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Combination and sequential evaluation of acute-on-chronic liver failure (ACLF) and hyponatremia and prognosis in cirrhotic patients

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ABSTRACT

Background: Few studies have evaluated whether combination and sequential evaluation of ACLF (acute-on-chronic liver failure) and hyponatremia aids prognosis.
Aims: Describe clinical course and determine prognostic capability of assessing ACLF and hyponatremia at specific time-points.
Methods: Prospective study with inclusion of 376 patients. ACLF and hyponatremia were evaluated at days 1 and 7 and classified as persistent, transient, *de novo* or absent. Follow-up was 90 days.
Results: At inclusion, ACLF was diagnosed in 99 patients. Reversal was observed in 57 patients and was associated with lower creatinine and ACLF grade. *De novo* ACLF developed in 19 patients, and MELD (model of end-stage liver disease) score and lower albumin were predictive factors. Hyponatremia was present in 76 patients (persistent, transient and *de novo* in 27, 24 and 25 respectively). ACLF at D7 had the lowest survival compared to transient or no ACLF (21, 57 and 80%, $p < 0.0001$). Hyponatremia at admission was associated with low survival (35%) whereas survival was higher for *de novo* or absent cases (70%), $p < 0.001$. In multivariate analysis ACLF at D7 and hyponatremia at D1 were predictors of survival.
Conclusion: ACLF and hyponatremia are dynamic and evaluation of both conditions at different time-points identifies patients at higher risk of short-term mortality.

1. Introduction

Acute-on-chronic liver failure (ACLF) is an increasingly recognized syndrome that develops in cirrhotic patients, characterized by organ failure and high short-term mortality [1–6]. A potential limitation of ACLF definition is that it does not take into account serum sodium concentration. Hyponatremia has been demonstrated as a good predictor of survival in patients with liver cirrhosis independently of MELD [7–9]. There is very little data available with respect to the interaction between ACLF and hyponatremia and a potential benefit of combining both conditions in terms of prognosis [10].

ACLF and hyponatremia are potentially dynamic conditions and reversal may translate in improved survival [11]. On the contrary, development of these complications throughout hospitalization may translate into increased morbidity and mortality. Most previous studies do not differentiate ACLF and hyponatremia in terms of clinical and laboratory characteristics and prognosis, or whether they are already present at admission or develop during hospital stay. Combination and sequential assessment of these conditions at specific time-points would characterize their evolution over time and may theoretically improve prognostic capability compared to a single time-point, inclusion-based model.

The objectives of the present study were to determine: (1) course and clinical characteristics of ACLF and hyponatremia at different time-points; (2) if sequential assessment of ACLF and hyponatremia better identifies patients with increased mortality than a single evaluation; and (3) the potential benefit of the assessment of both ACLF and hyponatremia in predicting survival in decompensated cirrhosis.

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2. Patients and methods

2.1. Study design and patients

This is a prospective, observational study of patients hospitalized at ward of Gastroenterology and Hepatology Unit of Bonsucesso General Hospital during the periods of October 2011–July 2014, and March 2015–February 2017. Inclusion criteria were diagnosis of cirrhosis, defined by a combination of clinical, laboratory, histological, ultrasonographic and endoscopic criterion, and age equal to or greater than 18 years. Patients admitted for elective therapeutic interventions, like large-volume paracentesis, were not included. Patients with HIV (human immunodeficiency virus) infection, pregnancy, previous solid organ transplantation, advanced hepatocellular carcinoma (BCLC (Barcelona clinic for liver cancer) stage C or D) or extrahepatic malignancy and those with advanced cardiac or respiratory failure were excluded. Patients were followed up for 3 months or until liver transplantation or death. During study period, 538 patients were evaluated. Of those, 162 were excluded either due to the presence of at least one exclusion criteria (n = 83), lack of data (n = 67), discharge or death before 1 week of hospitalization (n = 12). The study cohort included 376 patients.

2.2. Procedures

At admission, demographic and clinical data such as prior decompensation of cirrhosis, exacerbation of liver disease (flair of hepatitis B or autoimmune hepatitis, alcoholic hepatitis with concomitant liver cirrhosis) and potential precipitating factors for ACLF (gastrointestinal hemorrhage, bacterial infections, exacerbation of liver disease) were recorded. Liver, kidney, and circulatory function as well as parameters of systemic inflammation were assessed at days 1 and 7 of hospitalization. Presence and development of complications of cirrhosis were recorded throughout hospitalization. Diagnosis and treatment of complications of cirrhosis were done according to current guidelines [12–14]. The study was conducted in accordance with Declaration of Helsinki and was approved by local Institutional Review Board. Written informed consent was given by patients or a legal surrogate before inclusion.

2.3. Definitions

Acute-on-chronic liver failure (ACLF) was defined and graded according to CLIF C OF score [3].

Renal failure was defined as a serum creatinine value greater than 1.5 mg/dL [12,13].

Hyponatremia was defined by a serum sodium concentration lower than 130 mEq/L and classified as severe if lower than 125 mEq/L.

Presence of ACLF and hyponatremia was assessed at day 1 and day 7 of hospitalization and clinical course was characterized according to the following definitions: persistent: present at days 1 and 7; transient: present at day 1 but not at day 7; *de novo*: absent at day 1 but present at day 7; absent: absent at days 1 and 7.

2.4. Statistical analysis

Categorical variables were described as frequencies and percentages and compared using chi-square test. Continuous variables were described as means and standard deviations and compared using Student's t test. Factors associated with ACLF development and reversal were selected in univariate analysis and multivariate analysis using a stepwise logistic regression model.

Factors independently associated with 3-month survival were selected in univariate and multivariate analysis using Cox-regression method. Survival curves were constructed using the Kaplan–Meier method and comparisons were performed using the log-rank test. Prognostic capability of survival models using different combinations of ACLF and hyponatremia status was evaluated using ROC (receiver operating characteristic) curves. For surviving purposes, patients were censored at time of transplantation. In all analysis, a significance threshold of $p < 0.05$ was considered. Statistical analysis was performed using the IBM SPSS 21 for Windows program.

Table 1
Baseline characteristics of the 376 patients.

Age	56 ± 14
Male gender	206 (55%)
Etiology of cirrhosis	
Hepatitis C	121 (32%)
Alcohol	84 (22%)
HCV (hepatitis C virus) + alcohol	38 (10%)
Cryptogenic/NASH (non-alcoholic steatohepatits)	57 (15%)
Other	76 (20%)
Previous decompensations	
Ascites	244 (69%)
Hepatic encephalopathy	103 (28%)
Esophageal variceal bleeding	99 (27%)
Spontaneous bacterial peritonitis	24 (6%)
Any previous decompensation	287 (76%)
Complications at admission	
Ascites	251 (67%)
Hepatic encephalopathy	123 (33%)
Renal failure	109 (29%)
Gastrointestinal bleeding	52 (14%)
Bacterial infections	189 (50%)
Clinical and laboratorial data	
Mean arterial pressure (mmHg)	89 ± 15
Heart rate (bpm)	79 ± 14
AST (aspartate transaminase) (U/L)	94 ± 135
ALT (alanine transaminase) (U/L)	60 ± 91
Gamma glutamyltranspeptidase (U/L)	191 ± 244
Bilirubin (mg/dL)	3.3 ± 4.8
Albumin (g/L)	25 ± 6
International normalized ratio	1.5 ± 0.5
Creatinine (mg/dL)	1.5 ± 1.2
Sodium (mEq/L)	135 ± 6
Potassium (mEq/L)	4.3 ± 0.7
Hemoglobin (g/dL)	10.4 ± 2.7
Platelet count ($\times 10^9$/L)	134 ± 97
Leucocyte count ($\times 10^9$/L)	6.6 ± 4.1
C-reactive protein (mg/dL)	5.9 ± 12.1
Child–Pugh score	9 ± 2
A/B/C-(%)	30 /207/139 (8/55/37)
MELD score	17 ± 7
SIRS (systemic inflammatory response syndrome)	48/230 (21%)
ACLF	99 (26%)
(grade I/II/III)	88/10/1

3. Results

3.1. Characteristics of patients

The characteristics of the 376 patients at study inclusion are shown in Table 1. The majority of patients were male, had cirrhosis due to Hepatitis C and/or alcohol and had prior decompensation of disease. Ascites and hepatic encephalopathy were the most common complications at hospital admission, observed in 291 patients (77%). Presence of any precipitating event for ACLF was observed in 249 (66%) patients, and in 26 cases (7%), more than one factor was observed.

3.2. ACLF-prevalence, incidence and clinical evolution

At day 1, 99 patients (26%) were diagnosed with ACLF. The mean CLIF C OF score was 8.9 ± 1.4 (*versus* 6.5 ± 0.8 for patients without

ACLF, $p < 0.001$) and ACLF was classified as grade I in 88 patients. The most common type of organ failure was kidney, liver and cerebral failure, present in 79, 14 and 11 patients respectively. Cerebral dysfunction was frequently observed (42 patients).

At day 7, ACLF was still present in 57 patients (persistent ACLF) and was reversed in the remaining 42 patients (transient ACLF). Of those patients with persistent ACLF, 7 of the 47 patients with ACLF grade I at day 1 had progressed to grade II by day 7 (15%), whereas 4 of the 10 patients with grade II/III had improved to grade I ACLF ($p = 0.006$). Additionally, 19 out of 279 patients (7%) without ACLF at day 1 developed it within the first week of hospitalization (*de novo* ACLF). Overall, the prevalence of ACLF at day 7 was 20%.

Table 2 shows the clinical characteristics of patients with and without ACLF at different time points. At day 1, ACLF patients were older, predominantly male with alcoholic etiology and had more frequently presented prior decompensation of cirrhosis and precipitating events. Prevalence of ascites, hepatic encephalopathy and bacterial infections was higher in these patients. Presence of ACLF was associated with more severe liver, kidney and coagulation dysfunction, as evidenced by higher values of serum bilirubin, creatinine and INR (international normalized ratio), and lower values of albumin. Patients with ACLF also showed signs of more severe systemic inflammation, with higher leucocyte count. Interestingly, serum sodium values were lower and prevalence of hyponatremia higher in patients with ACLF, showing a correlation between these 2 conditions. On the other hand, presence of ACLF at day 7 was associated with different clinical characteristics. There was no correlation with gender, alcoholic etiology or precipitating events. Presence of ACLF was associated with significant changes in liver, kidney and cerebral function, and higher frequency of cardiorespiratory failure. Notably, presence of ACLF was correlated with strikingly higher leucocyte count. Similar to what was observed at day 1, serum sodium levels were lower, and hyponatremia was more frequent in patients with ACLF at day 7.

In order to identify possible predictors of reversal of ACLF, we compared the baseline characteristics of patients with persistent and transient ACLF (Supplementary Table S1). Reversal of ACLF was achieved by 41/88 patients with grade I but in only 1 of the 11 patients with grade II/III ACLF at D1 ($p = 0.022$). In multivariate analysis, only serum creatinine (OR (odds-ratio) 2.73 (95% CI (confidence interval) 1.58–3.84), $p < 0.001$) and D1 ACLF grade II/III (OR 18.03 (95% CI 1.49–210.9), $p = 0.023$) were predictors of ACLF persistence.

We also evaluated the predictors of ACLF development within the first 7 days of hospitalization. Supplementary Table S2 shows the baseline differences between patients without ACLF and *de novo* ACLF. The only independent predictors of ACLF development were MELD score (OR 1.19 (95% CI 1.07–1.32), $p = 0.001$) and serum albumin (OR 0.89 (95% CI 0.81–0.98), $p = 0.026$).

3.3. Hyponatremia-prevalence, incidence and clinical evolution

At hospital admission, hyponatremia was present in 51 (13%) patients (serum sodium concentration 125 ± 5 mEq/L *versus* 137 ± 4 mEq/L in patients without hyponatremia, $p < 0.0001$) and was classified as severe in 20 patients (39). At day 7, hyponatremia was classified as persistent in 27 and as transient in 24 patients. Patients with transient hyponatremia showed an increase in serum sodium concentration of 9 ± 6 mEq/L, with a final value of 135 ± 5 mEq/L. Corresponding values for patients with persistent hyponatremia were 2 ± 6 and 125 ± 3 mEq/L ($p < 0.0001$ for both comparisons).

At the end of first week of hospitalization, 25 out of 325 patients (7%) with serum sodium above 130 mEq/L at day 1 developed hyponatremia (*de novo* hyponatremia). Patients with *de novo* hyponatremia had a mean decrease in serum sodium concentration of 8 ± 3 mEq/L and a final value of 127 ± 3 mEq/L ($p = 0.062$ *versus* patients with persistent hyponatremia). Prevalence of hyponatremia at day 7 was similar to that observed on day 1 (14% and 13% respectively). However, severe hyponatremia was less common at this time point (39% *vs* 43% on day 1, p = NS). Overall, 76 patients (20%) presented hyponatremia within the first 7 days of hospitalization.

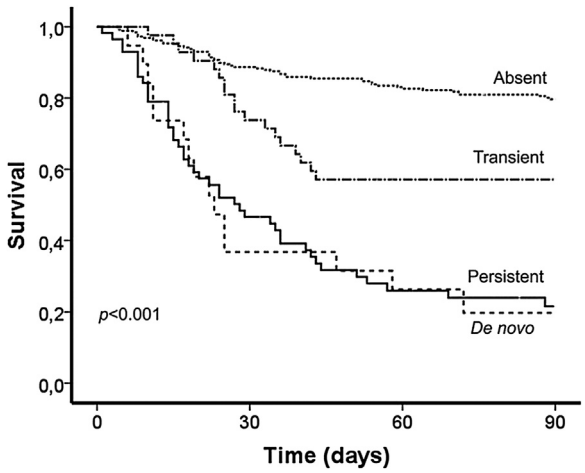

Fig. 1. Survival according to ACLF evolution.

Table 3 shows the clinical characteristics of patients with and without hyponatremia at different time points. Patients with hyponatremia on day 1 more frequently had prior decompensation of disease and presented more commonly with complications of cirrhosis. There was also a correlation between hyponatremia and worse liver, kidney and circulatory function, as well as higher frequency of bacterial infections and leucocyte count. Notably, ACLF was twice as common in patients with hyponatremia, mostly due to an increased prevalence of kidney and coagulation failure and cerebral failure/dysfunction. On the contrary, hyponatremia at day 7 was not associated with previous decompensation or current complications of cirrhosis, except for hepatic encephalopathy. In addition, there was no association between liver and circulatory function. Similar to what was observed on day 1, patients with hyponatremia at day 7 more commonly had ACLF than those without, mostly due to higher frequency of kidney and cerebral failure. There was also an association between the severity of hyponatremia and ACLF

3.4. Survival

Hospital mortality was 24% (92 patients) and median length of hospitalization was 16 [10–20] days. The most common cause of death was severe sepsis, being present in 60 patients (65%), associated with MODS and refractory septic shock in 37 and 13 patients respectively. At the end of 90 days, 214 patients were alive (57%), 10 were transplanted (3%), 34 (9%) were lost on follow-up (median follow-up 55 (33–76) days) and 118 (31%) died. The overall 90-day probability of transplant-free survival was 65%.

Fig. 1 shows the probability of survival according to clinical evolution of ACLF. The presence of ACLF at day 7, either persistent or *de novo*, was associated with a very low probability of survival. Among patients with persistent ACLF, survival was higher for those with grade I compared to grade II/III ACLF at day 7 (28 *vs* 0%, $p < 0.001$). Conversely, patients who did not develop ACLF within the first week of hospitalization had a good prognosis. Finally, patients with transient ACLF, in spite of having a much higher survival than patients with ACLF at day 7, showed a noticeably lower survival than patients without ACLF.

Table 2
Clinical features associated with ACLF at days 1 and 7.

	Day 1			Day 7		
	ACLF			ACLF		
	Yes (n = 99)	No (n = 277)	p-Value	Yes (n = 76)	No (n = 300)	p-Value
Age (years)	61 ± 11	55 ± 14	<0.001	61 ± 9	56 ± 14	<0.001
Male sex	66 (67%)	140 (50%)	0.006	45 (59%)	161 (54%)	0.38
Alcoholic ethology	47 (48%)	79 (29%)	0.001	29 (38%)	97 (32%)	0.33
Hepatitis C	42 (42%)	117 (42%)	0.97	34 (45%)	125 (42%)	0.63
Previous decompensation	88 (91%)	199 (72%)	<0.001	65 (86%)	222 (75%)	0.028
Ascites	75 (76%)	176 (64%)	0.027	67 (88%)	216 (72)%	0.004
Hepatic encephalopathy	55 (56%)	68 (25%)	<0.001	52 (68%)	111 (37%)	<0.001
GI bleeding	9 (9%)	43 (15%)	0.11	14 (18%)	66 (22%)	0.49
Bacterial infections	63 (63%)	126 (46%)	0.003	54 (83%)	144 (51%)	<0.001
Renal failure	76 (77%)	33 (12%)	<0.001	71 (93%)	89 (30%)	<0.001
Precipitating events	75 (76%)	174 (63%)	0.019	55 (72%)	194 (65%)	0.20
Exacerbation of liver disease	10 (10%)	13 (5%)	0.054	6 (8%)	17 (6%)	0.47
Hyponatremia	22 (22%)	29 (11%)	0.003	16 (21%)	36 (12%)	0.041
MAP (mean arterial pressure) (mmHg)	87 ± 14	89 ± 15	0.31	85 ± 14	87 ± 13	0.17
Heart rate (bpm)	77 ± 13	80 ± 15	0.069	74 ± 14	74 ± 14	0.99
Bilirubin (mg/dL)	5.3 ± 7.6	2.6 ± 3.0	0.001	5.5 ± 8.2	2.6 ± 3.9	0.005
Albumin (g/L)	23 ± 6	25 ± 7	0.05	24 ± 89	25 ± 64	0.43
INR	1.7 ± 0.8	1.5 ± 0.3	0.015	1.9 ± 1.0	1.5 ± 0.3	<0.001
AST (U/L)	111 ± 199	88 ± 105	0.32	105 ± 134	90 ± 135	0.43
ALT (U/L)	66 ± 136	57 ± 69	0.40	61 ± 80	59 ± 94	0.86
Creatinine (mg/dL)	3.0 ± 1.7	1.0 ± 0.3	<0.001	3.2 ± 1.7	1.0 ± 0.3	<0.001
Sodium (mEq/L)	133 ± 19	136 ± 5	0.009	135 ± 7	136 ± 6	0.52
Potassium (mEq/L)	4.6 ± 0.9	4.2 ± 0.6	0.001	4.5 ± 0.9	4.3 ± 0.6	0.024
Hemoglobin (g/dL)	103 ± 34	104 ± 24	0.9	95 ± 39	104 ± 50	0.18
Platelet count ($\times 10^9$/L)	127 ± 67	136 ± 106	0.34	123 ± 76	129 ± 100	0.63
Leucocyte count ($\times 10^9$/L)	8.6 ± 5.3	6.2 ± 14	<0.001	9.9 ± 7.4	5.6 ± 3.2	<0.001
C-reactive protein (mg/dL)	5.6 ± 4.1	6.0 ± 13.9	0.76	4.4 ± 3.8	10.3 ± 56	0.54
Child–Pugh	10 ± 2	9 ± 2	<0.001	10 ± 2	8 ± 2	<0.001
MELD	24 ± 6	14 ± 4	<0.001	24 ± 7	14 ± 4	<0.001
MELD–Na	26 ± 6	17 ± 5	<0.001	28 ± 7	17 ± 7	<0.001
SIRS	16/66 (24%)	32/164 (20%)	0.42	14/46 (30%)	39/187 (21%)	0.16
Organ failure						
Liver	14 (15%)	5 (2%)	<0.001	9 (13%)	9 (3%)	0.004
Kidney	79 (80%)	0 (0%)	<0.001	63 (80%)	0 (0%)	<0.001
Cerebral	11 (11%)	3 (1%)	<0.001	14 (19%)	2 (1%)	<0.001
Coagulation	7 (8%)	0 (0%)	<0.001	11 (16%)	3 (1%)	<0.001
Circulatory	0 (0%)	0 (0%)	NA	7 (9%)	0 (0%)	<0.001
Respiratory	1 (1%)	0 (0%)	0.26	8 (10%)	0 (0%)	<0.001
Grade II/III ACLF	11 (11%)	–	–	19 (25%)	–	
Clif C OF	8.4 ± 1.3	6.5 ± 0.8	<0.001	9.3 ± 2.5	6.4 ± 0.7	<0.001

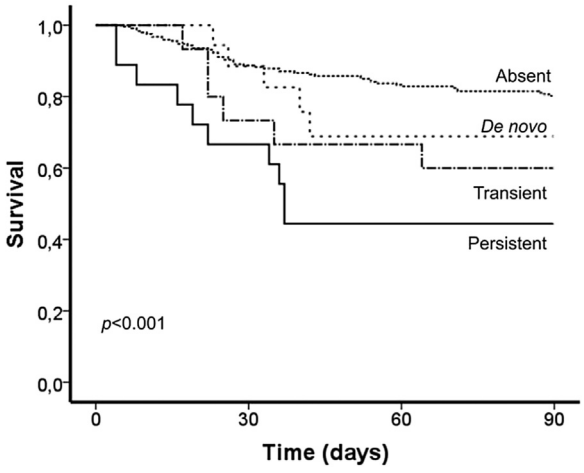

Fig. 2. Survival according to evolution of hyponatremia.

Fig. 2 shows the survival according to presence of hyponatremia at different time points. Patients with hyponatremia on day 1 had a very low probability of survival at 3-months, and this remained true even in the case of reversal of hyponatremia at day 7. On the contrary, absence of hyponatremia at day 1 conveys higher survival. Interestingly, prognosis remained good even for patients who developed hyponatremia within the first week of hospitalization, as demonstrated by the almost identical survival of patients without or *de novo* hyponatremia.

Univariate analysis showed that presence of ACLF, hyponatremia, age, alcoholic etiology, previous decompensation, ascites at inclusion, albumin, MELD, Child score leucocyte and platelet count were associated with 3-month survival. Among different combinations of ACLF and hyponatremia, the model including D7 ACLF and D1 hyponatremia showed the highest prognostic capability (AUROC 0.80, 95% CI 0.75–0.85, $p < 0.0001$). The corresponding AUROC for D7 ACLF and D1 hyponatremia was 0.70 (95% CI 0.64–0.76, $p < 0.0001$) and 0.59 (95% CI 0.53–0.65, $p = 0.03$). In multivariate analyses, ACLF at day 7 (HR (Hazard Ratio) 4.71, 95% CI 3.10–7.16, $p < 0.001$), transient ACLF (HR 1.79, 95% CI 1.008–3.18, $p = 0.047$) and hyponatremia at day 1 (HR 2.21, 95% CI 1.45–3.37, $p < 0.001$), as well as ascites (HR 2.19, 95% CI 1.33–3.63, $p = 0.002$) and leucocyte count (HR 1.042, 95%CI 1.002–1.082, $p = 0.037$) at day 1, were independent predictors of survival.

The effect of combination of ACLF and hyponatremia on survival is shown in Fig. 3. Presence of both D7 ACLF and hyponatremia at day 1, although uncommon, was associated with very low survival. Patients with D7 ACLF who did not present hyponatremia on day 1 still had a low probability of survival. Due to similarities in prognosis, patients with either D1 hyponatremia without ACLF

Table 3
Clinical features associated with hyponatremia at days 1 and 7.

	Day 1			Day 7		
	Hyponatremia			Hyponatremia		
	Yes (n = 51)	No (n = 325)	p-Value	Yes (n = 52)	No (n = 324)	p-Value
Age (years)	57 ± 14	55 ± 14	0.89	57 ± 13	57 ± 14	0.81
Male sex	29 (57%)	177 (54%)	0.74	32 (62%)	174 (54%)	0.29
Alcoholic ethology	21 (41%)	105 (32%)	0.13	19 (37%)	107 (33%)	0.19
Hepatitis C	15 (29%)	144 (44%)	0.045	13 (25%)	146 (45%)	0.007
Previous decompensation	46 (90%)	241 (75%)	0.017	43 (84%)	244 (76%)	0.19
Ascites	40 (78%)	65%	0.057	44 (86%)	234 (74%)	0.09
Hepatic encephalopathy	30 (59%)	93 (29%)	<0.001	32 (62%)	131 (40%)	0.004
GI bleeding	2 (4%)	50 (15%)	0.027	10 (19%)	70 (22%)	0.7
Bacterial infections	37 (73%)	152 (47%)	<0.001	35 (69%)	161 (55%)	0.076
Renal failure	20 (39%)	89 (28%)	0.081	28 (54%)	132 (40%)	0.076
Precipitating	40 (78%)	209 (64%)	0.047	33 (64%)	216 (67%)	0.65
Exacerbation	6 (12%)	17 (5%)	0.11	3 (6%)	20 (6%)	0.91
MAP (mmHg)	82 ± 11	90 ± 15	<0.001	85 ± 14	87 ± 12	0.19
Heart rate (bpm)	81 ± 15	78 ± 14	0.19	73 ± 14	74 ± 13	0.59
Bilirubin (mg/dL)	5.4 ± 6.9	2.9 ± 4.3	0.017	4.5 ± 6.9	3.0 ± 4.9	0.15
Albumin (g/L)	23 ± 6	25 ± 6	0.046	23 ± 8	25 ± 6	0.48
INR	1.8 ± 0.8	1.5 ± 0.4	0.011	1.7 ± 0.6	1.6 ± 0.6	0.19
AST (U/L)	98 ± 81	93 ± 141	0.72	93 ± 136	99 ± 172	0.81
ALT (U/L)	67 ± 90	58 ± 91	0.51	54 ± 70	58 ± 91	0.76
Creatinine (mg/dL)	1.9 ± 1.4	1.5 ± 1.2	0.033	1.8 ± 1.5	1.4 ± 1.2	0.082
Sodium (mEq/L)	125 ± 5	137 ± 4	<0.001	126 ± 3	137 ± 4	<0.001
Potassium (mEq/L)	4.7 ± 0.8	4.3 ± 0.7	0.001	4.6 ± 0.7	4.3 ± 0.7	<0.001
Hemoglobin (g/dL)	110 ± 21	103 ± 28	0.078	102 ± 23	102 ± 52	0.99
Platelet count (10^9/L)	127 ± 79	135 ± 100	0.34	131 ± 98	127 ± 96	0.80
Leucocyte count (10^9/L)	9.3 ± 6.7	6.4 ± 6.7	0.001	8.2 ± 6.1	6.2 ± 4.5	0.039
C-reactive protein (mg/dL)	5.0 ± 4.1	6.0 ± 12.9	0.70	5.8 ± 7.1	9.5 ± 55.4	0.75
Child–Pugh	10 ± 2	9 ± 2	<0.001	10 ± 2	9 ± 2	0.04
MELD	22 ± 8	16 ± 6	<0.001	19 ± 8	16 ± 7	0.04
MELD–Na	28 ± 5	18 ± 6	<0.001	26 ± 5	18 ± 7	<0.001
SIRS	9/34 (27%)	39/196 (20%)	0.42	2/33 (15%)	48/200 (24%)	0.26
ACLF	22 (43%)	77 (24%)	0.003	13 (31%)	60 (19%)	0.041
Organ failure						
Liver	5 (10%)	14 (4%)	0.15	4 (9%)	14 (5%)	0.25
Kidney	17 (33%)/14 (8%	62 (19%)/71 (22%)	0.06	15 (32%)	48 (16%)	0.02
Failure/dysfunction				5 (11%)	28 (9%)	
Cerebral	1 (2%)/(27 (52%))	13 (4%)/	<0.001	2 (4%)	14 (5%) 34 (11%)	0.03
Failure/dysfunction		(71 (22%))		14 (29%)		
Coagulation	3 (6%)	5 (2%)	<0.001	3 (7%)	11 (4%)	0.42
Circulatory	0 (0%)	0 (0%)	NA	1 (2%)	6 (2%)	0.95
Respiratory	1 (1%)	0 (0%)	0.26	1 (2%)	6 (2%)	0.96
Grade II/III ACLF	2 (9%)	9 (12%)	1.00	3 (19%)	16 (27%)	0.24
Clif C OF	7.6 ± 1.4	6.9 ± 1.2	0.001	7.6 ± 1.8	6.9 ± 1.7	0.007

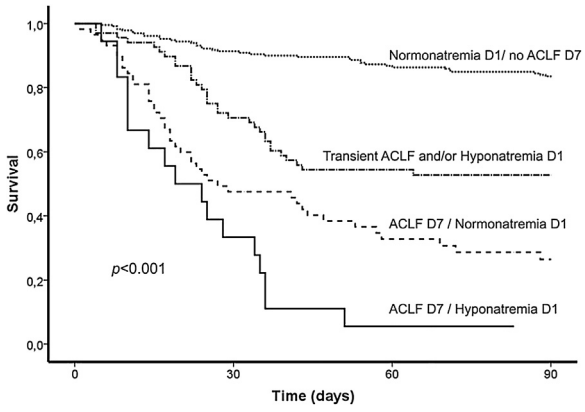

Fig. 3. Survival according to presence of ACLF and hyponatremia at different time points: ACLF D7/hyponatremia D1 (18 patients), ACLF D7/normonatremia D1 (58 patients); transient ACLF and/or hyponatremia D1 (68 patients), normonatremia D1/no ACLF D7 (232 patients), $p < 0.001$.

and those with transient ACLF (n = 68, both conditions in 7 patients) were grouped together. In patients without ACLF within first week of hospitalization, presence of hyponatremia on day 1 had a strong association with prognosis. Even in absence of ACLF, patients with hyponatremia at hospitalization had a survival probability closer to 50%, similar to patients with transient ACLF. Finally, patients without any of these complications constituted the group who had the best prognosis.

4. Discussion

The current study evaluated the presence and clinical course of both ACLF and hyponatremia, and their correlation with prognosis in a large cohort of cirrhotic patients. In the current study, we observed substantial differences in terms of frequency and evolution between ACLF and hyponatremia.

ACLF was present in almost one quarter of patients at hospital admission, a frequency similar to other studies [2,15,16]. In contrast to previous studies, the majority of patients were classified as grade I. There are several possible explanations for this discrepancy. Only patients admitted to regular ward were included, while previous studies also included patients initially admitted to ICU (intensive care unit). In most centers, cirrhotic patients are hospitalized in regular wards and this is probably a more realistic representation of the syndrome's prevalence. Nevertheless, a smaller European study with patients exclusively admitted to regular ward, authors observed a higher of frequency of cerebral and coagulation failure,

grade II/III ACLF and a lower number of patients with kidney failure [17]. In this study, the majority of patients had alcoholic cirrhosis presenting with the first decompensation of disease, and these are factors associated with more severe presentation. Our cohort was mainly composed of hepatitis C patients, an etiology associated with lower frequency of ACLF [15]. These data suggest that ACLF in patients with hepatitis C may have distinct clinical features and highlight the subtle differences of ACLF in specific populations.

ACLF is a dynamic condition and short-term (*i.e.*, 1 week) changes exerted a strong effect upon prognosis. The syndrome was reversible in almost 45% of patients within 7 days and reversibility was associated with improved survival.

The dynamism of ACLF has previously been demonstrated [18]. In this study, reversibility of ACLF was observed in a significant proportion of patients (42%) and was associated with improved prognosis. Also, ACLF grade at day 3–7, but not upon diagnosis, was the best predictor of survival, highlighting the superiority of assessing ACLF at different time-points early in the course of hospitalization rather than at initial moment alone.

This was achieved without any treatment directed specifically towards ACLF itself and corroborates the finding that regular management of complications of cirrhosis is appropriate for reversal of ACLF in a significant number of patients. Nevertheless, timely identification and proper treatment are crucial, as the presence of higher grades of ACLF and worse kidney function were associated with lower probability of reversal. This has recently been reported for patients with hepatorenal syndrome, for whom response to treatment with terlipressin and albumin was negatively related to ACLF grade [19].

Development of *de novo* ACLF was unusual, accounting for less than 10% of patients. This frequency is lower than previously reported, but in these studies the frequency was not evaluated within a defined period, but during the entire hospitalization period. Higher MELD score and lower albumin were associated with development of ACLF. MELD has previously been associated with higher frequency of bacterial infection [20] — a well-known precipitating for ACLF — and albumin infusion with improvement in kidney function [21]. These parameters may be useful for identification of patients at risk and for selection of potential candidates for future trials of ACLF prophylaxis.

Hyponatremia was diagnosed at hospital admission in 13% of patients, and approximately 50% of patients had resolution of hyponatremia within the first week of hospitalization — a surprisingly high frequency —, about twice as common as reported for placebo group and slightly inferior to that observed in treatment with vaptans [22,23]. Reversal was achieved without any specific treatment other than hypotonic fluid restriction, and irrespective of hyponatremia severity. This highlights the importance of correcting potential precipitating events (which are very similar to those of ACLF), through successful management of this complication, even in more severe cases. Development of hyponatremia was uncommon and overall frequency of hyponatremia after 1 week was 20%, similar to that reported in decompensated cirrhotic populations [24,25].

Sequential evaluation of ACLF turned out to be very useful and suggest that substantial differences in terms of risk factors and clinical characteristics between ACLF at days 1 and 7.

Day 1 ACLF was associated with a number of epidemiological and clinical characteristics, some of them well known, such as a higher frequency in cases of alcoholic cirrhosis. Surprisingly, ACLF was more common in patients with prior decompensation of cirrhosis, in contrast to previous descriptions [2]. Access to health-care systems may account for this difference and explain the effect of prior decompensation in distinct populations. In contrast, ACLF at day 7 was most associated with higher frequency of bacterial infections, more intense systemic inflammation, as well as higher frequency of cardio respiratory failure and more severe presentation. This may be explained by the worsening of organ failure in patients with persistent ACLF but in large part by the appearance of new cases of ACLF. Patients with *de novo* ACLF had the highest leukocyte count and accounted for the vast majority of cases of cardiorespiratory failure (data not shown). One can speculate these cases are largely due to nosocomial infections, which are commonly associated with multi-resistant bacteria, higher frequency of shock and death. Not surprisingly, worse liver and kidney function as evidenced by MELD and serum albumin — well-known risk factors for bacterial infections — were predictors of ACLF development. The prognosis of patients with day 7 ACLF was extremely poor and, as previously demonstrated, these patients should be urgently evaluated for liver transplantation, as this is associated with higher survival [18].

On the other hand, hyponatremia as a prognostic indicator seems to be restricted to its status at the time of hospitalization. Irrespective of resolution, presence of hyponatremia on D1 is associated with high mortality. Conversely, development within the first week was not associated with lower survival. A careful look at clinical characteristics of hyponatremia on days 1 and 7 possibly explains these findings. Hyponatremia on D1 was associated with worse liver, kidney and circulatory function, as well as systemic inflammation and bacterial infections. On the contrary, at D7 hyponatremia was only associated with hepatic encephalopathy and leucocyte count. These results argue in favor of hyponatremia on D1 as a consequence of non-osmolar secretion of ADH in the context of derangement of circulatory function likely triggered or exacerbated by bacterial infections. Conversely hyponatremia at D7 may be in large part due to iatrogenic reasons, such as over-administration of hypotonic IV solutions and/or diuretics and may not reflect a true circulatory disfunction. Not surprisingly, in this scenario hyponatremia may not be associated with prognosis, as described in patients treated with terlipressin for varicose upper GI (gastrointestinal) bleeding [26].

Finally, we were able to demonstrate that assessment of both conditions is important. There was a clear association of ACLF and hyponatremia, as evidenced by a higher frequency of hyponatremia in ACLF patients and *vice-versa* and poor prognosis in patients with these two conditions. Even in the absence of ACLF, serum sodium identifies a subgroup of patients with acute decompensation that deserve attention due to a high mortality rate. Finally, prognosis is good in the absence of both complications after 1 week of evaluation.

In conclusion, hyponatremia and ACLF are common in cirrhotic patients and are frequently associated complications of cirrhosis. Nevertheless, they have distinct risk factors and time-trends. Evaluation of both conditions in a sequential manner is better than a time-point assessment and properly identifies three distinct subgroups of cirrhotic patients in terms of prognosis.

Conflict of interest

None declared.

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Ethical statement

This study was approved with a waiver of informed consent by the Ethical Committee from Hospital Federal de Bonsucesso (IRB 01112912.5.0000.5253).

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.dld.2019.08.013.

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