 28- and 90-day mortality in patients with SAH. The use of LM4 instead of LM7 has various benefits: it would decrease exposure to corticosteroids, and spare up to 3 days of hospitalization in clinically stable patients. These benefits should translate into a decreased risk for infections, particularly nosocomial infections, and indirectly improve outcomes in this population. Without a doubt, this strategy would save costs to health-care systems worldwide. However, prospective studies systematically studying the frequency and type of infections in patients with early dismissal from hospital after LM4 are needed, in parallel with a cost-effectiveness analysis.

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CONFLICT OF INTEREST

Guarantor of the article: Mauricio Garcia-Saenz-de-Sicilia, MD.

Specific author contributions: Mauricio Garcia-Saenz-de-Sicilia: conception and design of the study, analysis and interpretation of the data, drafting, critical review, and final approval of the manuscript; Chitharanjan Duvoor: data collection and assembly and contributed with critical reviews to the manuscript; Jose Altamirano: data collection and assembly, interpretation of the data, contributed with drafting and critical review of the manuscript, and final approval; Veronica Prado, Roberta Chavez-Araujo, Ana de L. Candolo-Martinelli, Patricia Holanda-Almeida, Bernardo Becerra-Martins-de-Oliveira, and Simony Fernandez-de-Almeida: data collection and assembly of the data. Juan Caballeria and Ramon Bataller: interpretation of the data, drafting and critical review of the manuscript for final approval; Andres Duarte-Rojo: conception and design of the study, analysis and interpretation of the data, and drafting and critical review of the manuscript for final approval.

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Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ Severe alcoholic hepatitis is associated with significant morbidity and early mortality that can attain 50–75%.
- ✓ Early improvement in liver function with corticosteroid therapy is associated with a decrease in short-term mortality.
- ✓ Response to corticosteroid therapy is determined by Lille Model on day 7.
- ✓ Up to 40% of patients with alcoholic hepatitis are non-responders, increasing risk of infections with a 6-month survival as low as 25%.

WHAT IS NEW HERE

- ✓ Lille Model on day 4 is as good as Lille Model on day 7 to predict response to corticosteroids in patients with severe alcoholic hepatitis.
- ✓ Lille Model on day 4 is an independent predictor of 28- and 90-day mortality.
- ✓ Calculation of Lille Model on day 4 will allow decreased exposure to corticosteroids in non-responders.
- ✓ This novel strategy might decrease risk of nosocomial infections and health-care costs in severe alcoholic hepatitis.

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