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Acute-on-chronic liver failure is independently associated with lower survival in patients with spontaneous bacterial peritonitis

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ABSTRACT – **Background** – Spontaneous bacterial peritonitis (SBP) is a decompensation of cirrhosis with an in-hospital mortality ranging from 20% to 40%. **Objective** – The purpose of this study is to analyze if EASL-CLIF definition of acute-on-chronic liver failure (ACLF) is able to predict mortality in cirrhotic patients with SBP. **Methods** – Historical cohort study conducted in a public tertiary care teaching hospital. Data from medical records from January 2009 to July 2016 were obtained by searching the hospital electronic database for samples of ascites collected in the period. Electronic and physical medical records were analyzed and patients were included if they were over 18-years old, with cirrhosis and an ascites fluid compatible with SBP: 69 patients were included. Liver-specific scores were calculated and Kaplan-Meier survival analysis was used for univariate analysis and a stepwise approach to the Cox regression for multivariate analysis. **Results** – All cause mortality was 44%, 56.5% and 74% for 28-, 90- and 365-day, respectively. The prevalence of ACLF was 58%. Of these, 65% grade 1, 17.5% grade 2 and 17.5% grade 3. In multivariate analysis, the use of proton-pump inhibitors, alanine transaminase lower than 40 U/L, hemoglobin higher than 9 g/dL, absence of ACLF and lower CLIF-SOFA and MELD scores were independently associated with higher survival for both 28- and 90-day interval. **Conclusion** – The presence of ACLF and higher CLIF-SOFA scores were independently associated with higher 28- and 90-day mortality in cirrhotic patients admitted due to SBP.

Keywords – Liver cirrhosis; spontaneous bacterial peritonitis; end stage liver disease; organ dysfunction scores; prognosis; acute-on-chronic liver failure.

INTRODUCTION

Spontaneous bacterial peritonitis (SBP) is the most important infection of the cirrhotic patient with ascites, accounting for 24% of infections in these patients, carrying an inpatient prevalence of around 10%[1-3]. Although therapy has greatly improved, with the use of albumin[4] and broad spectrum antibiotics, the prognosis of SBP remains poor, with an in-hospital mortality revolving around 20% to 40%[5]. Therefore, the first episode of SBP should prompt referral for liver transplantation evaluation and the use of prophylactic antibiotics indefinitely[6].

The presence of ascites defines cirrhosis as decompensated. When SBP takes place, it is still defined as decompensated cirrhosis (DC), although SBP impairs prognosis greatly. A new concept, acute-on-chronic liver failure (ACLF), has been welcomed as an additional step between cirrhosis and death, which is characterized by multi-organ failure[7]. Although such concept has been introduced and discussed some time ago in an innovative supplement bridging the gap between hepatology and intensive care[8-14], a definitive definition of ACLF has only been introduced by the multi-centric prospective study CANONIC, developed in Europe and published in 2013[15].

The European Society for the Study of the Liver – Chronic Liver Failure Group (EASL-CLIF) adapted the Sequential Organ Failure Assessment (SOFA) score used by Intensive Care into the Chronic Liver-Failure – Sequential Organ Failure Assessment (CLIF-SOFA) score, which divided systems as sufficient or insufficient, stratifying patients either as DC or ACLF. ALCF was further stratified into three grades, which were independently associated with 28 and 90-day mortality[15].

Clinical factors that could predict prognosis for SBP patients has been already extensively studied. Age, serum bilirubin, serum creatinine, higher Model for End-Stage Liver Disease (MELD), integrated MELD (iMELD) and higher Child-Turcotte-Pugh (CTP) scores have been independently associated with higher mortality in patients with SBP[5,16-22].

The purpose of the present study is to analyze the association between ACLF and death in cirrhotic patients admitted with SBP in a teaching hospital in Brazil.

METHODS

Study population

The Research Ethics Committee of the hospital approved the study on September 2016, under protocol no. 56574016.0.0000.5341. Data from medical records from January 2009 to July 2016 were

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gathered, searching through the electronic database of the hospital for every ascites fluid collected. Electronic and physical medical records were analyzed and a data collection form was filled for each patient. Patients over 18 years old with the diagnosis of cirrhosis supported by laboratory and imaging data were included. SBP was defined as a neutrophil count equal or higher to 250/mm^3, without any other clinical or laboratory finding that suggested the diagnosis of secondary bacterial peritonitis. Patients were excluded if they did not have a diagnosis of cirrhosis, had incomplete medical records or a diagnosis for the ascites fluid infection other than SBP. Data regarding clinical and laboratory variables were gathered in order to calculate liver-specific scores and define the presence of ACLF and its grade.

Variables

Data was gathered through the analysis of electronic and physical medical records. Clinical data was obtained and each case was individually assessed. Standardized imaging criteria were used for the diagnosis of hepatocellular carcinoma[23]. Previously published clinical criteria were used for the diagnosis of Hepatorenal Syndrome type 1, published in 2007[24,25]:

- Cirrhosis with ascites;
- Serum creatinine >1.5 mg/dL;
- No improvement of serum creatinine (decrease to a level of 1.5 mg/dL or lower) after at least 2 days with diuretic withdrawal and volume expansion with human albumin. The recommended dose of human albumin is 1 g/kg of body weight per day up to a maximum of 100 g/day.
- Absence of shock.
- No current or recent treatment with nephrotoxic drugs.
- Absence of parenchymal kidney disease as indicated by proteinuria >500 mg/day, microhaematuria (>50 red blood cells per high power field) and/or abnormal renal ultrasonography.

Hepatic encephalopathy was defined and stratified according to West-Haven criteria[26]. Laboratory data is expressed in units commonly used in the hospital.

Liver-specific scores

Commonly used liver-specific scores were calculated to analyze their accuracy into predicting mortality. Child-Turcotte-Pugh is a score used in the clinical care for cirrhotic patients that aims to predict 1-year mortality for compensated and decompensated cirrhosis[27,28]. CTP was calculated using an online calculator.

MELD[29] and MELD-Na[30] are scores currently used for organ allocation in liver transplantation, developed to predict 90-day for cirrhotic patients. Both were calculated using online calculators.

CLIF-SOFA is a score developed by the EASL-CLIF Group, adapted from the SOFA score used in intensive care (TABLE 1). It aims to define ACLF and divide it in three grades[15]. Both CLIF-SOFA and ACLF grade were calculated using an online calculator developed by the CLIF Research Group (https://www.clifresearch.com/ToolsCalculators.aspx). CLIF-SOFA score defines failure of each system, and by the number of failures it further stratifies ACLF into grade 1, 2 and 3:

- DC (non-ACLF): no organ failure; or an isolated non-renal organ failure with creatinine <1.5 and absence of encephalopathy; or an isolated neurological failure with creatinine <1.5.
- ACLF grade 1: an isolated kidney failure; or an isolated non-renal and non-neurological organ failure with creatinine ranging between 1.5 1.9 or mild to moderate hepatic encephalopathy; or an isolated neurological failure with creatinine ranging between 1.5 to 1.9.
- ACLF grade 2: two organ failures.
- ACLF grade 3: three organ failures.

TABLE 1. Chronic liver failure – sequential organ failure assessment (CLIF-SOFA) score.

CLIF-SOFA score	0	1	2	3	4
Respiration					
PaO_2/FiO_2 or SpO_2/FiO_2	>400 >512	>300 to ≤400 >357 to ≤512	>200 to ≤300 >214 to ≤357	>100 to ≤200 89 to ≤214	≤100 ≤89
Coagulation					
INR	<1.1	≥1.1 to <1.25	≥1.25 to <1.5	≥1.5 to <2.5	≥2.5 or platelet ≤20
Liver					
Bilirubin, mg/dL (mol/L)	<1.2 (<20)	≥1.2 to <2.0 (20–32)	≥2.0 to <6.0 (33–101)	≥6.0 to <12.0 (102–204)	≥12.0 (>204)
Cardiovascular					
Hypotension	MAP ≥70 mmHg	MAP <70 mmHg	Dopamine ≤5 or dobutamine (any dose)* or terlipressin	Dopamine >5 or epinephrine ≤0.1 or norepinephrine ≤0.1*	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1*
CNS					
HE grade	No HE	I	II	III	IV
Renal					
Creatinine (mg/dL)	<1.2	≥1.2 to <2.0	≥2.0 to <3.5	≥3.5 to <5.0 or use of RRT	≥5.0

CNS: central nervous system; FiO2: fractional inspired oxygen; HE: hepatic encephalopathy; INR: international normalized ratio; MAP: mean arterial pressure; PaO2: arterial oxygen tension; RRT: renal replacement therapy; SpO2: pulse oximetric saturation. Gray shading in the table cells defines insufficiency of that organ. *Adrenergic agents administered for at least 1 h (doses are given in μg/kg/min).

Another scores developed by the EASL-CLIF Group, CLIF consortium acute decompensation (CLIF-C AD) score and CLIF-C ACLF, were developed with the purpose of predicting expected mortality for 28-day, 90-day, 180-day and 365-day for DC and ACLF patients[31]. They were also calculated using the online calculator developed by the EASL-CLIF Group, which is able to, after giving the result of the presence of ACLF and the value of CLIF-SOFA, automatically analyzes if CLIF-C AD or ACLF applies in each case and calculates accordingly.

Outcome

Death from all causes was used as the main outcome. Data was gathered using medical records and searching through national death databases (https://www.falecidosnobrasil.org.br/). If the patient was admitted to the hospital more than once for SBP, data regarding only the first admission was collected.

Therapy for SBP

In our hospital, SBP is treated by the clinical gastroenterology team accordingly to an institutional protocol, with insignificant variation in patient treatment. Community acquired SBP is treated with cefotaxime 2 g TID for 7 days and health-care associated and nosocomial SBP is treated with piperacillin-tazobactam 4.5 g QID for 7 days. Every patient with SBP receives albumin in the dose of 1.5 g/kg in the first day of antibiotics and 1.0 g/kg in the third day. Every patient undergoes control paracentesis in 2 days and treatment is adjusted accordingly. Post-treatment prophylaxis is made with the use of norfloxacin 400 mg Q.D. indefinitely.

Statistical analysis

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) 15.0. Categorical variables are described using frequency and corresponding percentage and continuous variables by mean and standard deviation. Kaplan-Meier survival univariate analyses were done and the cumulated risk of developing these events in the form a multivariate analysis was analyzed with a stepwise progression to the Cox regression. All statistical tests performed for the analysis of variables excluded missing data. Kaplan-Meier curves were used for the graphical description of survival.

RESULTS

Medical record analysis retrieved 77 hospital admissions due to SBP in the pre-determined time frame. Of these, eight admissions were excluded for being re-admissions for the same patients. After chart analysis, 69 patients in their first hospital admission due to SBP were included in the study (FIGURE 1). Demographic, clinical and laboratorial data are described in TABLE 2 for the study population and for either DC or ACLF and each grade. DC was present in 29 patients, while ACLF in 40 patients, according to EASL-CLIF criteria.

All cause mortality was 44%, 56.5% and 74% for 28-, 90- and 365-day, respectively. The prevalence of ACLF was 58%. Of these, 65% grade 1, 17.5% grade 2 and 17.5% grade 3. All cause-mortality was, respectively, 27.6%, 41.4% and 55.2% for 28-, 90- and 365-day for DC, 57.7%, 61.5% and 76.9% for

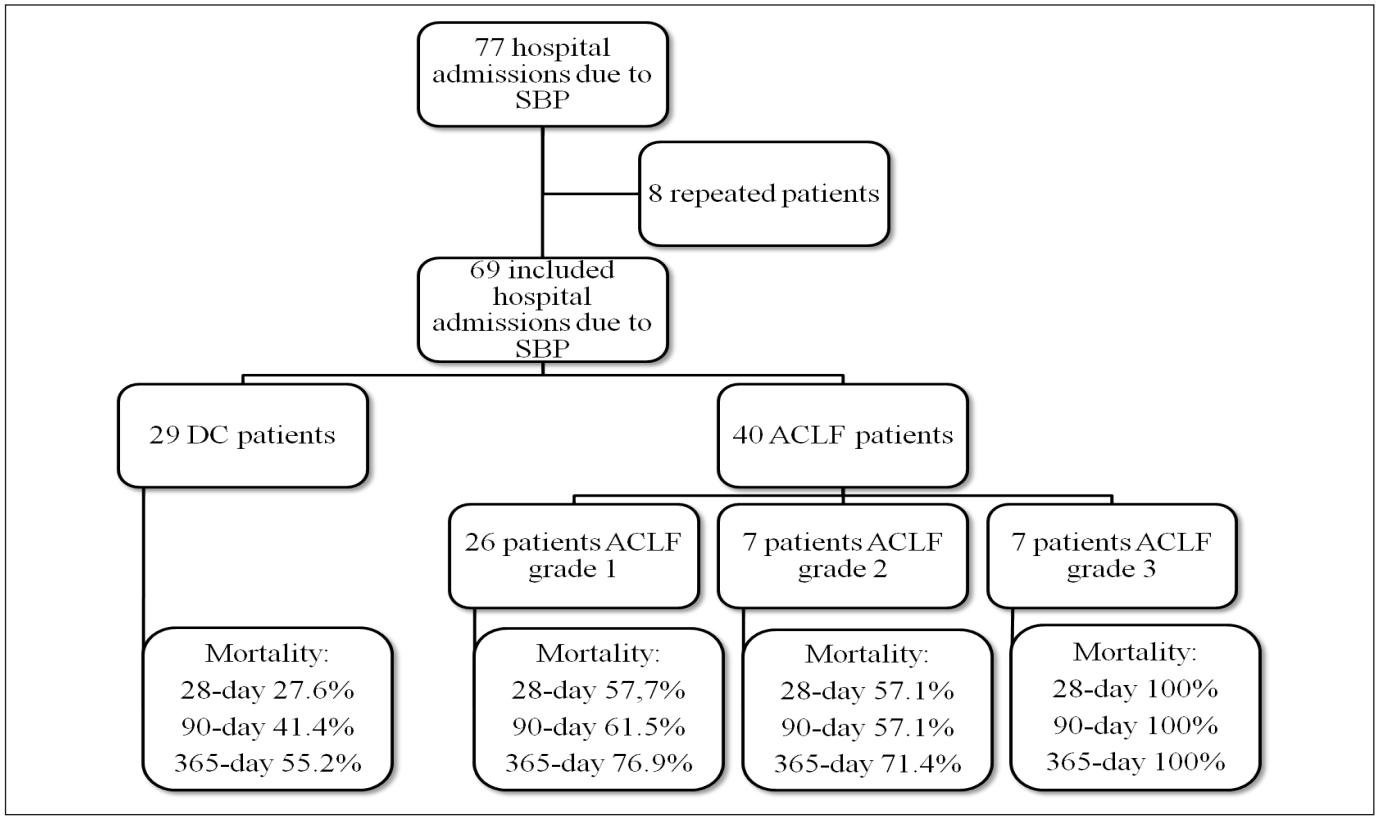

FIGURE 1. Fluxogram for study population and mortality for spontaneous bacterial peritonitis (SBP) patients according to the presence of decompensated cirrhosis (DC) or acute-on-chronic liver failure (ACLF) and each grade.

TABLE 2. Demographic, clinical and laboratory findings of the study population and for decompensated cirrhosis (DC) and for acute-on-chronic liver failure (ACLF) and each grade.

Variable	Study population (n=69)	DC (n=29)	ACLF (n=40)	ACLF grade 1 (n=26)	ACLF grade 2 (n=7)	ACLF grade 3 (n=7)
Age (years)*	56 (10.4)	56 (11.7)	55 (9.5)	56 (10.5)	57 (9)	54 (9)
Hemoglobin (g/dL)	10.4 (2.2)	10.2 (1.8)	10.4 (2.4)	10.5 (2.5)	10.3 (1.8)	10.4 (2.7)
Platelets (10^3/mm^3)*	115 (61)	115 (60)	114 (62)	116 (59)	96 (58)	124 (81)
Creatinine (mg/dL)*	1.6 (1.0)	0.96 (0.34)	2.1 (1.05)	2.3 (0.94)	1.6 (1.3)	1.9 (1.05)
Sodium (mmol/L)*	135 (6.6)	135 (4)	135 (7)	134 (7)	135 (6)	139 (9.6)
AST (U/L)*	103 (144)	89 (91)	114 (174)	133 (210)	83 (74)	75 (59)
ALT (U/L)*	60 (122)	39 (25)	75 (158)	85 (190)	68 (97)	46 (38)
GGT (U/L)*	254 (321)	228 (260)	272 (361)	333 (398)	124 (107)	197 (356)
INR*	1.6 (0.58)	1.4 (0.18)	1.8 (0.7)	1.6 (0.6)	1.8 (0.5)	2.2 (0.9)
Total bilirubin (mg/dL)*	5.5 (5.9)	4.5 (4.2)	6.3 (6.9)	5.2 (6.6)	6.4 (6.6)	10.1 (7.9)
Albumin (g/L)*	2.6 (0.7)	2.6 (0.6)	2.6 (0.7)	2.6 (0.7)	2.4 (0.9)	2.5 (0.6)
Liver scores*						
MELD	20 (7.2)	14.8 (4.3)	23 (6.5)	23.7 (5.9)	21.7 (7.7)	26.5 (7.7)
MELD-Na	22 (7)	17.6 (4.4)	26 (6.5)	26 (6)	24 (7.7)	28 (7.4)
CLIF-SOFA	7 (3)	5.1 (1.7)	8.8 (3.6)	7 (2.5)	10 (2.2)	14.2 (2.1)
CLIF-C AD/ACLF	57 (11)	52 (8.9)	61 (11.2)	60 (10.8)	62 (10.8)	64 (13.9)
CTP	11 (2)	10 (2.2)	11 (2.1)	11 (2.2)	11 (1.5)	13 (1.7)
Male sex**	52 (75.4)	20 (69)	32 (80)	21 (80.8)	5 (71.4)	6 (85.7)
Etiology**						
Alcohol	52 (75.4)	20 (69)	32 (80)	20 (76.9)	5 (71.4)	7 (100%)
Other	17 (24.6)	9 (31)	8 (20)	6 (23.1)	2 (28.6)	0
Virus**						
Hepatitis B	3 (4.3)	1 (3.4)	2 (5)	1 (3.8)	1 (14.3)	0
Hepatitis C	22 (31.9)	15 (51.7)	7 (17.5)	6 (23.1)	1 (14.3)	0
Ascites fluid						
Neutrophil count (/mm^3)*	2,764 (4,160)	2,919 (5,523)	2,652 (2,872)	2755 (3,132)	1,832 (1,926)	3,092 (2,825)
Ascites protein (g/dL)*	1.5 (1.1)	1.4 (1.2)	1.6 (0.9)	1.6 (0.8)	1.1 (0.8)	2.0 (1.2)
Positive culture**	32 (46.4)	11 (37.9)	21 (52.5)	15 (57.7)	2 (28.6)	4 (57.1)
Medications in use**						
PPI	41 (59.4)	22 (75.9)	19 (47.5)	14 (53.8)	3 (42.9)	2 (28.6)
Furosemide	34 (49.3)	15 (51.7)	19 (47.5)	14 (53.8)	2 (28.6)	3 (42.9)
Spironolactone	34 (49.3)	15 (51.7)	19 (47.5)	14 (53.8)	2 (28.6)	3 (42.9)
NSBB	25 (36.2)	13 (44.8)	12 (30)	9 (34.6)	0	3 (42.9)
Skin color**						
White	54 (78.3)	23 (79.3)	31 (77.5)	22 (84.6)	6 (85.7)	3 (42.9)
Black	5 (7.2)	2 (6.9)	3 (7.5)	2 (7.7)	0	1 (14.3)
Brown	10 (14.5)	4 (13.8)	6 (15)	2 (7.7)	1 (14.3)	3 (42.9)
Hepatorenal syndrome**	24 (34.8)	6 (20.7)	18 (45)	12 (46.2)	2 (28.6)	4 (57.1)
Hepatocellular carcinoma**	13 (18.8)	5 (17.2)	8 (20)	6 (23.1)	2 (28.6)	0
Portal vein thrombosis**	3 (4.3)	3 (10.3)	0	0	0	0
Acute variceal bleeding**	19 (27.5)	7 (24.1)	12 (30)	9 (34.6)	2 (28.6)	1 (14.3)
Active alcoholism**	19 (27.5)	6 (20.7)	13 (32.5)	7 (26.9)	4 (57.1)	2 (28.6)
Hepatic encephalopathy**						
Absent	38 (55.1)	20 (69)	18 (45)	16 (61.5)	2 (28.6)	0
Present	31 (44.9)	9 (31)	22 (55)	10 (38.5)	5 (71.4)	7 (100)
Grade I	8 (11.6)	5 (17.2)	3 (7.5)	1 (3.8)	1 (14.3)	1 (14.3)
Grade II	9 (12)	2 (6.9)	7 (17.5)	6 (23.1)	1 (14.3)	0
Grade III	12 (17.4)	2 (6.9)	10 (25)	3 (11.5)	2 (28.6)	5 (71.4)
Grade IV	2 (2.9)	0 (0)	2 (5)	0	1 (14.3)	1 (14.3)
Mortality**						
Intra-hospital	31 (44.9)	6 (20.7)	25 (62.5)	14 (53.8)	4 (57.1)	7 (100)
28-day	34 (49.3)	8 (27.6)	26 (65)	15 (57.7)	4 (57.1)	7 (100)
90-day	39 (56.5)	12 (41.4)	27 (67.5)	16 (61.5)	4 (57.1)	7 (100)
365-day	48 (69.6)	16 (55.2)	32 (80)	20 (76.9)	5 (71.4)	7 (100)

ACLF: acute-on-chronic liver failure; DC: decompensated cirrhosis; AST: aspartate transaminase; ALT: alanine transaminase; GGT: gamma-glutamyl transferase; INR: international normalized ratio; MELD: Model for End-Stage Liver Disease; MELD-Na: Modified Model Including Sodium; CLIF-C AD/ACLF: CLIF consortium acute decompensation / acute-on-chronic liver failure; CLIF-SOFA: Chronic Liver Failure Sequential Organ Failure Assessment; CTP: Child-Turcotte-Pugh score; PPI: proton pump inhibitor; NSBB: non-selective beta-blockers. *Mean (standard deviation). **Frequency (%).

28-, 90- and 365-day for ACLF grade 1, 57.1%, 57.1% and 71.4% for 28-, 90- and 365-day for ACLF grade 2 and 100% for 28-, 90- and 365-day for ACLF grade 3.

Kaplan-Meier univariate analysis was performed. ACLF absent, male sex, use of proton-pump inhibitor (PPI), furosemide and non-selective beta-blockers (NSBB), inactive alcoholism, total bilirubin lower than 4 mg/dL, INR (international normalizated ratio) lower than 1.3, AST and ALT lower than 40 U/L, hemoglobin higher than 9 g/dL, creatinine lower than 2 mg/dL, serum levels of albumin and lower MELD, CLIF-SOFA and CTP scores were associated with higher 28-day and 90-day survival (TABLE 3), using as statistically significant a *P* value below 0.2 for inclusion in multivariate analysis. FIGURE 2 presents a Kaplan-Meier curve for 28- and 90-day survival for ACLF.

Each one of these variables, except for AST and creatinine were used for the multivariate analysis using Cox regression. Using the stepwise approach, the model was reduced until every variable had a level of independent significance of $P \leq 0.05$. Use of PPI, ALT lower than 40 U/L, hemoglobin higher than nine, inactive alcoholism, absence of ACLF and lower values of MELD and CLIF-SOFA scores were independently associated with higher 28-day survival. Use of PPI, ALT lower than 40 U/L, hemoglobin higher than nine, higher levels of albumin in the serum, absence of ACLF and lower values of MELD and CLIF-SOFA scores were independently associated with higher 90-day survival (TABLE 4).

TABLE 3. Univariate analysis with the cumulated risk for survival⁺.

Variable	Statistical significance for survival	
	28-day	90-day
Male sex	0.06	0.05
Skin color (white X non-white)	NS	NS
Age	NS	NS
Etiology of cirrhosis (alcohol X other)	NS	NS
Viral hepatitis	NS	NS
Acute variceal bleeding	NS	NS
PPI use	<0.001	0.001
Furosemide use	0.09	0.02
Spironolactone use	NS	NS
NSBB use	0.17	0.07
Hepatorenal syndrome	NS	NS
Hepatocellular carcinoma	NS	NS
Positive culture of ascites fluid	NS	NS
Total bilirubin (<4.0 mg/dL)	0.11	0.03
INR (<1.3)	0.07	0.2
AST (<40 U/L)	0.17	0.06
ALT (<40 U/L)	0.06	0.04
GGT (<60 U/L)	NS	NS
Hemoglobin (>9 g/dL)	0.03	0.07
Platelets (>100x10³/mm³)	NS	NS
Sodium (>135 mmol/L)	NS	NS
Creatinine (<2.0 mg/dL)	0.15	0.7
Albumin (g/L)	0.01	0.01
Active alcoholism	0.19	NS
Liver scores		
Lower MELD	0.01	0.12
Lower CLIF-SOFA	<0.001	0.004
CTP (A x B x C)	0.09	0.19
ACLF absent	<0.001	0.01

NS: non-significant (*P*>0.2); PPI: proton pump inhibitor; NSBB: non-selective beta-blocker; AST: aspartate transaminase; ALT: alanine transaminase; GGT: gamma-glutamyl transferase; INR: international normalized ratio; MELD: Model for End-Stage Liver Disease; CLIF-SOFA: Chronic Liver Failure Sequential Organ Failure Assessment; CTP: Child-Turcotte-Pugh; ACLF Acute-on-chronic liver failure. ⁺Kaplan-Meier survival analysis

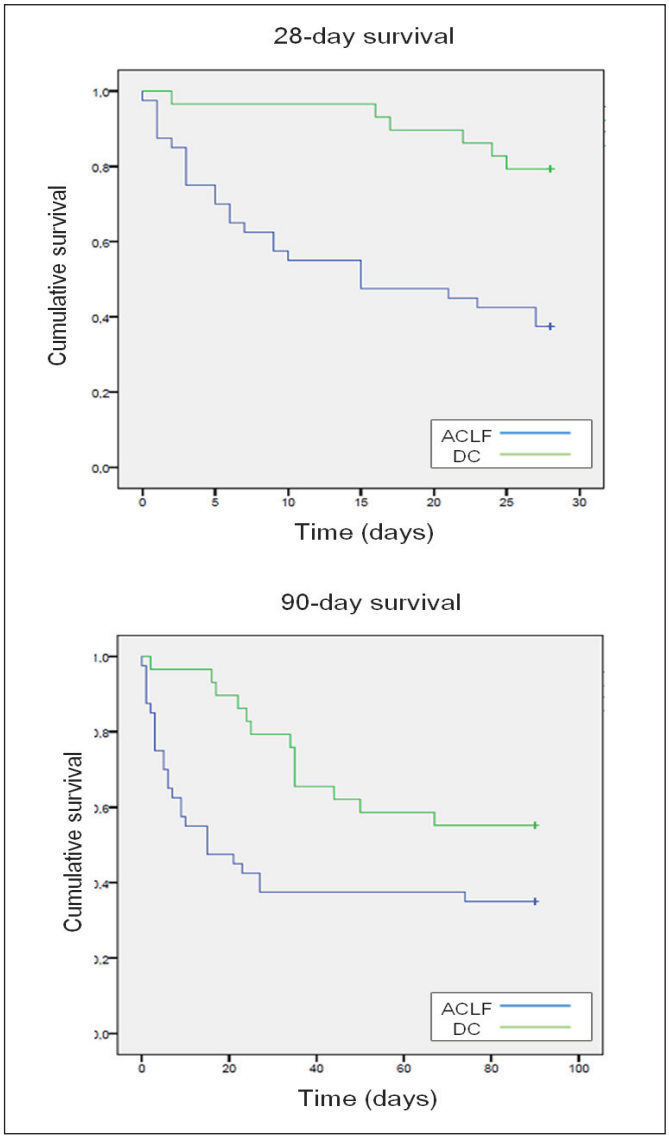

FIGURE 2. Kaplan-Meier curves for 28- and 90-day survival for decompensated cirrhosis (DC) or acute-on-chronic liver failure (ACLF).

DISCUSSION

The definition of ACLF developed by the EASL-CLIF has been a major improvement in the understanding of this syndrome and into adding the necessary step between DC and death[15]. Asia-Pacific Association for the Study of the Liver (APASL) has independently developed another set of criteria. Nevertheless, two different studies did not show superiority of APASL criteria over the one developed by the EASL-CLIF[32,33].

TABLE 4. Initial and final model for multivariate analysis for survival⁺.

Variable	Survival (Hazard ratio – 95%CI)			
	Initial Model		Final Model	
	28-day	90-day	28-day	90-day
Male sex	1.5 (0.5–4.7)	1.8 (0.7–4.4)	–	–
PPI use	2.7 (0.97–7.9)*	1.9 (0.8–4.5)	3.5 (1.4–8.4) P=0.005	2.5 (1.2–5.1) P=0.01
Furosemide use	0.76 (0.19–2.9)	1.4 (0.4–4.5)	–	–
NSBB use	0.67 (0.4–3.7)	1.5 (0.6–0.3.4)	–	–
Total bilirubin (<4.0 mg/dL)	1.5 (0.5–4.4)	1.9 (0.7–5.4)	–	–
INR (<1.3)	1.8 (0.4–7.4)	1.2 (0.4–2-4.2)	–	–
ALT (<40 U/L)	3.5 (1.2–10.1)*	1.9 (0.9–4.2)*	3.8 (1.5–9.4) P=0.004	2.4 (1.1–5.1) P=0.01
Hemoglobin (>9 g/dL)	8.8 (2.2–34.2)**	3.8 (1.4–10.2)**	12.5 (3.6–42.8) P<0.001	4.2 (1.7–10.8) P=0.002
Lower albumin (g/L)***	0.6 (0.2–1.2)	0.59 (0.32–1.09)*	–	0.56 (0.34–0.91) P=0.01
Inactive alcoholism	2.4 (0.8–6.7)*	2.1 (0.7–9.4)	3.1 (1.2–7.9) P=0.01	–
Liver scores				
Higher MELD***	0.83 (0.72–0.96)*	0.87 (0.78–0.-96)*	0.84 (0.75–0.93) P=0.002	0.9 (0.83–0.97) P=0.05
Lower CLIF-SOFA***	1.1 (0.9–1.3)	1.1 (0.97–1.2)	1.1 (1.04–1.3) P=0.01	1.1 (1.01–1.26) P=0.05
CTP (A x B x C)	7.8 (0.01–125)	8.2 (0.02–117)	–	–
ACLF absent	31 (5.2–185)**	8.3 (2.3–30.2)**	20.2 (3.9–103.2) P<0.001	6.1 (1.8–20.1) P=0.003

PPI: proton pump inhibitor; NSBB: non-selective beta-blocker; ALT: alanine transaminase; INR: international normalized ratio; MELD: Model for End-Stage Liver Disease; CLIF-SOFA: Chronic Liver Failure Sequential Organ Failure Assessment; CTP: Child-Turcotte-Pugh; ACLF: acute-on-chronic liver failure. ⁺Variables chosen for stepwise approach to Cox regression from univariate analysis (TABLE 2); *P≤0.1; **P<0.01; ***HR per unity.

Other studies have validated the EASL-CLIF criteria and analyzed the prevalence of ACLF in some settings, all of which were consistently lower than the one found in the present study (58%). CANONIC study found a prevalence of 22.6%[15], a North-American study found prevalence of 26.4%[34] and in two other Brazilian studies, one found a prevalence of 22.6%[35] and the other 35.3%[36].

ACLF Group presented higher 28-day mortality (65%) when compared with DC patients (27.6%). CANONIC study described a 28-day mortality of 33.9%, significantly lower than the reported here for patients with SBP[15]. Other two Brazilian studies reported both mortality rates of 39% for ACLF patients[34-37]. Since cirrhotic patients with bacterial infections such as SBP are generally more clinically compromised, a higher prevalence of ACLF and a higher mortality in the sample of the presented study is to be expected. This was demonstrated in a study developed by the North American consortium for the study of end-stage liver disease (NACSELD), which used the EASL-CLIF definition of ACLF to study its relations with infections. It has described that SBP was independently associated with higher 28-day mortality when compared to other infections[38]. Also, patients with SBP have higher mortality in the short and long term than other causes of acute decompensation[39-41].

A study by the EASL-CLIF consortium has specifically analyzed infections in ACLF patients. When a patient is admitted to the ward with ACLF and SBP, 28-day mortality was 46.3%, while 90-day was 58.5%. When the patient developed SBP while in the hospital, 28-day mortality was 45.5% and 90-day mortality was 59.1%[42]. The present study had a higher mortality – 65% for 28-day mortality and 67.5% for 90-day mortality for patients with both ACLF and SBP in the admission.

The 365-day mortality rate in this study for DC patients was 55.2% and 80% for ACLF patients. This high long-term mortality for SBP has been largely described. This is so relevant that the first episode of SBP should prompt referral for liver transplantation evaluation[6]. The activation of cytokines and vasoactive hormones and the alteration in circulatory function in advanced cirrhosis and ascites without overt sepsis are similar to that seen in sepsis and septic shock without cirrhosis, which results in a higher mortality associated with bacterial infections in most studies[43].

In this study, besides the presence of ACLF and the values of CLIF-SOFA score, other variables were also associated with mortality. Higher MELD scores were associated with lower survival, which has been demonstrated by other studies[5,19,20,22]. Previous studies have also associated the use of PPI with mortality and decompensation in cirrhotic patients[44], with a higher risk for the development of SBP and adverse events[45-47]. Nevertheless, two other studies have not found the same association, suggesting that such findings might be due to the retrospective nature of the other studies[48-50]. In the present study, the use of PPI was associated with higher 28- and 90-day survival.

The timing of treatment and the appropriate choice of antibiotics is paramount in order to ensure higher survival in SBP patients[51,52]. Although, adjusting antibiotic spectrum to an isolated pathogen was not possible in most cases in our study: the sensitivity of the ascites fluid culture was 46.4%. The most common pathogen causing SBP in our hospital is *Escherichia coli* (28.5%), although a higher than usual local prevalence of *Enterococcus sp.* (23.8%) has been previously described[53].

Kidney failure has been extensively associated with higher mortality for SBP patients[54,55]. Although in the univariate analysis higher creatinine was associated with lower survival, this did not translate into the multivariate analysis. The use of non-selective beta-blocker has been shown in a previous study to improve survival in ACLF patients[56]. In the present study, it was associated with higher survival in the univariate analysis, but not in the multivariate analysis.

Active alcoholism is a well-described cause of ACLF due to the possibility of causing alcoholic hepatitis[57]. In the present study, active alcoholism was independently associated with higher 28-day mortality. Since the region of this study is a wine producing region, we had expected a higher prevalence of alcohol-related cirrhosis and active alcoholism, and this could be associated with the higher incidence of ACLF and lower survival in this specific cohort when compared to other studies regarding ACLF and infections. Also, higher CLIF-SOFA values were associated with lower survival. This has been already demonstrated in previous studies for other causes of decompensation, such as alcoholic hepatitis and alcoholic cirrhosis[58,59], extra-hepatic insults[36,60], acute variceal bleeding[61,62], cirrhotic patients admitted to the intensive care unit[63], with hepatorenal syndrome[64] or SBP[65].

The largest drawback of the present study is the small sample size. This prevented the study from demonstrating higher mortality stratified by each ACLF grade. Most studies in this subject are multi-centric, which helps gather more data. Nevertheless, the extensive data accumulated has allowed a deep study of the population, providing us with a better understanding of the prognostication of SBP in cirrhotic patients from Brazil.

CONCLUSION

In conclusion, the presence of ACLF and higher CLIF-SOFA scores were independently associated with higher 28- and 90-day mortality in cirrhotic patients admitted due to SBP. The use of the EASL CLIF criteria and related scores for defining and prognosticating ACLF helps to stratify patients with SBP and worse prognosis, which might improve the quality of care for this subset of patients.

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Previous presentation

End of residency paper for MD. Raquel, MD. Lais and MD. Martina, presented in 2017, 2016 and 2015, respectively. Partial data presented as an electronic poster in *Congresso Brasileiro de Hepatologia*, October-2017, and as an oral presentation in *Semana Brasileira do Aparelho Digestivo*, November-2018. Complete data presented as an electronic poster in UEG week virtual, October-2020.

Authors' contribution

Jacques ROC: design, data collection, writing and review. Massignan LS: data collection, writing and review. Winkler MS: data collection, writing and review. Balbinot RS: data collection, writing and review. Balbinot SS: design, writing and review. Soldera J: design, statistical analysis, translation, writing and review. All authors have equally participated in the writing and review of the final manuscript.

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Jacques ROC, Massignan LS, Winkler MS, Balbinot RS, Balbinot SS, Soldera J. Insuficiência hepática crônica agudizada está independentemente associada com menor sobrevida em pacientes com peritonite bacteriana espontânea. Arq Gastroenterol. 2021;58(3):344-52.

RESUMO – **Contexto** – A peritonite bacteriana espontânea (PBE) é uma descompensação da cirrose com uma mortalidade intra-hospitalar de 20% a 40%. **Objetivo** – O objetivo deste estudo é analisar se a definição de insuficiência hepática crônica agudizada (IHCA) como definido pelo consórcio EASL--CLIF é capaz de predizer mortalidade em pacientes cirróticos com PBE. **Métodos** – Coorte histórica conduzida em um hospital de ensino público terciário. Foram obtidos dados de prontuários médicos de janeiro de 2009 até julho de 2016, buscando no banco de dados eletrônico do hospital por todas as amostras de ascite coletadas no período. Prontuários eletrônicos e físicos foram analisados e os pacientes com mais de 18 anos com cirrose e líquido de ascite compatível com PBE foram incluídos. Foram incluídos 69 pacientes. Escores específicos para o fígado foram calculados e a análise de sobrevida de Kaplan-Meier foi utilizada para a análise univariada, e uma abordagem progressiva para a regressão logística de Cox foi usada para a análise multivariada. **Resultados** – A mortalidade por todas as causas foi 44%, 56,5% e 74% para 28-, 90- e 365-dias, respectivamente. A prevalência de IHCA foi de 58%. Desses, 65% grau 1, 17,5% grau 2 e 17,5% grau 3. Na análise multivariada, o uso de inibidores da bomba de prótons, alanina transaminase menor que 40 U/L, hemoglobina acima de 9 g/dL, ausência de IHCA e menores valores dos escores CLIF-SOFA e MELD foram independentemente associados com maior sobrevida para ambos intervalos de 28- e 90-dias. **Conclusão** – A presença de IHCA e maiores valores de CLIF-SOFA foram independentemente associados em maior mortalidade para pacientes cirróticos admitidos por PBE no intervalo de 28- e 90-dias.

Palavras-chave – Cirrose hepática; peritonite bacteriana espontânea; doença hepática em estágio terminal; escores de disfunção hepática; prognóstico; insuficiência hepática crônica agudizada.

REFERENCES

1. Fernández J, Navasa M, Gómez J, Colmenero J, Vila J, Arroyo V, Rodés J. Bacterial infections in cirrhosis: epidemiological changes with invasive procedures and norfloxacin prophylaxis. Hepatology. 2002;35:140-8. DOI: 10.1053/jhep.2002.30082.
2. Nousbaum JB, Cadranel JF, Nahon P, Khac EN, Moreau R, Thévenot T, et al. Diagnostic accuracy of the Multistix 8 SG reagent strip in diagnosis of spontaneous bacterial peritonitis. Hepatology. 2007;45:1275-81. DOI: 10.1002/hep.21588.
3. Coral G, de Mattos AA, Damo DF, Viégas AC. Prevalence and prognosis of spontaneous bacterial peritonitis. Experience in patients from a general hospital in Porto Alegre, RS, Brazil (1991-2000)]. Arq Gastroenterol. 2002;39:158-62. DOI: 10.1590/s0004-28032002000300005.
4. Salerno F, Navickis RJ, Wilkes MM. Albumin infusion improves outcomes of patients with spontaneous bacterial peritonitis: a meta-analysis of randomized trials. Clin Gastroenterol Hepatol. 2013;11:123-30. DOI: 10.1016/j.cgh.2012.11.007.
5. Nobre SR, Cabral JE, Gomes JJ, Leitão MC. In-hospital mortality in spontaneous bacterial peritonitis: a new predictive model. Eur J Gastroenterol Hepatol. 2008;20:1176-81. DOI: 10.1097/MEG.0b013e32830607a2.
6. Moore KP, Wong F, Gines P, Bernardi M, Ochs A, Salerno F, et al. The management of ascites in cirrhosis: report on the consensus conference of the International Ascites Club. Hepatology. 2003;38:258-66. DOI: 10.1053/jhep.2003.50315.
7. Jalan R, Gines P, Olson JC, Mookerjee RP, Moreau R, Garcia-Tsao G, et al. Acute-on chronic liver failure. J Hepatol. 2012;57:1336-48. DOI: 10.1016/j.jhep.2012.06.026.
8. Jalan R. Acute-on-chronic liver failure: from concept to a new syndrome. Curr Opin Crit Care. 2011;17:152. DOI: 10.1097/MCC.0b013e3283455c57.
9. Olson JC, Kamath PS. Acute-on-chronic liver failure: concept, natural history, and prognosis. Curr Opin Crit Care. 2011;17:165-9. DOI: 10.1097/MCC.0b013e328344b42d.
10. Mookerjee RP. Acute-on-chronic liver failure: the liver and portal haemodynamics. Curr Opin Crit Care. 2011;17:170-6. DOI: 10.1097/MCC.0b013e328344a076.
11. García-Martínez R, Cordoba J. Acute-on-chronic liver failure: the brain. Curr Opin Crit Care. 2011;17:177-83. DOI: 10.1097/MCC.0b013e328344b37e.
12. Cárdenas A, Ginès P. Acute-on-chronic liver failure: the kidneys. Curr Opin Crit Care. 2011;17:184-9. DOI: 10.1097/MCC.0b013e328344b3da.
13. Liu H, Lee SS. Acute-on-chronic liver failure: the heart and systemic hemodynamics. Curr Opin Crit Care. 2011;17:190-4. DOI: 10.1097/MCC.0b013e328344b397.
14. Hassanein TI, Schade RR, Hepburn IS. Acute-on-chronic liver failure: extracorporeal liver assist devices. Curr Opin Crit Care. 2011;17:195-203. DOI: 10.1097/MCC.0b013e328344b3aa.
15. Moreau R, Jalan R, Gines P, Pavesi M, Angeli P, Cordoba J, et al. Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. Gastroenterology. 2013;144:1426-37. DOI: 10.1053/j.gastro.2013.02.042.
16. Follo A, Llovet JM, Navasa M, Planas R, Forns X, Francitorra A, et al. Renal impairment after spontaneous bacterial peritonitis in cirrhosis: incidence, clinical course, predictive factors and prognosis. Hepatology. 1994;20:1495-501. DOI: 10.1002/hep.1840200619.
17. Soylu AR, Dökmeci G, Tezel A, Umit H, Amuca H, Akova M, et al. Predictors of short-term outcome of spontaneous bacterial peritonitis in Turkish cirrhotic patients. J Gastroenterol Hepatol. 2005;20:657-60. DOI: 10.1111/j.1440-1746.2005.03772.x.
18. Bert F, Panhard X, Johnson J, Lecuyer H, Moreau R, Le Grand J, et al. Genetic background of Escherichia coli isolates from patients with spontaneous bacterial peritonitis: relationship with host factors and prognosis. Clin Microbiol Infect. 2008;14:1034-40. DOI: 10.1111/j.1469-0691.2008.02088.x.
19. Terg R, Gadano A, Cartier M, Casciato P, Lucero R, Muñoz A, et al. Serum creatinine and bilirubin predict renal failure and mortality in patients with spontaneous bacterial peritonitis: a retrospective study. Liver Int. 2009;29:415-9. DOI: 10.1111/j.1478-3231.2008.01877.x.
20. Luca A, Angermayr B, Bertolini G, Koenig F, Vizzini G, Ploner M, et al. An integrated MELD model including serum sodium and age improves the prediction of early mortality in patients with cirrhosis. Liver Transpl. 2007;13:1174-80. DOI: 10.1002/lt.21197.
21. Musskopf MI, Fonseca FP, Gass J, de Mattos AZ, John JA, de Mello Brandão AB. Prognostic factors associated with in-hospital mortality in patients with spontaneous bacterial peritonitis. Ann Hepatol. 2012;11:915-20.
22. Cho JH, Park KH, Kim SH, Bang JH, Park WB, Kim HB, et al. Bacteremia is a prognostic factor for poor outcome in spontaneous bacterial peritonitis. Scand J Infect Dis. 2007;39:697-702. DOI: 10.1080/00365540701299582.
23. Soldera J, Balbinot SS, Balbinot RA, Cavalcanti AG. Diagnostic and Therapeutic Approaches to Hepatocellular Carcinoma: Understanding the Barcelona Clínic Liver Cancer Protocol. Clin Med Insights Gastroenterol. 2016;9:67-71. DOI: 10.4137/CGast.S30190.
24. Salerno F, Gerbes A, Ginès P, Wong F, Arroyo V. Diagnosis, prevention and treatment of hepatorenal syndrome in cirrhosis. Gut. 2007;56:1310-8. DOI: 10.1136/gut.2006.107789.
25. Terres AZ, Balbinot RS, Muscope ALF, Longen ML, Schena B, Cini BT, et al. Evidence-based protocol for diagnosis and treatment of hepatorenal syndrome is independently associated with lower mortality. Gastroenterol Hepatol. 2021:S0210-5705(21)00086-8. English, Spanish. DOI: 10.1016/j.gastrohep.2021.02.007. Epub ahead of print.
26. Vilstrup H, Amodio P, Bajaj J, Cordoba J, Ferenci P, Mullen KD, et al. Hepatic encephalopathy in chronic liver disease: 2014 Practice Guideline by the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver. Hepatology. 2014;60:715-35. DOI: 10.1002/hep.27210.
27. Child CG, Turcotte JG. Surgery and portal hypertension. Major Probl Clin Surg. 1964;1:1-85.
28. Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. Br J Surg. 1973;60:646-9. DOI: 10.1002/bjs.1800600817.
29. Kamath PS, Wiesner RH, Malinchoc M, Kremers W, Therneau TM, Kosberg CL, et al. A model to predict survival in patients with end-stage liver disease. Hepatology. 2001;33:464-70. DOI: 10.1053/jhep.2001.22172.
30. Kim WR, Biggins SW, Kremers WK, Wiesner RH, Kamath PS, Benson JT, et al. Hyponatremia and mortality among patients on the liver-transplant waiting list. N Engl J Med. 2008;359:1018-26. DOI: 10.1056/NEJMoa0801209.
31. Hernaez R, Solà E, Moreau R, Ginès P. Acute-on-chronic liver failure: an update. Gut. 2017;66:541-53. DOI: 10.1136/gutjnl-2016-312670.
32. Selva Rajoo A, Lim SG, Phyo WW, Tun T, Dan YY, Lee YM, et al. Acute-on-chronic liver failure in a multi-ethnic Asian city: A comparison of patients identified by Asia-Pacific Association for the Study of the Liver and European Association for the Study of the Liver definitions. World J Hepatol. 2017;9:1133-40. DOI: 10.4254/wjh.v9.i28.1133.
33. Dhiman RK, Agrawal S, Gupta T, Duseja A, Chawla Y. Chronic Liver Failure-Sequential Organ Failure Assessment is better than the Asia-Pacific Association for the Study of Liver criteria for defining acute-on-chronic liver failure and predicting outcome. World J Gastroenterol. 2014;20:14934-41. DOI: 10.3748/wjg.v20.i40.14934.
34. Hernaez R, Kramer JR, Liu Y, Tansel A, Natarajan Y, Hussain KB, et al. Prevalence and short-term mortality of acute-on-chronic liver failure: A national cohort study from the USA. J Hepatol. 2019;70:639-647. DOI: 10.1016/j.jhep.2018.12.018.
35. Silva PE, Fayad L, Lazzarotto C, Ronsoni MF, Bazzo ML, Colombo BS, et al. Single-centre validation of the EASL-CLIF consortium definition of acute-on-chronic liver failure and CLIF-SOFA for prediction of mortality in cirrhosis. Liver Int. 2015;35:1516-23. DOI: 10.1111/liv.12597.
36. Grochot RM, Luz LB, Garcia R, Balbinot RA, Balbinot SS, Soldera J. CLIF-SOFA is superior to other liver-specific scores for predicting mortality in acute-on-chronic liver failure and decompensated cirrhosis. Austin J Gastroenterol. 2019;6:1105. Available from: https://austinpublishinggroup.com/gastroenterology/fulltext/ajg-v6-id1105.php
37. Grochot RM, Luz LB, Garcia R, Balbinot RA, Balbinot SS, Soldera J. Acute–on–chronic liver failure data from a teaching hospital in Brazil. A Historical Cohort. Intenational Journal of Scientific Research 2020;9(5):1-6. Available from: https://www.worldwidejournals.com/international-journal-of-scientific-research-(IJSR)/article/acuteandndash-onandndash-chronic-liver-failure-data-from-a-teaching-hospital-in-brazil-a-historical-cohort/MjUzNTk=/
38. Bajaj JS, O'Leary JG, Reddy KR, Wong F, Biggins SW, Patton H, Fallon MB, et al; North American Consortium For The Study Of End-Stage Liver Disease (NACSELD). Survival in infection-related acute-on-chronic liver failure is defined by extrahepatic organ failures. Hepatology. 2014;60:250-6. DOI: 10.1002/hep.27077.
39. Díaz-Hernández HA, Vázquez-Anaya G, Miranda-Zazueta G, Castro-Narro GE. The impact of different infectious complications on mortality of hospitalized patients with liver cirrhosis. Ann Hepatol. 2020. pii: S1665-2681(20)30022-3. DOI: 10.1016/j.aohep.2020.02.005.

40. Niu B, Kim B, Limketkai BN, Sun J, Li Z, Woreta T, Chen PH. Mortality from Spontaneous Bacterial Peritonitis Among Hospitalized Patients in the USA. Dig Dis Sci. 2018;63:1327-33. DOI: 10.1007/s10620-018-4990-y.
41. Gustot T, Felleiter P, Pickkers P, Sakr Y, Rello J, Velissaris D, Pierrakos C, et al. Impact of infection on the prognosis of critically ill cirrhotic patients: results from a large worldwide study. Liver Int. 2014;34:1496-503. DOI: 10.1111/liv.12520.
42. Fernández J, Acevedo J, Wiest R, Gustot T, Amoros A, Deulofeu C, et al. Bacterial and fungal infections in acute-on-chronic liver failure: prevalence, characteristics and impact on prognosis. Gut. 2018;67:1870-80. DOI: 10.1136/gutjnl-2017-314240.
43. Krag A, Bendtsen F, Burroughs AK, Moller S. The cardiorenal link in advanced cirrhosis. Med Hypotheses. 2012;79:53-5. DOI: 10.1016/j.mehy.2012.03.032.
44. De Roza MA, Kai L, Kam JW, Chan YH, Kwek A, Ang TL, Hsiang JC. Proton pump inhibitor use increases mortality and hepatic decompensation in liver cirrhosis. World J Gastroenterol. 2019;25:4933-44. DOI: 10.3748/wjg.v25.i33.4933.
45. Tergast TL, Wranke A, Laser H, Gerbel S, Manns MP, Cornberg M, Maasoumy B. Dose-dependent impact of proton pump inhibitors on the clinical course of spontaneous bacterial peritonitis. Liver Int. 2018;38:1602-113. DOI: 10.1111/liv.13862.
46. Min YW, Lim KS, Min BH, Gwak GY, Paik YH, Choi MS, et al. Proton pump inhibitor use significantly increases the risk of spontaneous bacterial peritonitis in 1965 patients with cirrhosis and ascites: a propensity score matched cohort study. Aliment Pharmacol Ther. 2014;40:695-704. DOI: 10.1111/apt.12875.
47. Lin L, Hou L, Deng Y, Zhao T, Wang B, Sun C. Acid suppression therapy and its association with spontaneous bacterial peritonitis incidence: A systemic review and meta-analysis. Hepatol Res. 2020;50:233-45. DOI: 10.1111/hepr.13447.
48. Miozzo SA, Tovo CV, John JA, de Mattos AA. Proton pump inhibitor use and spontaneous bacterial peritonitis in cirrhosis: An undesirable association? J Hepatol. 2015;63:529-30. DOI: 10.1016/j.jhep.2015.03.041.
49. Wang J, Wu Y, Bi Q, Zheng X, Zhang J, Huang W. Adverse outcomes of proton pump inhibitors in chronic liver disease: a systematic review and meta-analysis. Hepatol Int. 2020;14:385-398. DOI: 10.1007/s12072-019-10010-3.
50. Miozzo SAS, John JA, Appel-da-Silva MC, Dossin IA, Tovo CV, Mattos AA. Influence of proton pump inhibitors in the development of spontaneous bacterial peritonitis. World J Hepatol. 2017;9:1278-85. DOI: 10.4254/wjh.v9.i35.1278] [PMID: 29290909.
51. Engelmann C, Berg T. Management of Infectious Complications Associated with Acute-on-Chronic Liver Failure. Visc Med. 2018;34:261-8. DOI: 10.1159/000491107.
52. Wieser A, Li H, Zhang J, Liss I, Markwardt D, Hornung R, et al. Evaluating the best empirical antibiotic therapy in patients with acute-on-chronic liver failure and spontaneous bacterial peritonitis. Dig Liver Dis. 2019;51:1300-7. DOI: 10.1016/j.dld.2019.02.015.
53. Soldera J, Caldieraro FK, Luz LB, Marini SS, Balbinot SS, Balbinot RA, Cavalcanti AG. Microbiologic and bacterial resistance profile of spontaneous bacterial peritonitis of Hospital Geral of Caxias do Sul. Rev. AMRIGS. 2015;59:101-5.
54. Marciano S, Díaz JM, Dirchwolf M, Gadano A. Spontaneous bacterial peritonitis in patients with cirrhosis: incidence, outcomes, and treatment strategies. Hepat Med. 2019;11:13-22. DOI: 10.2147/HMER.S164250.
55. Yang L, Wu T, Li J, Li J. Bacterial Infections in Acute-on-Chronic Liver Failure. Semin Liver Dis. 2018;38:121-33. DOI: 10.1055/s-0038-1657751.
56. Mookerjee RP, Pavesi M, Thomsen KL, Mehta G, Macnaughtan J, Bendtsen F, et al. Treatment with non-selective beta blockers is associated with reduced severity of systemic inflammation and improved survival of patients with acute-on-chronic liver failure. J Hepatol. 2016;64:574-82. DOI: 10.1016/j.jhep.2015.10.018.
57. Moreau R, Jalan R, Arroyo V. Acute-on-Chronic Liver Failure: Recent Concepts. J Clin Exp Hepatol. 2015;5:81-5. DOI: 10.1016/j.jceh.2014.09.003.
58. Lee M, Lee JH, Oh S, Jang Y, Lee W, Lee HJ, et al. CLIF-SOFA scoring system accurately predicts short-term mortality in acutely decompensated patients with alcoholic cirrhosis: a retrospective analysis. Liver Int. 2015;35:46-57. DOI: 10.1111/liv.12683.
59. Kim HY, Kim CW, Kim TY, Song DS, Sinn DH, Yoon EL, et al. Assessment of scoring systems for acute-on-chronic liver failure at predicting short-term mortality in patients with alcoholic hepatitis. World J Gastroenterol. 2016;22:9205-13. DOI: 10.3748/wjg.v22.i41.9205.
60. Maipang K, Potranun P, Chainuvati S, Nimanong S, Chotiyaputta W, Tanwandee T, Charatcharoenwitthaya P. Validation of the prognostic models in acute-on-chronic liver failure precipitated by hepatic and extrahepatic insults. PLoS One. 2019;14:e0219516. DOI: 10.1371/journal.pone.0219516.
61. Wong MW, Chen MJ, Chen HL, Kuo YC, Lin IT, Wu CH, et al. Application of chronic liver failure-sequential organ failure assessment score for the predication of mortality after esophageal variceal hemorrhage post endoscopic ligation. PLoS One. 2017;12:e0182529. DOI: 10.1371/journal.pone.0182529.
62. Terres, AZ, Balbinot, RS, Muscope, ALF, et al. Predicting mortality for cirrhotic patients with acute oesophageal variceal haemorrhage using liver-specific scores. GastroHep. 2021; 3: 236– 246. DOI: 10.1002/ygh2.460
63. Kulkarni S, Sharma M, Rao PN, Gupta R, Reddy DN. Acute on Chronic Liver Failure-In-Hospital Predictors of Mortality in ICU. J Clin Exp Hepatol. 2018;8:144-55. DOI: 10.1016/j.jceh.2017.11.008.
64. Terres AZ, Balbinot RS, Muscope ALF, Longen ML, Schena B, Cini BT, et al. Predicting mortality for Hepatorenal Syndrome with liver-specific scores. GastroHep. 2020;2:336-43. DOI:10.1002/ygh2.429.
65. Jacques ROC, Massignan LS, Winkler MS, Balbinot RS, Balbinot RA, Balbinot SS, Soldera J. Liver-specific scores as predictors of mortality in spontaneous bacterial peritonitis. GastroHep. 2020;2:224-31. DOI: 10.1002/ygh2.419.

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