Hepatic encephalopathy and MELD-Na predict treatment benefit in autoimmune hepatitis-related decompensated cirrhosis

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Financial support: MCL received support from the *Instituto de Salud Carlos III (ISCIII) through the project "*PI21/00800*" and co-funded by the European Union.* PA was supported by the Hellenic Association for the Study of the Liver (HASL) and Mobility Research Fellowship of the European Network of Rare Diseases. IO was funded by the Contractes Clínic de Recerca “Emili Letang - Josep Font” 2022 granted by the Hospital Clínic Barcelona. BE was supported by the PRACTIS Clinician Scientist Program of Hannover Medical School, funded by the German Research Foundation (DFG, ME 3696/3).

Abbreviations: AIH, autoimmune hepatitis; ALBI, albumin-bilirubin score; ALT, alanine aminotransferase; ALP, alkaline phosphatase; ANA, antinuclear antibodies; anti-LKM-1, antibodies against liver/kidney microsomal type 1; anti-SLA/LP, soluble liver antigens/liver pancreas; AST, aspartate aminotransferase; AUC, are under the curve; AZA, azathioprine; CBR, complete biochemical response; CI, confidence interval; CIF: cumulative incidence function; CP, Child–Pugh score; GGT, gamma glutamyl transferase; HR, hazard ratio; INR, international normalized ratio; LT, liver transplantation; MELD, model for end-stage liver disease; mHAI, modified hepatic activity index; MMF, mycophenolate mofetil; Na, sodium; OHE, overt hepatic encephalopathy; OR, odds ratio; PRED, prednisone; SMA, smooth muscle antibodies; ROC, receiver operating curve.

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Disclosures: AL reports receiving consulting fees from Advanz Pharma, AlfaSigma, Takeda, Ipsen, and GSK and speaker fees from Gilead, GSK, AbbVie, MSD, Advanz Pharma, AlfaSigma, GSK, and Incyte. MCL has received consulting fees from Advanz Pharma, GSK, Ipsen, and Falk and speaker fees from Advanz Pharma, Ipsen, Gilead, and Cyma Bay.

Authors contributions: Maria-Carlota Londoño and Pinelopi Arvaniti: concept and design of the study, collection and statistical analysis of the data, interpretation of the results, and conclusions of the study. Sergio Rodríguez-Tajes, Marlene Padilla, Ignasi Olivas, Ezequiel Mauro, Cautar el Maimouni, Ellina Lytvyak, Xavier Verhelst, Bastian Engel, Sara Lorente-Pérez, Isabel Conde, Mar Riveiro-Barciela, Juan-Carlos Ruiz-

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Data transparency statement: Data will be made available to other researchers upon reasonable request and can be obtained through the principal investigator.

Abstract

Background & Aims: Management of patients with autoimmune hepatitis (AIH)-related decompensated cirrhosis is challenging because of the risk of treatment-related complications and lack of clinical recommendations. We investigated the predictive factors for treatment benefit in AIH-related decompensated cirrhosis at diagnosis and developed an algorithm to guide treatment decisions in clinical practice.

Methods: This retrospective, international, multicenter study included 232 patients with histologically confirmed AIH-related decompensated cirrhosis at diagnosis. The sub-hazard ratio (SHR) of mortality was determined by competing risk analysis, considering liver transplantation as competing event. A decision tree analysis was used to develop a treatment algorithm.

Results: At diagnosis, 89% of patients had ascites and 41% had overt hepatic encephalopathy (OHE). Treated patients (n=214, 92%) had higher aminotransferases, bilirubin and modified hepatic activity index. The SHR of mortality was significantly lower in treated patients (0.438, 95%CI 0.196-0.981, p=0.045). Patients without OHE grade 3/4 and MELD-Na score ≤ 28 at diagnosis were more likely to benefit from treatment. In these patients, a decline in MELD-Na ≥ 11 after 4 weeks of treatment had a 100% negative predictive value for death/LT. Forty-nine percent of treated patients recompensated during follow-up. Twenty percent of patients had to discontinue treatment, 65% during the first 4 weeks, and only 4% due to infectious complications. OHE ≥ grade 2 and MELD-Na at diagnosis predicted the need for treatment discontinuation.

Conclusions: Immunosuppression is beneficial in patients with AIH-related decompensated cirrhosis and active disease. OHE and MELD-Na at diagnosis, along with a decline in MELD-Na at 4 weeks of treatment, are the most important determinants of outcome and can guide treatment decisions.

Keywords: autoimmune hepatitis; decompensated cirrhosis; liver transplant-free survival; recompensation

Introduction

Autoimmune hepatitis (AIH) is a chronic liver disease characterized by an increase in aminotransferase and immunoglobulin G (IgG) levels, circulating autoantibodies, interface hepatitis on liver histology and a favorable response to immunosuppression. However, more than two-thirds of the patients have an insidious presentation with non-specific symptoms, leading to a significant delay in disease diagnosis. Consequently, approximately 30% of patients have cirrhosis at the time of AIH diagnosis.[1,2]

Clinical practice guidelines strongly recommend the immediate initiation of immunosuppression in all patients with active disease (modified hepatitis activity index [mHAI] ≥ 4 in liver biopsy) and/or compensated cirrhosis.[3,4] However, in cases of decompensated cirrhosis, treatment is probably not indicated unless severe inflammation is detected in the liver biopsy. Very few studies have addressed the safety and efficacy of immunosuppressive treatment in patients with decompensated disease at the time of AIH initial diagnosis.[5,6] These studies consisted of small and heterogeneous cohorts in which the presence of advanced fibrosis or cirrhosis was not always histologically confirmed, and various definitions for decompensation were applied. As a consequence, there is no clear information regarding the effectiveness and safety of immunosuppression in patients with AIH and decompensated disease at initial presentation, and its benefits in terms of liver transplant (LT)-free survival and recompensation[3,4].

Therefore, we conducted an international multicenter retrospective study aimed at 1) identifying patients with AIH-related decompensated cirrhosis at diagnosis who benefit from immunosuppressive treatment, 2) developing a decision-making tool to avoid unnecessary immunosuppression, 3) detecting the factors associated with treatment-related adverse events and need for treatment discontinuation, 4) assessing treatment response and recompensation during follow-up and 5) evaluating post-LT survival and complications.

Materials and Methods

Study design

This was an international multicenter retrospective study performed in 34 liver units across Europe, Asia, North, and South America, on behalf of the European Reference Network on Hepatological Diseases (ENR RARE-LIVER), the International

Autoimmune Hepatitis Group (IAIHG), and the Spanish Registry for Autoimmune and Cholestatic Diseases (ColHai). All patients over 16 years of age followed by each of the participating centers from January 1994 to June 2023 were evaluated for inclusion in the study. The number of patients included from each participating center is shown in Supplementary Figure 1.

The inclusion criteria were: 1) definite diagnosis of AIH based on the criteria set by the IAIHG (simplified score ≥7)[7,8]; 2) liver biopsy at the time of diagnosis (percutaneous, endoscopic, or transjugular) confirming the presence of advanced fibrosis or cirrhosis (mHAI staging ≥ 5)[9,10]; and 3) at least one decompensating event at the initial diagnosis of AIH (ascites, overt hepatic encephalopathy [OHE], and/or variceal bleeding). Patients with AIH variants, other concomitant liver diseases, and/or previous immunosuppressive treatment were excluded. Patients with acute-on-chronic liver failure (ACLF) with precipitants other than an AIH flare or ACLF > 3a were also excluded[11].

Data collection

Clinical, histological, laboratory, and serological data were evaluated at diagnosis; at 3 days, 7 days, 4 weeks, 6 months, and 12 months after treatment initiation (or diagnosis in case of non-treated patients); and at the last follow-up (LFUP). The Child-Pugh (CP), Model for End-stage Liver Disease (MELD/MELD-Na) and Albumin-Bilirubin (ALBI) scores were calculated based on individual variables. Treatment initiation was decided by each participating center after careful evaluation of patient's characteristics. All treated patients initially received predniso(lo)ne (PRED) followed (or not) by a second immunosuppressive agent (azathioprine [AZA] or mycophenolate mofetil [MMF]). Changes in or withdrawal from the initial treatment regimen at any time point during follow-up were recorded. Conventional treatment with diuretics, β-blockers, and/or rifaximin was administered when indicated.

Definitions

ACLF was defined according to the recommendations of the European Association for the Study of the Liver (EASL)-Chronic Liver Failure (CLIF) Consortium (CLIF-C)[11]. The treatment response at the respective time points was defined according to the criteria set by the IAIHG[12], as >50% decrease of transaminases at 4 weeks of treatment, and as complete normalization of transaminases and IgG at 6 and 12 months of treatment, respectively. Recompensation was defined as the absence of ascites after diuretic discontinuation and/or the absence of OHE after resolution of the initial event once

prophylactic treatment was withdrawn, and the absence of recurrent variceal bleeding (for at least 12 months). Disease progression was defined as the continuous deterioration of liver biochemistry or development of new decompensating events[13].

Ethical issues

This study was approved by the Ethics Committee of the Hospital Clinic of Barcelona (HCB/2022/0331) and adhered to the principles of the Declaration of Helsinki. The research protocol was approved by the ethics committee of each participating center.

Statistical analysis

Statistical analysis was performed using SPSS 26 and Stata 18 software. Graph Pad Prism 8.0 was used for graphical representation of the data. The results are expressed as median (interquartile range [IQR]). Data were analyzed using the Mann-Whitney U-test to compare independent samples. Chi-square and Fisher's exact tests were used to compare categorical variables. The time of entry (time 0) was the date of treatment initiation for treated patients and the date of diagnosis for untreated patients. A Fine-Gray regression model considering LT as a competing event was used to calculate the sub-hazard ratio (SHR) of mortality between treated and untreated patients. To confirm the impact of treatment on survival, we performed two sensitivity analyses: 1) a time-dependent Cox regression analysis adjusting for center (according to access to LT at each participating center), and 2) a Fine-Gray regression model considering non-liver-related death as a competing event. Predictive models of LT-free survival were calculated using Cox proportional hazard models. Variables that were significantly associated with LT-free survival in the univariate analysis, clinically relevant, and those without collinearity were included in the multivariate analysis. A decision tree analysis was used to establish a treatment algorithm. Survival curves were presented using Kaplan-Meier curves. Binary logistic regression analysis was used to detect predictors of treatment discontinuation, treatment response, and recompensation. Receiver operating curve (ROC) analysis was used to assess the accuracy of model predictions by calculating the area under the curve (AUC). Two-sided p-values <0.05 were considered statistically significant with a 95% confidence interval (CI).

Results

Baseline characteristics

Table 1 summarizes the baseline characteristics of the 232 patients. Of these, 163 (70%) were female, with a median age of 57 years (IQR 45-67) and a median follow-up of 27 months (IQR 4-66). Ascites was present in 207 patients (89%), OHE in 94 (41%), variceal bleeding in 20 (9%), and 97 (42%) had multiple decompensating events at diagnosis. Sixty-nine patients (30%) met ACLF criteria. The median MELD, MELD-Na, and CP scores were 18 (IQR 14-23), 19 (IQR 14-25), and 10 (IQR 8-11), respectively. Immunosuppressive treatment was given to 214 patients (92%), with 83% (n=177) starting PRED at diagnosis and the rest initiating treatment after a median of 30 days (IQR 19-75). Seventy percent (n=149) received an initial PRED dose ≥ 0.5 mg/kg, tapered according to EASL recommendations[3], while the remainder received < 0.5 mg/kg, unchanged for the first month. The accumulated PRED dose in the first month was 980 mg (IQR 700-1260). A second immunosuppressive agent was started in 62% (n=132) of patients after a median of one-month post-PRED initiation. Consequently, 70% (n=151) received PRED monotherapy in the first month. Treatment details are in Supplementary Table 1.

Impact of immunosuppressive treatment on LT-free survival

The differences in the baseline characteristics between the treated and untreated patients are shown in Table 2. Treated patients less frequently had variceal bleeding (7% vs. 28%, p=0.012) as the initial decompensating event, had a higher inflammatory activity index (mHAI grade 7 vs. 3, p<0.001) on liver biopsy, and higher aspartate aminotransferase (AST, 352 vs. 69, p<0.001), alanine aminotransferase (ALT, 304 vs. 46, p<0.001), and bilirubin (5.4 vs. 2.9, p=0.018) levels, suggesting that patients who received treatment had biochemically and/or histologically active disease.

Among untreated patients, 7 (39%) died of end-stage liver disease (median time 17 months, IQR 4-39) and 9 (50%) underwent LT (median time 2 months, IQR 1.0-8.5). Among the treated patients, 41 (19%) died (median time, 21 months, IQR 2-79) and 54 (25%) underwent LT (median time 2.5 months, IQR 1-19) (Supplementary Figure 2A). The causes of death are shown in Supplementary Figure 2B. Using a Fine-Gray regression model, considering LT as a competing event, treatment initiation was associated with a significantly lower SHR of mortality (0.438, 95%CI 0.196-0.981, p=0.045). The cumulative incidence of mortality at 12 and 36 months of follow-up is shown in Supplementary Figure 3A. These results were confirmed by sensitivity analysis, which accounted for the differences in access to LT among participating centers (Supplementary Figure 3B) and considered non-liver-related deaths as a competing event (Supplementary Figure 3C).

Overt hepatic encephalopathy and MELD-Na at diagnosis predict LT-free survival in treated patients

As shown in Table 3, age, OHE, presence of more than one decompensating event, bilirubin, INR, sodium, albumin, MELD, MELD-Na, and CP scores were significantly associated with LT-free survival. Variables without collinearity were included in the multivariate analysis, and only the absence of OHE and MELD-Na score at diagnosis were independently associated with LT-free survival. Based on this observation, we performed a decision tree analysis to determine the subgroups of patients with greater benefit from immunosuppressive treatment initiation. Almost all patients with OHE grade 3 or 4 died or required LT. In contrast, after a median follow-up of 27 months, patients without OHE or with OHE ≤ grade 2 at diagnosis had a 60% survival rate ($p<0.001$ vs. OHE grade 3 or 4). MELD-Na further determined the subgroup of patients with the highest probability of treatment benefit, as 88% of patients with OHE ≤ grade 2 and MELD-Na > 28 died or required LT, whereas among those with MELD-Na ≤ 28, the LT-free survival rate was 64% ($p<0.001$) (Figure 1). In this subgroup, the evolution of laboratory parameters (ΔINR, ΔBilirubin, ΔMELD-Na) at consecutive time points (3 days, 7 days, 4 weeks) was assessed and only ΔMELD-Na after 4 weeks of treatment was independently associated with final outcome (HR 1.112; 95%CI 1.017-1.214, $p=0.020$), as shown in Supplementary Table 2. In addition, a ΔMELD-Na ≥ 11 at 4 weeks of treatment had a negative predictive value of death or LT of 100%.

Treatment response improves LT-free survival and induces recompensation

Figure 2A illustrates treatment response at week 4, and months 6 and 12. Biochemical response at week 4 correlated with higher LT-free survival (92% vs. 64% at 12 months and 88% vs 53% at 36 months, $p<0.001$) (Figure 2B). During follow-up, 49% of treated patients reversed to compensated disease. Recompensated patients had higher LT-free survival than those who remained decompensated and/or developed a new decompensating event (99% vs.49% at 12 months and 97% vs.37% at 36 months, $p<0.001$) (Figure 2C). Among treated patients with favorable outcomes (n=119), recompensated patients had higher AST (380 vs. 174, $p=0.035$), ALT (312 vs.128, $p=0.010$), and bilirubin (4.4 vs.2.5, $p=0.006$) levels at diagnosis (Supplementary Table 3), indicating that patients with biochemically active disease at diagnosis are more likely to benefit from treatment initiation. Initial and accumulated PRED doses during the first month were not associated with treatment response at week 4 or recompensation during follow-up.

Treatment-related adverse events

As shown in Figure 3A, 56 patients (26%) developed infectious complications during follow-up (median time of 27 months, IQR 2.5-73.0), of which 8 were opportunistic infections. Prophylactic antibiotics were not routinely administered. Neither the initial and accumulated PRED dose, nor the type of treatment were significantly associated with the development of infections during follow-up. In contrast, the presence of OHE ≥ grade 2 at diagnosis was positively associated with the development of infections after treatment initiation (OR 2.996; 95%CI1.473-6.094, p=0.002). Prophylactic antibiotic treatment was not routinely used

Treatment discontinuation

During follow-up, 13 patients changed AZA to MMF due to intolerance or insufficient response after a median time of 3 months (IQR 1.0-4.5), 4 patients discontinued AZA due to intolerance and remained in PRED monotherapy, and 4 patients were switched to tacrolimus (TAC) because of insufficient response.

Forty-three of the 214 treated patients (20%) had to discontinue immunosuppression after a median time of 1 month (IQR 0.5-10.0). Among them, 13 (30%) died and 27 (63%) required LT. The reasons for treatment discontinuation are shown in Figure 3B. Supplementary Table 4 summarizes the predictors of treatment discontinuation. Among them, the combination of the presence of OHE ≥ grade 2 and MELD-Na at diagnosis was the best predictive model and could effectively predict the need for prompt treatment withdrawal within the first 4 weeks after treatment initiation (AUC0.902; 95%CI 837-944, p<0.001) (Figure 3C).

Treatment initiation is not associated with an increased risk of post-LT complications

In our cohort, 63 (27%) patients required LT after a median follow-up period of 2 months (IQR1-17). At the time of LT, the majority of treated patients (n=36, 67%) were on PRED monotherapy. Prophylactic antibiotic treatment was not routinely administered in the majority of cases during the preoperative period, whereas antibiotic prophylaxis in the post-LT period was administered based on specific patient and donor characteristics.

Overall, 10 patients (16%) experienced post-LT complications: six had surgical issues (biliary obstruction [n=2], ascites [n=2], hepatic artery stenosis [n=2]), and four had treatment-related complications (acute kidney injury [n=2], sinusoidal obstruction syndrome [n=1], acute rejection [n=1]). Twenty-one patients (33%) developed post-LT infections, including 12 with opportunistic infections. Six patients (10%) died, three from

surgical complications and three from infections. No significant differences in post-LT complication rates were observed between treated and untreated patients. Neither the initial nor accumulated doses of PRED during the first month correlated with an increased risk of post-LT complications or infections.

Discussion

On analyzing a large cohort of patients with AIH presenting with decompensated cirrhosis, we found that selected patients with active disease benefited from immunosuppressive treatment. However, careful selection of candidates for immunosuppression is of paramount importance, as patients presenting with OHE grade 3 or 4 and MELD-Na > 28 have a significantly higher risk of dying or requiring LT despite treatment administration. In the remaining patients, immunosuppression should be administered, and a decrease in the MELD-Na score after 4 weeks of treatment can guide subsequent treatment decisions. These findings have significant implications as current clinical practice guidelines lack evidence to provide clear recommendations on how to treat patients with AIH-related decompensated disease.

Most of the patients in this cohort received immunosuppressive treatment. Treated patients included those with active disease as indicated by higher aminotransferase levels and mHAI scores. These results are not unexpected, as clinical practice guidelines[3,4] recommend the initiation of immunosuppression in patients with active disease and/or advanced fibrosis or cirrhosis[14,15], and discourage immunosuppression in decompensated patients with “burn-out” cirrhosis in whom the risk of infections and cirrhosis-related complications outweighs the potential benefit of treatment. However, whether some untreated patients could have benefited from immunosuppression could not be explored[16–21], because of the retrospective nature of the study. Therefore, these results should only be applied to patients with active disease, in whom treatment administration was associated with significantly better LT-free survival.

Despite the clear benefits of immunosuppressive treatment in clinical practice, the decision to initiate immunosuppression in an individual patient with decompensated cirrhosis is always challenging. This is mainly due to the elevated risk of treatment-related complications that may prevent access to LT. Therefore, the identification of baseline predictive factors that can guide treatment decisions is important from a clinical point of view. Here, we found that patients with OHE grade 3 or 4 should be considered for LT, as the potential benefit of treatment in these patients is low. In contrast, treated patients without HE or with OHE ≤ grade 2 at diagnosis benefited from treatment initiation, with a LT-free survival rate of 60%. In this subgroup of patients, the

MELD-Na score helped guide further treatment decisions, as patients with a baseline MELD-Na score ≤ 28 at diagnosis showed significantly better LT-free survival rates than those with a MELD-Na score > 28. These results suggest that treatment should be considered in patients without OHE grade 3 or 4 and a MELD-Na score ≤ 28 at diagnosis. However, these patients still died or had a LT rate of 36%, indicating that close monitoring is mandatory. A decrease in MELD-Na at 4 weeks of treatment was the most important predictor of survival in this group of patients. In agreement with previous studies[5,6], these results indicate that the type and severity of the initial decompensating event strongly affect the final outcome, confirming the importance of the MELD score at baseline as a predictor of outcome in patients with AIH-related decompensation and emphasizing the prognostic role of OHE in patients with AIH-related cirrhosis, as has been described for other etiologies of liver disease [22].

In addition to the impact on LT-free survival, treatment was also associated with recompensation in almost 50% of treated patients. Similar to what has been previously described[16,17,23–26], recompensation was associated with reduced mortality risk and/or need for LT. In agreement with previous data[6], disease activity was strongly associated with recompensation, indicating that the more severe the liver inflammation, the higher the probability of reversal to compensated disease.

Immunosuppressive treatment was associated with infectious complications in 56 patients (six with sepsis and eight with opportunistic infections), although the number of deaths attributed to infectious complications was rather low (4%). Again, the grade of OHE in combination with MELD-Na score at diagnosis was proved the most important predictor of treatment-related complications and could effectively predict the need for prompt treatment discontinuation, within the first 4 weeks after treatment initiation. Interestingly, neither the initial PRED dose, accumulated dose during the first month, nor the type of treatment were associated with the development of infections during follow-up. Moreover, when patients who required LT were analyzed separately, post-LT complications and infections were not associated with the initial PRED dose and/or type of treatment. These results support the idea that immunosuppression can be attempted in selected patients without increasing the incidence of post-LT complications[27–29].

Our study had several limitations. Firstly, it was a retrospective study but given the limited number of patients diagnosed at the stage of decompensated disease, the realization of prospective studies in this field is extremely difficult. Secondly, while our cohort included AIH patients with histologically confirmed advanced fibrosis or

cirrhosis, it is important to acknowledge that post-necrotic collapse may be misinterpreted as cirrhosis, even by experienced pathologists. Consequently, the possibility that some patients with subacute AIH were inadvertently included in the study cannot be entirely excluded. Nevertheless, all patients included in the study exhibited additional clinical and/or radiological indicators of cirrhosis. Thirdly, the analysis evaluating the impact of immunosuppression on survival should be interpreted with caution as the number of untreated patients is small and the decision to initiate immunosuppression may be subject to bias, given that patients in more critical condition were likely not considered suitable candidates for corticosteroid treatment. Consequently, larger cohorts are needed to confirm our results. Finally, owing to the retrospective nature of the study, data on post-LT survival/complications were only available for a small number of patients. However, to the best of our knowledge, this is the largest study conducted on this topic, including patients from several referral centers worldwide, thereby increasing the reliability of our data.

In conclusion, the severity of HE and MELD-Na score at the time of diagnosis significantly impact decision-making regarding the initiation of immunosuppressive treatment. The ΔMELD-Na score 4 weeks after treatment initiation serves as a valuable parameter for refining prognosis and guiding further therapeutic decisions. This metric allows for the identification of a subset of patients with a high probability of recompensation, as well as a subset in which the risk of requiring LT remains substantial despite the benefits of immunosuppression.

Acknowledgments

We would like to thank Katja Füssel and Claudia Kroll from the University Medical Center Hamburg-Eppendorf Martinistr for their help with the data collection, and Enric Reverter for the revision of the statistical analysis.

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Table 1: Baseline characteristics of the patients included in the study.

Variable	**n=232**
Female sex (n, %)	163 (70%)
Age (years)	57 (45-67)
Ascites Grade 1/2/3	207 (89%) 80/106/21
OHE Grade 1/2/3-4	94 (41%) 36/41/17
Variceal bleeding	20 (9%)
More than one events	97 (42%)
Splenomegaly (n, %)	152 (71%)
ANA (n,%)	189 (81%)
SMA (n,%)	112 (48%)
LKM-1 (n,%)	5 (2%)
SLA/LP (n,%)	16 (7%)
Platelets (x 10^9/L)	118 (88-165)
INR	1.6 (1.3-1.9)
Creatinine (mg/dL)	0.8 (0.6-1)
Albumin (g/dL)	2.9 (2.4-3.3)
Na (mEq/L)	136 (133-138)
AST (U/L)	332 (132-741)
ALT (U/L)	277 (118-545)
Bilirubin (mg/dL)	4.8 (2.1-11.6)
GGT (U/L)	123 (75-190)
ALP (U/L)	170 (129-246)
IgG (mg/dL)	2350 (1819-3200)
ACLF (n, %) Grade 1a Grade1b Grade 2 Grade 3a	69 (30%) 1 (2%) 49 (71%) 14 (20%) 5 (7%)
MELD	18 (14-23)
MELD-Na	19 (14-25)
CP	10 (8-11)
ALBI	-1.02 [-1.63- (-0.58)]

Values are expressed as median (interquartile range, IQR)

Abbreviations as in the text

Table 2: Comparison of baseline characteristics between treated and untreated patients.

Characteristics	Untreated (n=18)	Treated (n=214)	p value
Age (years)	61 (51-71)	57 (45-67)	0.157
Female sex (n, %)	13 (72%)	150 (70%)	0.850
mHAI grading	3 (3-3)	7 (6-12)	**<0.001**
Ascites (n,%)	15 (83%)	192 (90%)	0.422
Ascites ≥ grade 2 (n,%)	13 (72%)	114(53%)	0.302
OHE (n,%)	10 (56%)	84 (39%)	0.465
OHE ≥ grade 2 (n,%)	6 (33%)	52 (24%)	0.590
Variceal bleeding (n,%)	5 (28%)	15 (7%)	**0.012**
More than one events (n,%)	10 (56%)	87 (41%)	0.226
Splenomegaly (n,%)	15 (83%)	137 (65%)	0.126
Platelets (x 10^9/L)	106 (79-146)	122 (88-165)	0.357
INR	1.4 (1.3-1.7)	1.6 (1.3-1.9)	0.147
Creatinine (mg/dL)	1.02 (0.78-1.22)	0.8 (0.61-0.96)	0.056
Albumin (g/dL)	2.9 (2.5-3.5)	2.9 (2.5-3.3)	0.642
Na (mEq/L)	134 (131-138)	136 (134-139)	0.087
AST (U/L)	69 (43-98)	352 (148-750)	**<0.001**
ALT (U/L)	48 (37-66)	304 (139-563)	**<0.001**
Bilirubin (mg/dL)	2.9 (1.3-4.8)	5.4 (2.2-12.7)	**0.018**
GGT (U/L)	77 (42-133)	125 (78-194)	**0.005**
ALP (U/L)	176 (133-206)	170 (129-250)	0.850
IgG (mg /dL)	1843 (1400-3252)	2420 (1850-3200)	0.060
ACLF (n, %)	4 (22%)	65 (30%)	0.596
MELD	16 (14-21)	18 (14-23)	0.285
MELD-Na	18 (14-24)	19 (14-25)	0.941
CP score	9 (7-11)	10 (8-11)	0.250
ALBI	-0.99 [-1.63- (-0.54)]	-1.37 [-1.78-(-0.90)]	0.077

Values are expressed as median (IQR)

Abbreviations as in the text.

Table 3: Univariate and multivariate Cox proportional hazard models of final outcome among treated patients.

Characteristics	Alive (n=119)	Death/LT (n=95)	p value	Univariate analysis			Multivariate analysis		
				HR	CI95%	p value	HR	CI95%	p value
Age (years)	60 (50-69)	52 (32-64)	**0.001**	0.989	0.977-1.000	**0.047**	0.994*	0.983-1.006	0.378
Female sex (n, %)	88 (59%)	62 (41%)	0.179						
mHAI grading	8 (5-12)	9 (6-12)	0.086						
Ascites (n, %)	108 (91%)	84 (88%)	0.653						
OHE (n,%)	26 (22%)	58(61%)	**<0.001**	3.410	2.238-5.197	**<0.001**	2.642*	1.678-4.162	**<0.001**
Grade of ascites (≥Grade 2)	59 (50%)	55(58%)	0.198						
Grade of encephalopathy (≥Grade 2)	13 (11%)	39 (41%)	**<0.001**						
Variceal bleeding (n, %)	9 (8%)	6 (6%)	0.793						
More than one event (n, %)	33 (28%)	54 (57%)	**<0.001**	2.326	1.539-3.515	**<0.001**			
Splenomegaly (n, %)	69 (59%)	68 (72%)	0.059						
Time to treatment initiation (months)	0 (0-0)	0 (0-0)	0.122						
Initial corticosteroid dose (≥0.5-1mg/kg/day)	81(68%)	68 (71%)	0.427						
Accumulated PRED dose during first month (mg)	980 (700-1260)	980 (700-1260)	0.762						
Time to second IS (months)	1 (0.5-2)	1 (0-3)	0.227						
Type of treatment first month									
PRED monotherapy	80	71							
PRED+AZA	37	20	0.163						
PRED+MMF	2	4							
Platelets (10^9/L)	124 (92-168)	115 (85-158)	0.232						

INR	1.5 (1.3-1.8)	1.7 (1.4-2.1)	**<0.001**	1.494	1.239-1.802	**<0.001**			
Creatinine (mg/dL)	0.78 (0.60-0.92)	0.8 (0.64-0.97)	0.369						
Albumin (g/dL)	3 (2.5-3.3)	2.7 (2.2-3.2)	**0.013**	0.952	0.923-0.983	**0.002**			
Na (mEq/L)	137 (135-139)	135 (132-138)	**0.002**	0.911	0.866-0.959	**0.001**			
AST(U/L)	330 (145-765)	424 (182-741)	0.308						
ALT(U/L)	286 (126-548)	358 (147-621)	0.193						
Bilirubin (mg/dL)	3.7 (1.9-9.5)	8.4 (3.0-16.2)	**<0.001**	1.039	1.018-1.061	**<0.001**			
GGT (U/L)	136 (87-231)	106 (64-184)	**0.009**	0.999	0.997-1	0.087			
ALP (U/L)	157 (124-224)	198 (134-286)	**0.034**	1.001	1-1.002	0.118			
IgG (mg/dL)	2265 (1731-3200)	2587 (2010-3227)	0.087						
MELD	17 (14-21)	21 (15-25)	**<0.001**	1.067	1.038-1.095	**<0.001**			
MELD Na	17 (13-22)	22 (15-29)	**<0.001**	1.069	1.040-1.095	**<0.001**	1.043*	1.016-1.071	**0.002**
CP score	9 (8-10)	11 (9-12)	**<0.001**	1.256	1.145-1.378	**<0.001**			
ALBI score	-1.16 [-1.78- (-0.69)]	-0.79 [-1.36- (-0.36)]	**0.007**	1.329	0.992-1.779	0.057			

Values are expressed as median (IQR)

*Since significant variables are included in MELD-Na and to avoid collinearity, only age, OHE, and MELD-Na were considered in the multivariate analysis.

Abbreviations as in the text.

Figure 1

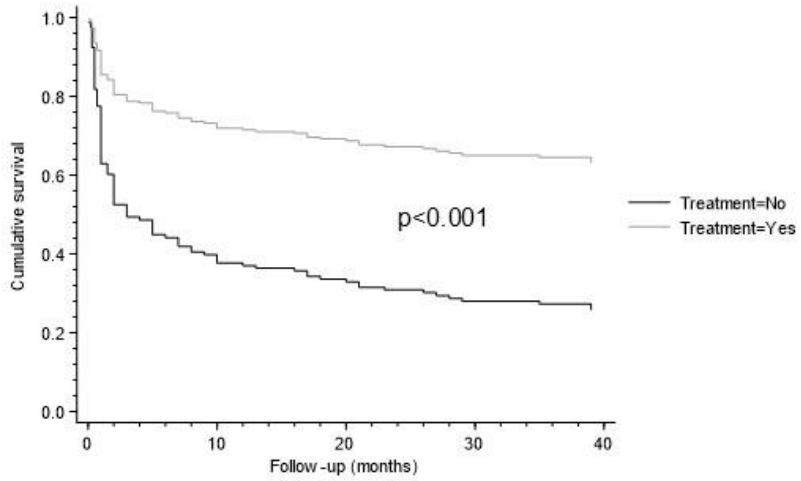
1.0
0.8
0.6
0.4
0.2
0.0
Cumulative survival
0
10
20
30
40
Follow-up (months)
p<0.001
Treatment=No
Treatment=Yes

Figure 2

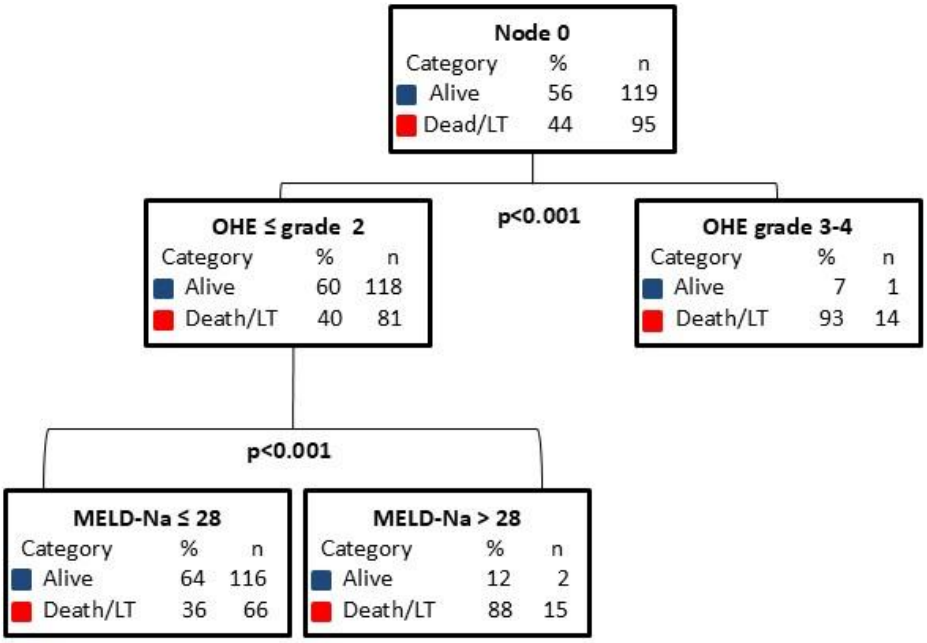
Node 0
Category % n
Alive 56 119
Dead/LT 44 95
p<0.001
OHE ≤ grade 2
Category % n
Alive 60 118
Death/LT 40 81
OHE grade 3-4
Category % n
Alive 7 1
Death/LT 93 14
p<0.001
MELD-Na ≤ 28
Category % n
Alive 64 116
Death/LT 36 66
MELD-Na > 28
Category % n
Alive 12 2
Death/LT 88 15

Figure 3

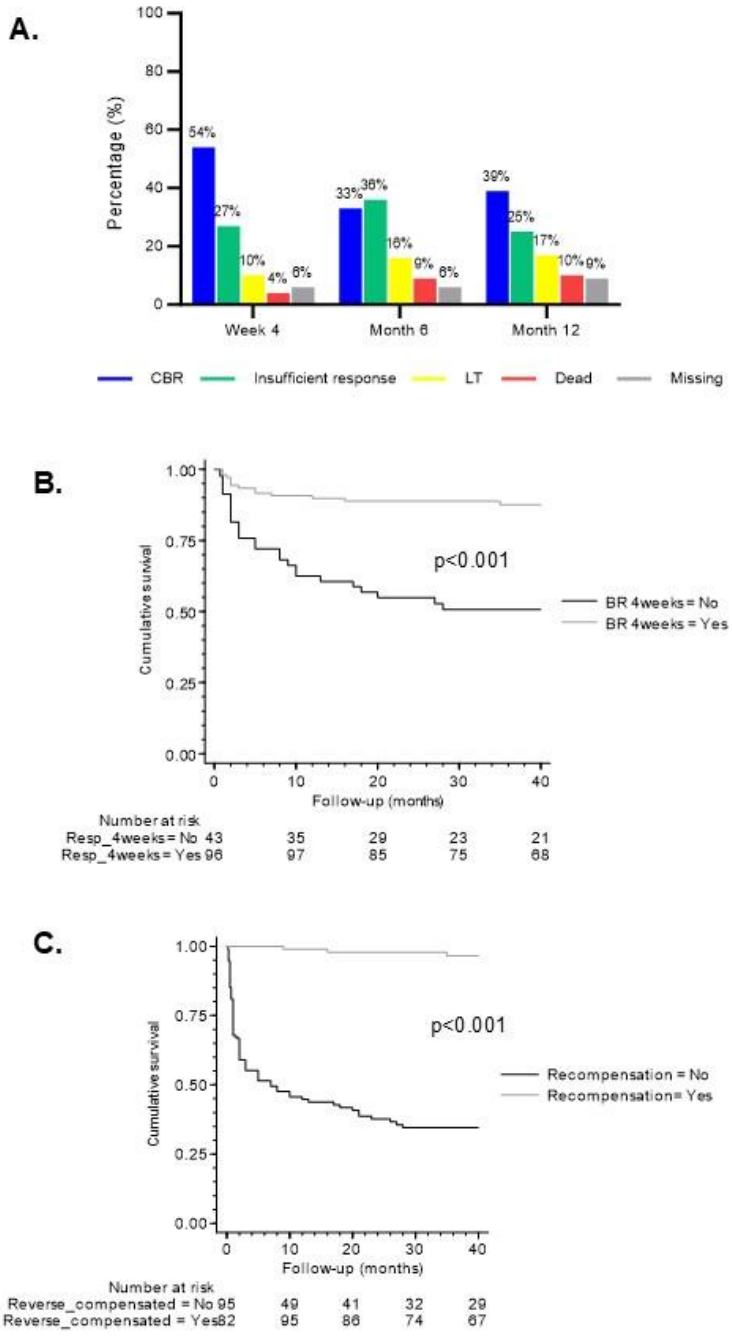
A.
Percentage (%)
100
80
60
40
20
0
54%
27%
10%
4%
6%
33%
36%
16%
9%
6%
39%
25%
17%
10%
9%
Week 4
Month 6
Month 12
CBR
Insufficient response
LT
Dead
Missing
B.
Cumulative survival
1.00
0.75
0.50
0.25
0.00
p<0.001
BR 4weeks = No
BR 4weeks = Yes
0
10
20
30
40
Follow-up (months)
Number at risk
Resp_4weeks = No 43 35 29 23 21
Resp_4weeks = Yes 96 97 85 75 68
C.
Cumulative survival
1.00
0.75
0.50
0.25
0.00
p<0.001
Recompensation = No
Recompensation = Yes
0
10
20
30
40
Follow-up (months)
Number at risk
Reverse_compensated = No 95 49 41 32 29
Reverse_compensated = Yes 82 95 86 74 67

Figure Legends

Figure 1. Decision tree analysis of treatment benefit according to the grade of OHE and the MELD-Na score at diagnosis.

Figure 2. A) Treatment response at 4 weeks, 6 and 12 months. **B)** Cumulative survival according to biochemical response at 4 weeks of treatment. **C)** Cumulative survival according to recompensation during follow-up.

Figure 3. A) Type of infection among treated patients during follow-up. * Opportunistic infections included Cytomegalovirus (n=2), Candida (n=3), and Aspergillus (n=3). **B)** Reasons for treatment discontinuation during follow-up. **C)** ROC curve of the combination of OHE ≥ Grade 2 and MELD-Na score at diagnosis for predicting the need for prompt treatment withdrawal.