Supplementary Materials

Definition of Organ Failure and ACLF grades.

Definition of OF was based on the cut-off values proposed by the CLIF-SOFA score. Liver failure was defined by serum bilirubin levels of 12.0 mg/dL or more. Kidney failure was considered when serum creatinine levels exceeded 2.0 mg/dL, or when renal-replacement therapy was used. Cerebral and coagulation failures was defined by grade III or IV HE or by an International Normalized Ratio (INR) of more than 2.5 and/or platelet count of 20 $\times 10^9$/L or less, respectively. Circulatory failure was considered when the use of catecholamines or terlipressin was necessary to maintain arterial pressure. Respiratory failure was defined by a ratio of partial pressure of arterial oxygen to fraction of inspired oxygen (FiO$_2$) of 200 or less or a pulse oximetry (SpO$_2$) to FiO$_2$ ratio of 200 or less.

ACLF-grades were defined as follows: i) No ACLF, this group comprises three subgroups: (1) patients with no OF, (2) patients with a single "non-kidney" OF who had a serum creatinine level <1.5 mg/dL and no HE, and (3) patients with single cerebral failure who had a serum creatinine level <1.5 mg/dL; ii) ACLF-grade 1 was considered when one of the following occurred (1) patients with single kidney failure, (2) patients with single failure of the liver, coagulation, circulation or respiration, who had serum creatinine ranging from 1.5 to 1.9 mg/dL or grade I or II HE or both and (3) patients with single cerebral failure who had serum creatinine ranging from 1.5 to 1.9 mg/dL; iii) ACLF-grade 2 comprised patients with two OF and iv) ACLF-grade 3 included patients with ≥3 OF.

Effect of treatment on laboratory data and hepatic encephalopathy at day 4 in the whole patients included in the MA.

The use of MARS was associated with a significant improvement in serum bilirubin [25.3 (13.4) mg/dL vs. 18.2 (8.27) mg/dL; p<0.001)] and creatinine [2.14 (1.85) mg/dL vs. 1.57 (1.08) mg/dL; p< 0.001)] but not in INR [1.87 (0.64) vs. 1.95 (0.85); p= 0.284], with a significant decrease in MELD score [30.45 (7.42) points vs. 27.80 (6.39) points; p<0.001]. The proportion of patients with improvement of HE (reduction of two stages or more at day-4) was significantly higher (21.0% vs 33.3%, p=0.020) in the MARS group.

Significant improvement in bilirubin, creatinine and MELD was observed in patients treated with MARS [delta bilirubin: -7.04 (9.17) mg/dl Vs. -1.34 (6.67) mg/dl; p=0.03; delta creatinine: -0.56 (1.34) mg/dl Vs. 0.27 (1.23) mg/dl; p=0.079 and delta MELD: -2.64 (6.07) points Vs. -0.59 (5.00) points; p=0.007].

Supplementary table 1.

	CANONIC	Meta-analysis					
	ACLF all grades (n=303)	ACLF all grades (n=165)	P value	ACLF grade 1 (n=49)	ACLF grade 2 (n=53)	ACLF grade 3 (n=63)	P value
Background and exploratory data							
Age (years)	56 (11)	50 (11)	0.001	48.6 (11.1)	53.0 (11.4)	47.1 (8.7)	0.171
Male sex (%)	64.4	66.1	0.712	63.3	69.8	65.1	0.899
Alcoholic cirrhosis (%)	60.3	72.1	0.011	71.4	75.5	69.8	0.132
Mean arterial pressure (mmHg)	79.1 (12.9)	79.8 (14.6)	0.543	82.7 (8.9)	84,1 (16.9)	73.8 (14.3)	0.001
ACLF grade:							
ACLF 1	148 (48.8%)	49 (29.7%)	<0.001				
ACLF 2	108 (35.6%)	53 (32.1%)	0.4435				
ACLF 3	47 (15.5%)	63 (38.2%)	<0.001				
Type and number of organ failures							
Liver (%)	43.6	79.4	0.001	83.7	67.9	85.7	0.011
Kidney (%)	55.8	44.2	0.022	10.2	47.2	68.3	0.001
Brain (%)	24.1	46.7	0.001	4.1	41.5	84.1	0.001
Coagulation (%)	27.7	15.2	0.003	0.0	7.5	33.3	0.001
Circulation (%)	16.8	21.8	0.230	0.0	20.8	39.7	0.001
Respiration (%)	9.2	24.2	0.001	2.0	15.1	49.2	0.001
Laboratory data							
Serum bilirubin (mg/dL)	12.8 (17.7)	25.1 (14)	0.001	27.9 (12.9)	22.4 (15.6)	25.1 (13.2)	0.096
INR	2.1 (0.9)	2.0 (0.7)	0.217	1.7 (0.3)	1.8 (0.5)	2.4 (1.0)	0.001
Serum creatinine (mg/dL)	2.3 (1.6)	2.5 (1.9)	0.228	1.5 (0.9)	2.4 (2.0)	3.2 (2.0)	0.001

Serum Na (mEq/L)	133 (6)	135 (11)	0.011	133 (6)	135 (11)	137 (14)	0.144
Blood leucocytes (x10^3/μL)	10.1 (0.4)	14.7 (10.4)	0.001	13.8 (10.2)	13.5 (8.7)	16.4 (11.6)	0.301
Platelets (x103/μL)	100 (69)	110 (71)	0.139	116 (73)	109 (76)	105 (64)	0.069
MELD	27.4 (7.0)	32.0 (8.0)	<0.001	28.3 (3.9)	29.8 (8.3)	36.8 (7.8)	<0.001

Treatment and mortality

Number of MARS sessions	NA	3.6 (3.5)	NA	4.3 (4.1)	3.3 (3.3)	3.1 (3.1)	0.204
10-day mortality (%)	16.3	18.8	0.473	12.2	20.8	22.2	0.369
30-day mortality (%)	30.9	36.4	0.240	22.4	39.6	44.4	0.047

Supplementary table 1. Baseline characteristics of patients according to the presence and severity of ACLF. Quantitative variables are expressed as mean (SD). Qualitative variables are expressed as percentages.

ACLF: acute on chronic liver failure. SMC: Standard Medical Care. MARS: Molecular adsorbent recirculating system. INR: International Normalized Ratio.

| | | | MODEL 1 n=251 | | MODEL 2 n=201 | | MODEL 3 n= 201 | |
Variable	Univariate HR (CI 95 %)	p	Multivariate HR (CI 95 %)	p	Multivariate HR (CI 95 %)	p	Multivariate HR (CI 95 %)	p
Age (years)	1.03 (1.015-1.053)	0.000	1.03 (1.01-1.05)	0.002	1.03 (1.01-1.06)	0,002	1.05 (1.03-1.08)	0.001
Gender	1.09 (0.71-1.68)	0.677						
Mean Arterial Pressure (mmHg)	0.99 (0.98-1.00)	0.096	0.99 (0.98-1.01)	0.1	0.95 (0.97-1.01)	0.1	0.99 (0.97-1.01)	0.186
Hepatic encephalopathy (West-Haven)	1.11 (0.97-1.28)	0.138						
Hepatic encephalopathy (severe Vs. absent or mild)	1.26 (0.83-1.90)	0.279						
Creatinine (mg/dL)	1.26 (1.16-1.38)	0.000	Not included*		Not included**		Not included**	
Serum Bilirubin (mg /dl)	1.00 (0.99-1.02)	0.439						
INR	1.19 (0.88-1.61)	0.275						
MELD	1.06 (1.04-1.09)	0.000	1.07 (1.04-1.10)	0.000	Not Included***		Not Included***	
CLIF organ failure score	1.22 (1.10-1.35)	0.000	Not Included***		Not Included***		Not Included***	
Number of organ failure	1.31 (1.1-1.56)	0.004	Not Included***		Not Included***		Not Included***	
Severity of ACLF (ACLF 0 as reference category)	1.42 (1.13-1.79)	0.003	Not Included***		1,39 (1,09-1,77)	0.008	1.55 (1.19-2.03)	0.001
Intensity of MARS therapy (High Vs. Low intensity)	0.63 (0.38-1.04)	0.057	0.50 (0.28-0.87)	0.015	0,55 (0,30-0,99)	0.045	Not Included***	
Number of MARS sessions	0.93 (0.87-0.99)	0.037	Not included***		Not included***		0.90 (0.83-0.98)	0.021

Supplementary table 2. Univariate and multivariate Cox Regression Analysis.

*Individual components of MELD score were not included in multivariate analysis to avoid collinearity ** Creatinine, bilirubin and INR are included in the assessment of ACLF severity and were not included to avoid collinearity. ***See methods section

ACLF: Acute on chronic liver failure. INR: International normalized ratio. MELD: model for end-stage liver disease. MARS: Molecular adsorbent recirculating system. High intensity: denotes patients who received five or more MARS sessions.

Type of adverse event	No ACLF					ACLF grade 1					ACLF grade 2					ACLF grade 3				
	SMC		MARS		p value	SMC		MARS		p value	SMC		MARS		p value	SMC		MARS		p value
	n/total	%	n/total	%		n/total	%	n/total	%		n/total	%	n/total	%		n/total	%	n/total	%	
Infection	1/15	6,7	3/15	20	0,283	5/22	22,7	3/25	12	0,329	1/14	7,1	5/23	21,7	0,243	2/14	14,3	3/11	27,3	0,420
Coagulopathy	0/15	0	0/15	0	NA	2/22	9,1	1/25	4	0,476	0/14	0	1/23	4,3	0,429	0/14	0	3/11	27,3	0,037
Bleeding	1/15	6,7	4/15	26,7	0,142	2/22	9,1	3/25	12	0,747	1/14	7,1	4/23	17,4	0,377	2/14	14,3	3/11	27,3	0,420
Worsening liver failure	1/15	6,7	0/15	0	0,309	4/22	18,2	4/25	16,0	0,843	2/14	14,3	2/23	8,7	0,595	3/14	21,4	1/11	9,1	0,404
Hemodynamic	0/15	0	0/15	0	NA	0/22	0	0/25	0	NA	2/14	14,3	0/23	0	0,062	3/14	21,4	2/11	18,2	0,840
SAE related death	1/15	6,7	1/15	6,7	1	0/22	0	2/25	8	0,175	2/14	14,3	3/23	13	0,915	2/14	14,3	0/11	0	0,191
Any adverse event	7/15	46,7	8/15	53,3	0,715	12/22	54,5	14/25	56	0,921	7/14	50	14/23	60,9	0,517	9/14	64,3	8/11	72,7	0,653

Supplementary Table 3: Adverse events in the standard medical care and MARS groups.

SMC: Standard medical care. MARS: Molecular adsorbent recirculating system. ACLF: Acute on chronic liver failure. SAE: Severe adverse event.

Type of adverse event	No ACLF					ACLF grade 1					ACLF grade 2					ACLF grade 3				
	Low-intensity		High-intensity		p value	Low-intensity		High-intensity		p value	Low-intensity		High-intensity		p value	Low-intensity		High-intensity		p va
	n/total	%	n/total	%		n/total	%	n/total	%		n/total	%	n/total	%		n/total	%	n/total	%	
Infection	2/23	8,7	2/7	28,6	0,176	6/31	19,4	2/16	12,5	0,553	5/25	20	1/12	8,3	0,367	3/17	17,6	2/8	25	0,66
Coagulopathy	0/23	0	0/7	0	NA	2/31	6,5	1/16	6,3	0,979	0/25	0	1/12	8,3	0,143	2/17	11,8	1/8	12,5	0,95
Bleeding	4/23	17,4	1/7	14,3	0,847	3/31	9,7	2/16	12,5	0,766	3/25	12	2/12	16,7	0,698	3/17	17,6	2/8	25	0,66
Worsening liver failure	1/23	4,3	0/7	0	0,575	6/31	19,4	2/16	12,5	0,553	3/25	12	1/12	8,3	0,737	3/17	17,6	1/8	12,5	0,74
Hemodynamic	0/23	0	0/7	0	NA	0/31	0	0/16	0	NA	2/25	8	0/12	0	0,314	4/17	23,5	1/8	12,5	0,52
SAE related death	1/23	4,3	1/7	14,3	0,356	0/31	0	2/16	12,5	0,212	4/25	16	1/12	8,3	0,523	2/17	11,8	0/8	0	0,31
Any adverse event	11/23	47,8	4/7	57,1	0,665	17/23	73,9	9/16	56,3	0,249	14/25	56	7/12	58,3	0,893	12/17	70,6	5/8	62,5	0,68

Supplementary Table 4: Adverse events in the low- and high-intensity groups.

Low-Intensity: patients who received four or less MARS sessions. High-Intensity: patients who received five or more MARS sessions. ACLF: Acute on chronic liver failure.

SAE: Severe adverse event.

Supplementary Figure 1: 10-day survival according to allocation to low-intensity or high-intensity therapy, excluding the 5 patients who died within 48 hours after MARS discontinuation.

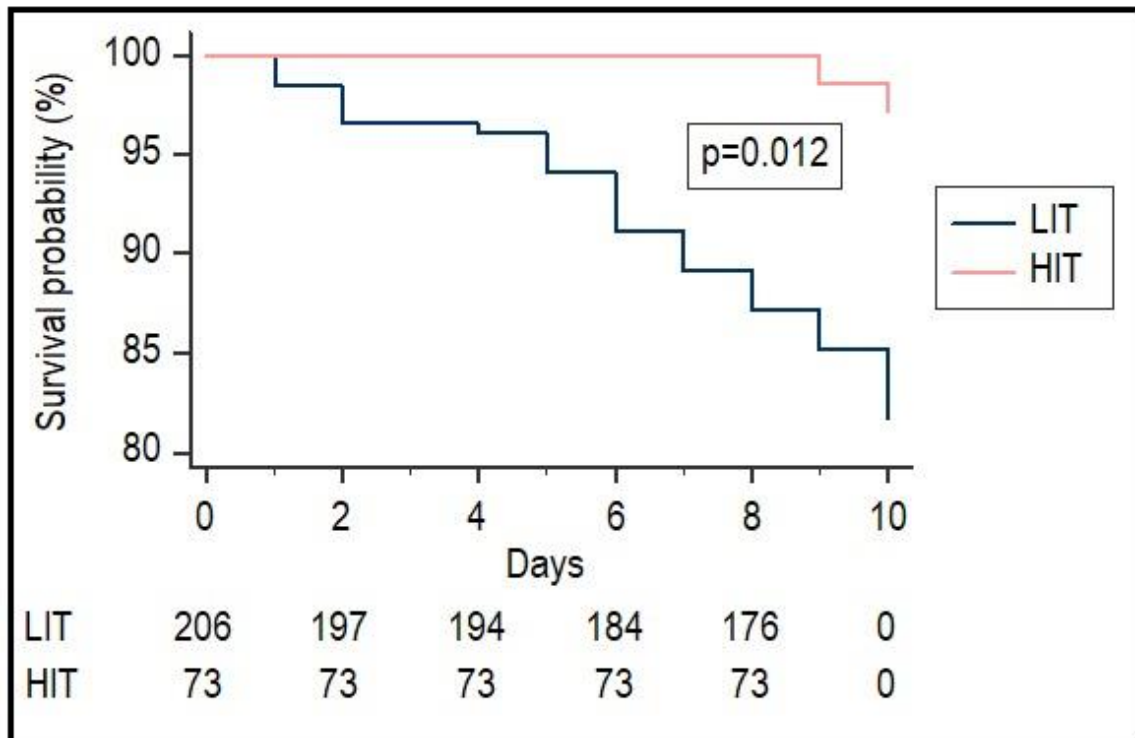LIT: Low-Intensity Therapy. HIT: High Intensity Therapy.

Supplementary Figure 2: Estimated probability of death at 30 days in ACLF patients in LIT, HIT and CANONIC patients for the different values of the CLIF-C ACLF score.

LIT: Low-Intensity Therapy. HIT: High Intensity Therapy. ACLF: Acute on Chronic Liver Failure.
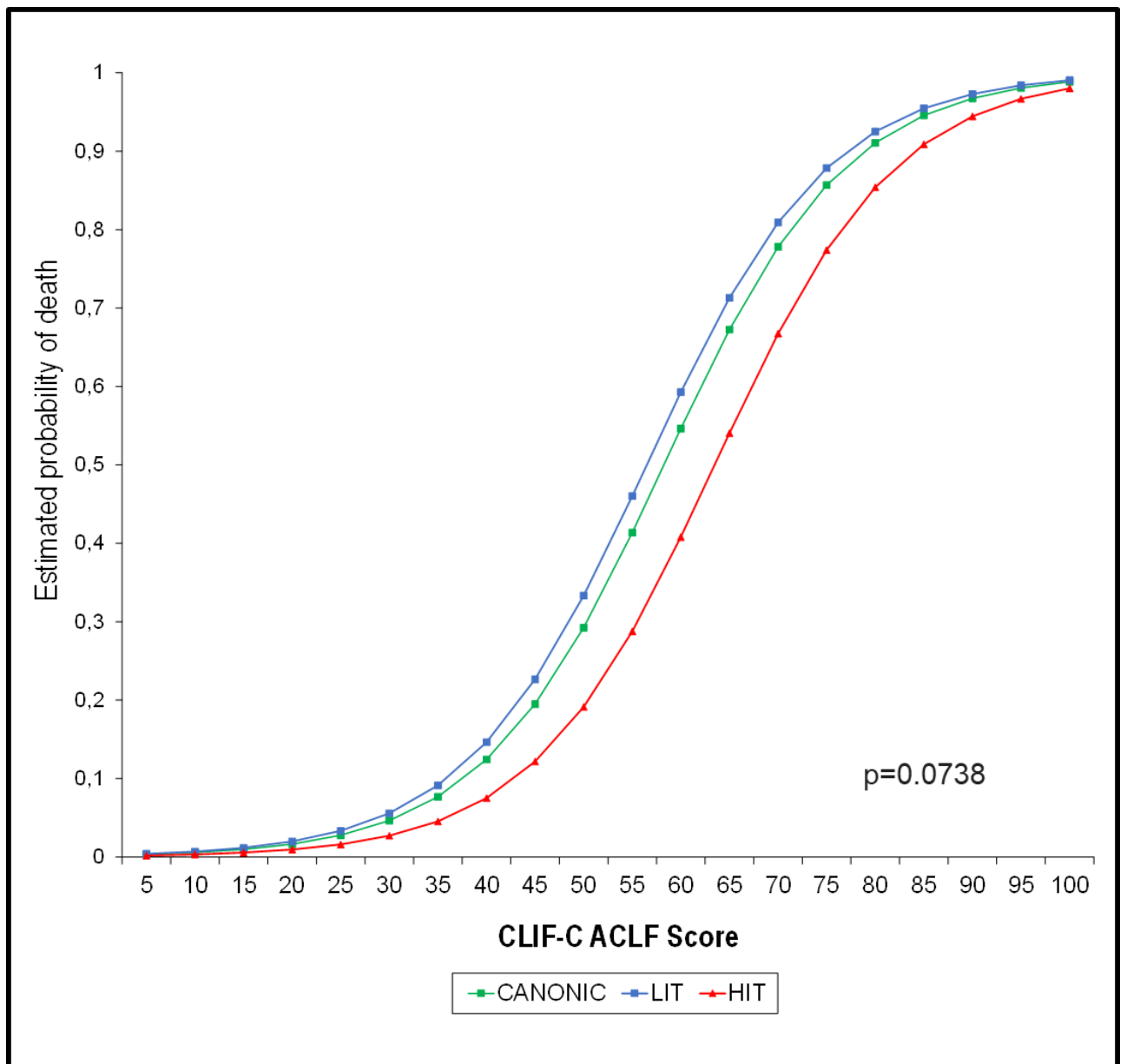
Supplementary Figure 3: 30-day survival of low-intensity and high-intensity therapy groups compared with the survival probability from the CANONIC study.

LIT: Low-Intensity Therapy. HIT: High Intensity Therapy.

Supplementary Figure 1

Supplementary figure 2

Supplementary Figure 3