# Lille Score Predicts Outcome in an ELAD Clinical Study of Severe Alcoholic Hepatitis

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## BACKGROUND

Alcoholic Hepatitis (AH) is an inflammatory disease, characterized by cell injury, oxidative stress, cell death and impaired regeneration. In patients with sAH, 6-month survival probability with a Lille score above 0.45 is approximately 25%[1].

## STUDY OBJECTIVE

We aimed to determine whether the Lille score predicted outcome in a prospective randomized controlled trial of an extracorporeal human allogeneic cellular liver system (ELAD) in treating severe Alcoholic Hepatitis (sAH) subjects..

## MATERIALS & METHODS

A randomized, open-label, multicenter, controlled study was conducted in subjects ≥18yrs old with a clinical or histologic diagnosis of sAH, bilirubin ≥8mg/dL, Maddrey discriminant function (DF) score ≥32, MELD score of 18-35 and platelet counts ≥40,000/mm$^3$, without severe concomitant disease, uncontrolled sepsis or bleeding, hemodynamic instability or need for chronic dialysis. Subjects were randomized to either protocol-specified standard of care (SOC, Control group) or SOC plus 3-5 days continuous treatment with an investigational extracorporeal human allogeneic cellular liver system (ELAD) consisting of human C3A hepatoblastoma cells contained in four cartridges (ELAD group). SOC was based on AASLD and EASL guidelines. Baseline biochemistry and 7-day change in serum bilirubin were used to calculate and compare Lille score between ELAD and Control groups.

## RESULTS

203 sAH subjects were randomized (ELAD 96, Control 107). Using an intent-to-treat (ITT) analysis, the overall and 3-month survival rates were similar in the ELAD and Control groups. Excluding 12 subjects who died within 7 days after randomization or had missing bilirubin data, 116/191 (61%) subjects were Lille responders

## RESULTS (cont.)

(LR: Lille score<0.45) and 75/191 (39%) subjects were non-Lille responders (non-LR: Lille ≥0.45). 91-d survival rate was significantly higher for the LR (88/116, 76%) compared to the non-LR (29/75, 39%; p<0.0001) (Figure 1 and Table 1). Steroid use at randomization and during the first 7 days in LR and non-LR was similar (34% vs 31%, p= N.S.).

Figure 1. 91-d Survival vs Lille Response

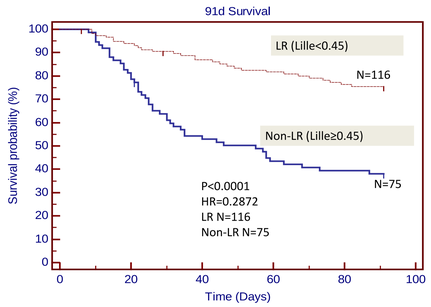



Table 1. 91-d Survival vs Lille Response

| N=203 | # Subjects excluded * | Total | Alive | Dead | % Alive | p-value |
|---|---|---|---|---|---|---|
| LR (Lille<0.45) | 12 | 116 | 88 | 28 | 88/116 (76%) | <0.0001 |
| Non-LR (Lille≥0.45) | | 75 | 29 | 46 | 29/75 (39%) | |

*Number of subjects excluded from analysis due to death within 7 days or missing bilirubin data

There were significantly more LR in the ELAD group (75% vs 47%, p<0.01). LR had better survival compared to non-LR in both the ELAD group (74% vs 22%, p<0.01) and the Control group (79% vs 46%, p<0.01). LR survival rate was the same for ELAD and Control (74% vs 79%, p=0.55). Non-LR survival was significant lower for the ELAD group than the Control group (22% vs 46%, p<0.05) (Table 2, Figure 3). In a subgroup analysis (N=138) that excluded patients with creatinine ≥1.5mg/dL and/or INR >2.5, the survival rate of LR was superior to non-LR in both treatment groups (ELAD 82% vs 36%, p<0.01; Control 78% vs 44%, p<0.01). However, non-LR survival was the same for ELAD and Control (44% vs 36%, p= N.S.) (Table2, Figure 3).

Table 2. 91-d Survival vs Lille Response by treatment group (ITT Population and Subgroup)

| Treatment group | # Subjects excluded from analysis due to death within 7 days or missing bilirubin data | Total number of responders (Lille<0.45) | % Alive of responders (Lille<0.45) | % Alive of non-responders (Lille ≥0.45) | p-value (responders vs non-responders) |
|---|---|---|---|---|---|
| **Total ITT population (N=203)** | | | | | |
| Control | 9 | 47/99 (47%) | 37/47 (79%) | 24/52 (46%) | <0.01 |
| ELAD | 3 | 69/92 (75%) | 51/69 (74%) | 5/23 (22%) | <0.01 |
| p-value (ELAD vs Control) | | <0.01 | 0.55 | <0.05 | |
| **Subgroup excluding subjects with creatinine ≥1.5mg/dL and/or INR >2.5 (N=138)** | | | | | |
| Control | 2 | 32/71 (45%) | 25/32 (78%) | 17/39 (44%) | <0.01 |
| ELAD | 1 | 50/64 (78%) | 41/50 (82%) | 5/14 (36%) | <0.01 |
| p-value (ELAD vs Control) | | <0.01 | 0.67 | 0.61 | |

## RESULTS (cont.)

Figure 2. 91-d Survival vs Lille Response by Treatment Group (ITT Population)

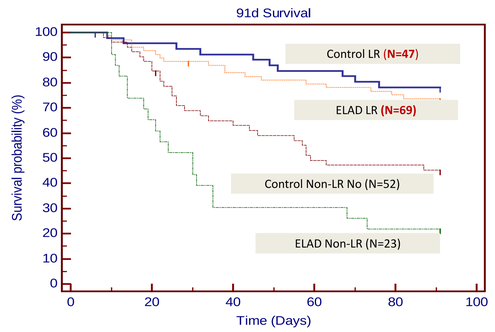
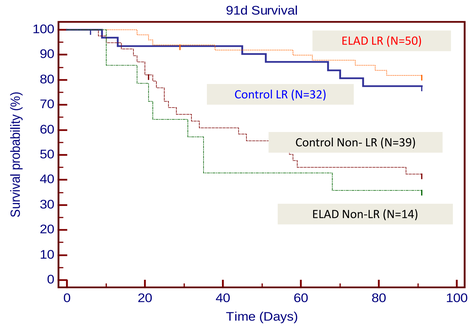



Figure 3. 91-d Survival vs Lille Response by Treatment Group (Creatinine <1.5 mg/dL) and INR ≤2.5)




## CONCLUSIONS

ELAD-treated sAH subjects were significantly more likely to be LR than Control subjects. LR had a significantly higher 91-day survival when compared to non-LR. Steroid use did not affect survival. LR appeared to accurately predict outcome independent of steroid use in both ELAD and Control subjects. Renal failure and coagulopathy portended poor outcome.

## REFERENCES

[1]Louvet, Alexandre, et al. "The Lille model: a new tool for therapeutic strategy in patients with severe alcoholic hepatitis treated with steroids." *Hepatology* 45.6 (2007): 1348-1354.

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