Clinical Course of acute-on-chronic liver failure syndrome and effects on prognosis

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Supplementary table 1. Clinical and laboratory data at ACLF diagnosis, treatments administered and 28-day and 90-day tx-free survival in patients with ACLF-1 or ACLF-2/ACLF-3 at diagnosis who resolve the ACLF during the hospitalization.

	ACLF-1 at DX (n=110)	ACLF-2/ACLF-3 at DX (n=55)	P
28-day tx-free mortality	7/104 (6.73 %)	2/50 (4.00 %)	0.499
90-day tx-free mortality	19/95 (20.00 %)	6/47 (12.77 %)	0.287
Clinical data			
Age (years)	57.13 + 11.89	53.89 + 11.96	0.102
Alcohol (%)	56.73	63.64	0.399
HCV (%)	13.46	10.91	0.644
No prior decompensation(%)	18.27	36.54	0.012
Ascites at ACLF diagnosis (%)	71.56	79.63	0.267
Bacterial infection as PE* (%)	36.11	30.91	0.508
Active Alcoholism as PE (%)	16.00	46.00	<.0001
Laboratory data , organ failures and scores at the diagnosis of ACLF			
Leucocyte (x10^9/L)	8.72 + 5.39	9.86 + 5.21	0.115
CRP (mg/L)	38.21 + 36.55	41.31 + 49.89	0.74
Bilirubin (mg/dL)	7.26 + 9.05	11.48 + 11.20	0.002
INR	1.67 + 0.60	2.29 + 0.83	<.0001
Creatinine (mg/dL)	1.99 + 1.10	1.56 + 0.98	0.005
Na (mEq/L)	133.54 + 6.57	134.51 + 7.11	0.386
Renal failure (%)	51.82	34.55	0.036
Cerebral failure (%)	4.55	40.00	<.0001
Respiratory failure (%)	6.36	20.00	0.008

Circulatory failure (%)	6.36	34.55	<.0001
Coagulation failure (%)	7.27	47.27	<.0001
Liver failure (%)	23.64	40.00	0.03
Child-Pugh score	9.93 + 1.96	11.40 + 1.81	<.0001
MELD score	22.70 + 5.30	26.83 + 8.01	0.001
CLIF-C ACLF score	44.19 + 6.45	50.37 + 6.56	<.0001
ACLF-1(%)	110	0	<.0001
ACLF-2(%)	0	47	
ACLF-3(%)	0	8	
Treatments (%)**			
ICU admission	23.64	52.73	0.0002
Variceal bleeding ***	15.45	32.73	0.01
Antibiotics	65.45	89.09	0.001
Transfusion ****	26.36	54.55	0.0004
Vasoactive agents*****	29.09	56.36	0.0007
Mechanical ventilation	6.36	29.09	<.0001
Renal replacement	7.27	16.36	0.07

* PE means precipitating event: active alcohol as PE means within the last 3 months prior to diagnosis and bacterial infection as PE means from admission to ACLF diagnosis.

** At any time during the follow-up.

*** It includes vasoactive (somatostatin/terlipresine), endoscopic therapy and TIPS insertion

**** It includes transfusion of red cells package, fresh frozen plasma, platelets and cryoprecipitates.

***** They include any vasoactive drug used for circulatory support or hepatorenal syndrome.

Supplementary Table 2. 28-day and 90-day mortality rates based on clinical course patterns and main precipitating events (bacterial infection and/or active alcoholism within the last 3 months prior the diagnosis).

Groups (n)		Patients without bacterial infection and without active alcoholism		Patients with bacterial infection and without active alcoholism		Patients without bacterial infection and with active alcoholism		Patients with bacterial infection and active alcoholism	
Mortality rates (%)		28-day	90-day	28-day	90-day	28-day	90-day	28-day	90-day
Initial ACLF grades	1	22/95 (23.2%)	34/94 (36.2%)	11/59 (18.6%)	17/57 (29.8%)	4/20 (20.0%)	7/19 (36.8%)	5/12 (41.7%)	6/12 (50.0%)
	2	13/51 (25.5%)	18/51 (35.3%)	14/38 (36.8%)	21/38 (55.3%)	7/28 (25.0%)	12/28 (42.9%)	2/7 (28.6%)	3/7 (42.9%)
	3	10/12 (83.3%)	10/12 (83.3%)	14/20 (70.0%)	16/20 (80.0%)	6/11 (54.6%)	6/11 (54.6%)	4/7 (57.1%)	4/7 (57.1%)
d3-7 ACLF grades	0	8/62 (12.9%)	16/62 (25.8%)	3/41 (7.3%)	8/40 (20.0%)	1/23 (4.4%)	5/22 (22.7%)	0/10	0/10
	1	5/32 (15.6%)	11/31 (35.5%)	5/20 (25.0%)	9/19 (47.4%)	1/9 (11.1%)	1/9 (11.1%)	1/2 (50.0%)	2/2 (100%)
	2	9/17 (52.9%)	9/17 (52.9%)	3/15 (20.0%)	7/15 (46.7%)	7/15 (46.7%)	9/15 (60.0%)	2/2 (100%)	2/2 (100%)
	3	23/26 (88.5%)	25/26 (96.2%)	27/30 (90.0%)	28/30 (93.3%)	8/11 (72.7%)	10/11 (90.9%)	8/10 (80.0%)	9/10 (90.0%)
Final ACLF grades	0	3/68 (4.4%)	11/68 (16.2%)	3/43 (7.0%)	7/43 (16.3%)	1/29 (3.5%)	4/28 (14.3%)	0/10	0/10
	1	7/38 (18.4%)	14/37 (37.8%)	4/19 (21.1%)	7/17 (41.2%)	0/5	0/5	0/1	0/1
	2	5/18 (27.8%)	6/18 (33.3%)	4/21 (19.1%)	11/21 (52.4%)	6/13 (46.2%)	9/13 (69.2%)	2/4 (50.0%)	3/4 (75.0%)
	3	30/34 (88.2%)	31/34 (91.2%)	28/34 (82.4%)	29/34 (85.3%)	10/12 (83.3%)	12/12 (100%)	9/11 (81.8%)	10/11 (90.9%)

No statistical difference was observed.

Supplementary table 3. Predictors of severe course in patients with ACLF. Clinical course A and B: no severe course; Clinical course C and D: severe course.

	Non Severe Course (n=235)	Severe Course (n=153)	P
28-day mortality	**21 (9.5%)**	**98(73.7%)**	**<0.001**
90-day mortality	**48 (23.9%)**	**115 (91.3%)**	**<0.001**
Clinical data			
Age (years)	**56.9±12**	**53.3±10.9**	0.0027
Alcohol (%)	**59.2**	**57.7**	0.780
HCV (%)	**13.5**	**15.4**	0.592
No prior decompensation(%)	**21.6**	**31.1**	0.04
Ascites at ACLF diagnosis (%)	**75**	**85.5**	0.013
Bacterial infection as PE* (%)	**33.5**	**47.7**	0.0055
Active Alcoholism as PE (%)	**21.1**	**27.2**	0.181
Laboratory data , organ failures and scores at the diagnosis of ACLF			
Leucocyte (x10^9/L)	**9.0±5.5**	**11.2±7.2**	0.0024
CRP (mg/L)	**38.3±44.1**	**44.4±37.8**	0.027
Bilirubin (mg/dL)	**7.9±9.4**	**15.6±11.4**	<0.001
INR	**1.8±0.7**	**2.5±1.0**	<0.001
Creatinine (mg/dL)	**2.1±1.4**	**2.3±1.7**	0.7674
Na (mEq/L)	**134.0±7.0**	**132.8±6.2**	0.871
Renal failure (%)	**54.0**	**48.4**	0.274

Cerebral failure (%)	15.7	30.7	0.0005
Respiratory failure (%)	9.4	14.4	0.127
Circulatory failure (%)	13.6	23.5	0.0121
Coagulation failure (%)	19.2	42.5	<0.0001
Liver failure (%)	25.1	57.5	<0.0001
Child-Pugh score	10.3±2.1	12.1±1.5	<0.001
MELD score	24.3±6.3	30.7±6.3	<0.001
CLIF-C ACLF score	46.0±7.1	53.2±9.4	<0.001
ACLF-1(%)	67.7	28.1	<0.001
ACLF-2(%)	28.1	45.8	0.0004
ACLF-3(%)	4.3	26.1	<0.0001
Treatments (%)**			
ICU admission	36.2	75.2	<0.001
Variceal bleeding ***	20.9	26.8	0.1750
Antibiotics	74.9	90.2	0.0002
Transfusion ****	41.3	64.1	<0.0001
Vasoactive agents*****	40.0	76.5	<0.0001
Mechanical ventilation	13.6	48.4	<0.0001
Renal replacement	14.5	43.1	<0.0001

* PE means precipitating event: active alcohol as PE means within the last 3 months prior to diagnosis and bacterial infection as PE means from admission to ACLF diagnosis.

** At any time during the follow-up.

*** It includes vasoactive (somatostatin/terlipresine), endoscopic therapy and TIPS insertion

**** It includes transfusion of red cells package, fresh frozen plasma, platelets and cryoprecipitates.

***** They include any vasoactive drug used for circulatory support or hepatorenal syndrome.

Supplementary Table 4. Time course profiles in clinical course patterns. Prevalence and relation to 28-day and 90-day transplant(tx)-free mortality rates.

	n (%)	28-day tx-free Mortality	90-day tx-free Mortality
Resolution of ACLF			
Very rapid resolution	105 (63.64 %)	8/99 (8.08 %)	17/92 (18.48 %)
Rapid resolution	31 (18.79 %)	1/30 (3.33 %)	5/28 (17.86 %)
Late resolution	29 (17.58 %)	0/25 (0.00 %)	3/22 (13.64 %)
Total	**165 (42.52 %)**	**9/154 (5.84 %)**	**25/142 (17.61 %)**
Final ACLF-1			
Very rapid improvement	9 (12.86 %)	2/8 (25.00 %)	2/8 (25.00 %)
Rapid improvement	8 (11.43 %)	0/7 (0.00 %)	3/7 (42.86 %)
Late improvement	4 (5.71 %)	0/4 (0.00 %)	1/3 (33.33 %)
Steady course	31 (44.29 %)	4/29 (13.79 %)	9/26 (34.62 %)
Fluctuating course	18 (25.71 %)	6/18 (33.33 %)	8/15 (53.33 %)
Total	**70 (18.04%)**	**12/66 (18.18 %)**	**23/59 (38.98 %)**
Final ACLF-2			
Very rapid improvement	4 (6.78 %)	4/4 (100.00 %)	4/4 (100.00 %)
Late improvement	2 (3.39 %)	0/2 (0.00 %)	0/2 (0.00 %)

Very rapid worsening	11 (18.64 %)	5/9 (55.56 %)	6/8 (75.00 %)
Rapid worsening	2 (3.39 %)	0/1 (0.00 %)	0/1 (0.00 %)
Late worsening	5 (8.47 %)	3/5 (60.00 %)	4/4 (100.00 %)
Steady course	17 (28.81 %)	2/9 (22.22 %)	4/7 (57.14 %)
Fluctuating course	18 (30.51 %)	6/18 (33.33 %)	14/16 (87.50 %)
Total	**59 (15.2%)**	**20/48 (41.67 %)**	**32/42 (76.19 %)**
Final ACLF-3			
Very rapid worsening	27 (28.72 %)	24/26 (92.31 %)	26/26 (100.00 %)
Rapid worsening	16 (17.02 %)	15/15 (100.00 %)	15/15 (100.00 %)
Late worsening	17 (18.09 %)	11/15 (73.33 %)	14/14 (100.00 %)
Steady course	29 (30.85 %)	24/24 (100.00 %)	24/24 (100.00 %)
Fluctuating course	5 (5.32 %)	4/5 (80.00 %)	4/5 (80.00 %)
Total	**94 (24.22 %)**	**78/85 (91.76 %)**	**83/84 (98.81 %)**

Clinical course pattern was assessed by comparing initial and final ACLF grades. Initial ACLF grade was that measured at diagnosis of the syndrome, either at enrolment of the CANONIC study or during follow-up. Final ACLF grade was that measured at the last available assessment of organ function within the first 28-day after diagnosis, before death, liver transplantation or discharge from hospital. *Resolution* was defined by changes from ACLF-3, ACLF-2 or ACLF-1 to no ACLF. *Improvement* was defined by changes from ACLF-3 to ACLF-2 or ACLF-1 and from ACLF-2 to ACLF-1. *Worsening* was defined by changes from ACLF-1 to ACLF-2 or ACLF-3 and from ACLF-2 to ACLF-3. S*teady course* was defined by absence of change of ACLF grades during the follow-up. Finally, *fluctuating course with unchanged final ACLF grade* defined by variations of ACLF grades during the follow-up with similar initial and final grades. *Very rapid*, *rapid* or *slow* resolution, improvement or worsening when the final ACLF-grade was reached within 48 hours, 3-7 days or 8-28 days after diagnosis, respectively.

Supplementary Table 5. Pre-transplant characteristics of patients who has ACLF at diagnosis and were liver transplanted during the 28-day follow-up while exhibiting or not resolved ACLF at the time of liver transplantation.

	Patients without ACLF at the time of Transplantation (n=10)	Patients with ACLF at the time of transplantation (n=25)
Clinical data		
Age (years)	52.9 + 10.8	46.7 + 13.8
Alcohol (%)	5/9 (55.6%)	5/24 (20.8%)
HCV (%)	9/9 (100%)	7/24 (29.2%)
No prior decompensation(%)	2/10 (20%)	6/25 (24%)
Ascites at ACLF diagnosis (%)	9/10 (90%)	21/24 (87.5%)
Bacterial infection from admission to LT (%)	6/10 (60%)	19/25 (76%)
Active Alcoholism as PE (%) * §	0/9	2/23 (8.7%)
Laboratory data #		
Leucocyte (x10^9/L)	8.1 + 3.8	10.1 + 10.5
CRP (mg/L)	59.9 + 31.2	38.3 + 36.6
Bilirubin (mg/dL)	19.1 + 12.4	19.1 + 13.5

INR	1.9 + 0.4	2.9 + 1.5
Creatinine (mg/dL)	1.1 + 0.3	1.8 + 0.96
Na (mEq/L)	134.1 + 6.2	135.8 + 6.9
Renal failure (%)	0	16/25 (64.0%)
Cerebral failure (%)	0	5/23 (21.7%)
Respiratory failure (%)	0	0
Circulatory failure (%)	0	8/22 (36.4%)
Coagulation failure (%)	1/10 (10%)	15/25 (60.0%)
Liver failure (%)	6/10 (60%)	14/25 (56.0%)
Child-Pugh score	10.3 + 0.9	11.7 + 1.4
MELD score	25.8 + 3.5	34 + 6
CLIF-C ACLF score	41.0+7.4	50.3+11.6
ACLF-1 at diagnosis (%)	5/10 (50%)	7/25 (28.0%)
ACLF-2 at diagnosis (%)	5/10 (50%)	13/25 (52.0%)
ACLF-3 at diagnosis (%)	0	5/25 (20.0%)
Treatments (%) **		
ICU	5/10 (50%)	18/25 (72.0%)
Variceal bleeding ***	2/10 (20%)	2/25 (8.0%)
Antibiotics	8/10 (80%)	22/25 (88.0%)
Transfusion ****	2/10 (20 %)	13/25 (52.0 %)
Vasoactive agents *****	5/10 (50%)	13/25 (52.0%)
Mechanical ventilation	1/10 (10%)	7/25 (28.0%)
Renal replacement	0	10/25 (40.0%)

* PE means precipitating event: active alcohol as PE means within the last 3 months prior to diagnosis.

** At any time during the follow-up.

*** It includes vasoactive (somatostatin/terlipresin), endoscopic therapy and TIPS insertion

**** It includes transfusion of red cells package, fresh frozen plasma, platelets and cryoprecipitates.

***** They include any vasoactive drug used for circulatory support or hepatorenal syndrome.

§ The two liver transplanted patients with ACLF at the time of transplantation and with active alcoholism as precipitating event had severe biopsy-proven alcoholic hepatitis.

Laboratory data just prior liver transplantation

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