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Prognostic factors of liver cirrhosis mortality after a first episode of spontaneous bacterial peritonitis. A multicenter study

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ABSTRACT

Introduction: Spontaneous bacterial peritonitis is an infectious complication with a negative impact on survival of patients with cirrhosis.

Objective: To analyze the short- and long-term survival after a first episode of bacterial peritonitis and the associated prognostic factors.

Patients and methods: This was a retrospective, multicenter study of patients admitted to hospital for spontaneous bacterial peritonitis between 2008 and 2013. Independent variables related to mortality were analyzed by logistic regression. The prognostic power of the Child Pugh Score, the Model for End-Stage Liver Disease

(MELD) and the Charlson index was analyzed by ROC curve.

Results: A total of 159 patients were enrolled, 72% were males with a mean age of 63.5 years and a mean MELD score of 19 (SD ± 9.5). Mortality at 30 and 90 days and one and two years was 21%, 31%, 55% and 69%, respectively. Hepatic encephalopathy (p = 0.008, OR 3.5, 95% CI 1.4-8.8) and kidney function (p = 0.026, OR 2.7, 95% CI 1.13-16.7) were independent factors for short- and long-term mortality. MELD was a good marker of short- and long-term survival (area under the curve [AUC] 0.7: 95% CI 1.02-1.4). The Charlson index was related to long-term mortality (AUC 0.68: 95% CI 0.6-0.77).

Conclusions: Short- and long-term mortality of spontaneous bacterial peritonitis is still high. The main prognostic factors for mortality are impairment of liver and kidney function. MELD and the Charlson index are good markers of survival.

Key words: Spontaneous bacterial peritonitis. Liver cirrhosis. Mortalities. Acute kidney injury. Hepatic encephalopathy. Proton pump inhibitors. Antibiotic prophylaxis.

INTRODUCTION

Spontaneous bacterial peritonitis (SBP), first described by Conn in 1964 (1), is a spontaneous infection of the ascitic fluid in patients with liver cirrhosis or fulminant hepatic failure and ascites (2). Bacterial translocation is the key pathogenic mechanism for SBP development (3). Bacteria from the intestinal flora, especially Gram-negative germs, diffuse to mesenteric lymph nodes and from there, to the ascitic fluid or systemic circulation.

SBP has a negative impact on survival of cirrhotic patients (4). Several prognostic factors have been associated with mortality in these patients, including acute kidney failure, hepatocellular failure, bacteremia, shock, nosocomial infections (5) and delayed diagnosis (6). In-hospital mortality of SBP ranges from 20% to 30% (7,8). Despite advances in the management of these patients such as preventive measures, early diagnosis and adequate treatment, one-year mortality is still high, up to 50% in some reported series (9,10).

The primary objective of this multicenter study was to assess the short- and long-term survival of patients with cirrhosis after a first episode of SBP and the associated prognostic factors. The prognostic power of indices routinely used in clinical practice, such as the Child Pugh Score (CPT), Model for End-Stage Liver Disease (MELD) score and Charlson comorbidity index (CCI), were also analyzed.

PATIENTS AND METHODS

Study design

This was a retrospective, observational, multicenter study that analyzed hospital discharge of patients with liver cirrhosis and a primary or secondary diagnosis of SBP from January 2008 to December 2013. Patients were followed up until two years after diagnosis. The study sample consisted of all consecutive cases from three Catalonian hospitals, Hospital Universitari Parc Taulí in Sabadell, Hospital Universitari Joan XXIII in Tarragona and Hospital Universitari Sant Joan in Reus. The total reference population was approximately 1,200,000 people. The study was approved by the ethics committee of the Hospital Universitari Parc TaulÍ (CEIC 2013/587).

Patient selection

The study population was patients consecutively admitted with a diagnosis of liver cirrhosis based on clinical, laboratory or ecographic criteria or a liver biopsy. The study inclusion criteria included cases with a biochemical study of ascitic fluid (AF) consistent with SBP (presence of more than 250 polymorphonuclears [PMNs] in AF and positive microbiological culture) or with culture negative neutrocytic ascitis (more than 250 PMNs and negative culture). In clinical practice it is not usual to differentiate between SBP and culture negative neutrocytic ascites; the manuscript will generically refer to SBP and the two conditions will only be distinguished when necessary.

The study exclusion criteria included: a) patients with suspected secondary bacterial peritonitis based on one of the following: a positive polymicrobial culture, glucose levels < 50 mg/dl or suggestive radiographic signs; b) patients with bacterial ascites (pathological AF culture but less than 250 PMNs/ml); and c) patients with a prior episode of SBP.

Study variables

The following variables were collected: demographic data (age, sex), clinical variables (unit of hospitalization, etiology of cirrhosis, CPT, associated comorbidities, CCI, drug treatment at diagnosis, blood pressure, temperature and heart rate, associated complications such as hepatic encephalopathy, upper gastrointestinal bleeding and acute kidney injury), laboratory variables (white blood cells [WBCs] in plasma, creatinine, blood urea nitrogen [BUN], sodium, albumin, bilirubin and prothrombin time); microbiological data (AF and blood cultures resistance profile of isolated germs and community-acquired/nosocomial infections) and therapeutic data (antibiotic administered, treatment duration, albumin dose administered and changes in treatments).

In-patients who suffered an infection between two weeks to 48 hours before the SBP episode were considered as nosocomial. Acute kidney injury (AKI) was defined using the AKIN (Acute Kidney Injury Network) criteria (11). CPT, MELD and CCI were calculated at the time of SBP diagnosis. CPT indicates the degree of hepatic failure on a scale from 5 to 15 based on laboratory and clinical variables (12).

The MELD index is a mathematical model for the prediction of survival of patients with liver disease (13). Finally, the CCI is a prognostic index of mortality that considers patient age and the presence and severity of 19 comorbidity conditions including diseases such as cancer, diabetes, cirrhosis and ischemic heart disease (14). The presence of bacterial resistance or a decrease lower than 25% in PMN count at 48 hours were considered as treatment failure in analysis of the impact of treatment on mortality.

According to the main clinical guidelines (15), patients with hyperbilirubinemia (conjugated bilirubin > 4 mg/dl) or impaired kidney function (serum creatinine > 1 mg/dl) were considered as candidates for treatment with serum albumin.

Statistical analysis

Continuous variables were described as mean ± standard deviation (SD) and were compared using the Student's t test. Continuous variables with an associated non-

linear risk were categorized by risk groups. Categorical variables were presented as percentages and were analyzed using a Chi-squared test.

Both short-term (at 30 and 90 days) and long-term (at one and two years) inhospital mortality was analyzed. Overall survival was analyzed using KaplanMeier curves, the dependent variable was death or liver transplantation, and the follow-up time considered, as up to occurrence of the event or two years after diagnosis of SBP. The relapse rate of SBP in the same follow-up time was recorded.

For each time interval (30 and 90 days/one and two years), logistic regression univariate analysis was performed. Variables with values of $p < 0.05$ were considered as statistically significant. Variables with values of $p < 0.2$ in the univariate study were subsequently compared using a log-rank test in a multivariate study. Independent short-term (30 and 90 days) and long-term (one and two years) prognostic factors were sought and values of $p < 0.05$ were considered as statistically significant. Logistic regression and Kaplan-Meier analyses were subsequently performed.

The short- and long-term prognostic power of CPT, MELD and CCI was analyzed. For CPT, the classification of Child A, B and C was maintained. MELD and CCI were categorized in homogeneous groups with a comparable number of patients. The following groups were created for MELD: MELD < 15, MELD 15-21 and MELD ≥ 22. CCI groups were categorized as follows: CCI 1-4, CCI 5-7 and CCI ≥ 8. A ROC curve was constructed with the cut-off points for sensitivity and specificity with the best discrimination of survival for all three indices. Data were analyzed using the SPSS version 21 statistical software (SPSS Inc, Chicago Illinois, USA).

RESULTS

Baseline characteristics

A total of 159 patients who met all the inclusion criteria and none of the exclusion criteria were enrolled into the study. Table 1 shows patient characteristics. Most patients were male (71.7%) with a mean age of 63.5 years (SD ± 13.3).

Upon admission, 21% of patients were receiving primary prophylaxis for SBP with norfloxacin (7.5%) or were taking rifaximin due to prior episodes of hepatic encephalopathy (13.5%). Paracentesis was performed within 24 h of attendance to the

Emergency Room or day hospital in all patients with community-acquired SBP. The study design did not allow for the assessment of a delay in diagnosis of inpatients.

Fifty-six per cent of patients had some sort of complication at diagnosis. The most common complication was hepatic encephalopathy, followed by AKI. According to the AKIN classification, 54.5% had AKIN 1, 30.9% had AKIN 2 and 14.5%, AKIN 3.

SA was administered for volume expansion in 86.8% (138) of patients. Of these, 102 had creatinine levels of 1 mg/dl or higher and/or bilirubin levels greater than 4 mg/dl at diagnosis. Twenty-one patients did not receive SA and volume expansion was indicated in 12 of these patients.

The microbiological study of AF was positive in 59 patients (37%) and the remaining patients had a negative culture of neutrocytic ascites. Eighteen patients (11%) had bacteremia (Table 1).

Antibiotic therapy was started within 24 hours of diagnosis in 156 patients (98%) and the mean treatment duration was 8.3 days (SD ± 4.2). The failure rate of antibiotic treatment was 35%. No significant biochemical improvement was seen at 48 hours in 32 patients and coverage was adjusted based on susceptibility testing in 23 patients.

Analysis of mortality

In-hospital mortality was 23%. Mortality rates at 30 days, 90 days, one year and two years were 21%, 31%, 55% and 68.8%, respectively. Mean survival after two years of follow-up was 368 days (SD ± 23.8) (Fig. 1). Four patients underwent transplants during follow-up. Even though all patients were discharged with antibiotic prophylaxis, the relapse rate was 22%.

Analysis of short-term mortality (30 and 90 days)

Table 2 summarizes the prognostic factors in the univariate study. Chronic renal failure, unit of hospitalization and development of hepatic encephalopathy or AKI were short-term prognostic factors for mortality. Bacteremia increased mortality at 30 days ($p = 0.007$) but not at 90 days.

Of all the laboratory parameters examined, WBCs in plasma were significantly related with 30-day mortality ($p = 0.012$) but did not follow a linear distribution. The

continuous variable was categorized into three groups: a) WBCs in the normal range; b) leukopenia (WBCs < 4,500/mm^3); and c) leukocytosis (> 11,000/mm^3). At 30 days, leukopenia and leukocytosis decreased survival (leukocytosis OR 4.78, 95% CI 1.8-12.24, p = 0.002; leukopenia OR 3.44, 95% CI 1.8-12.6, p = 0.026) and no differences in mortality were found between patients with leukocytosis or leukopenia (p = 0.57). No significant differences were found with regard to short-term mortality between patients with or without volume expansion with SA (at 30 days p = 0.43, and at 90 days p = 0.84).

With regard to the sub-analysis based on SA treatment indication, mortality was significantly lower in the group of patients who received volume expansion without an indication than in patients who received SA based on a clinical indication or who were not given SA (at 30 days, OR 0.08, 95% CI 0.01-0.63, p = 0.003; at 90 days, OR 0.15, 95% CI 0.04-0.51, p = 0.001). Mean survival at 90 days was 65.2 days (SD 3.1) *versus* 86.6 (SD 2.5 p = 0.001). Short-term mortality was higher when antibiotic therapy failed (at 30 days, OR 3.4, 95% CI 1.54-7.48, p = 0.002; at 90 days, OR 4.4, 95% CI 2.15-9, p = 0.001), regardless of the reason for the change of antibiotic. Failure of antibiotic treatment was significantly related to risk of bacteremia (OR 3.4, 95% CI 1.23-9.71, p = 0.01).

In the multivariate analysis (Table 3), the presence of leukopenia or leukocytosis, hepatic encephalopathy, elevated BUN and unit of hospitalization were independent risk factors for 30-day mortality. At 90 days, BUN and the unit of hospitalization continued to be independent factors, as well as age, temperature > 37.5 °C, creatinine and serum bilirubin.

Analysis of long-term mortality (one and two years)

In the univariate study of long-term mortality (Table 2), patients treated with proton pump inhibitors (PPIs) had a higher mortality (p = 0.02). When patients on chronic antibiotic treatment (with norfloxacin or rifaximin) were considered as a single group, bowel decontamination had a protective effect at one year (OR 0.32, 95% CI 0.13-0.78, p = 0.012) and at two years (OR 0.25, 95% CI 0.083-0.76, p = 0.015).

After two years of follow-up, no significant increase in mortality was found in patients with SBP relapse OR 0.5 (95% CI 0.23-1.10; p = 0.89). No significant differences were found with regard to long-term mortality between patients with and without volume expansion with SA (at one year p = 0.7, and at two years p = 0.8). One-year survival was 209.8 days (SD 14.3) in patients who received SA for volume expansion without having an indication, as compared to 291.1 days (SD 18.8) in patients administered SA based on a clinical indication or not given SA (p = 0.009; OR 0.37, 95% CI 0.17-0.82 p = 0.01). There were no significant differences in mortality between patients who did not receive SA or who received SA based on an indication (p = 0.5).

There were no significant differences in long-term mortality in patients in whom antibiotic treatment failed (p = 0.79 at one year, p = 0.94 at two years). Age and hepatic encephalopathy at diagnosis were independent predictors of mortality at one and two years (Table 3).

Assessment of prognostic indices

At 30 days, neither CPT (p = 0.25) nor CCI (p = 0.93) were significantly related to mortality. However, there was a trend for a longer survival in Child A patients. MELD was found to be a good predictor of short-term mortality (OR 1.067, 95% CI 1.023-1.4, p = 0.002). Survival with a MELD ≥ 15 was 24.4 days (SD 0.95) and that of patients with MELD < 15 was 28.5 days (SD 0.8, p < 0.005). In ROC curve analysis, the AUC for short-term mortality was 0.71 (95% CI 0.63-0.79, p = 0.001). The optimum cut-off point was a MELD value of 16.5.

At two years, all three indices were predictors of mortality according to Kaplan-Meier curve analysis: CPT (p = 0.03), CCI (p = 0.001) and MELD (p = 0.021). Survival analysis (Fig. 2) showed that MELD continued to be a predictor of higher mortality in patients with scores ≥ 15, AUC 0.63 (95% CI 0.53-0.72, p = 0.008).

With regard to CCI, survival was poorer in patients with CCI ≥ 8 (p = 0.001) and there were no differences between patients with a lower CCI (p = 0.79). Mean survival after two years of follow-up was 447 days (SD 30.3) in patients with CCI < 8, and 240 days (SD 32.3) in those with CCI ≥ 8 (p = 0.001). The ROC curve had an AUC of 0.68 (95% CI 0.6-0.77, p = 0.001) with a CCI of 7.5, which was an optimum cut-off point according to

the Youden index.

Finally, the analysis of CPT as a prognostic factor for long-term survival showed that Child C patients had a greater mortality than those with Child A (p = 0.011). Child B patients have a dual behavior. During the first few months, the mortality rate was very similar to that of Child C patients but the survival curve then became less steep. Therefore, despite a clear trend, survival was not statistically significantly higher in Child B patients as compared to Child A patients (p = 0.2). ROC analysis of CPT, considered as a continuous variable, was not statistically significant (AUC 0.58; p = 0.08).

DISCUSSION

A first episode of SBP modifies the natural course of cirrhosis. AF infections in cirrhotic patients are associated with systemic changes that persist after resolution of the acute condition (4). Despite advances in treatment, our study confirms that mortality from SBP is still high, particularly if the episode is associated with the impairment of liver and kidney function.

Different reports have shown that liver function is a determinant variable of mortality in patients with SBP (16-18). Our study confirms that the development of hepatic encephalopathy that clinically results in impaired liver function is an independent risk factor that increases short- and long-term mortality.

Tandon et al. (7) showed that kidney function impairment was a key factor that determined a poorer prognosis in SBP with greatest consistency (5). Multiple reports have confirmed that volume expansion with SA decreases the incidence of kidney failure and mortality (15,19-21). Most patients received SA in this study, and patients with a history of chronic kidney failure or with AKI at the time of SBP diagnosis had a poorer survival. According to our data, AKI development is a predictor of long-term mortality, and elevated BUN levels are also an independent factor for short-term mortality. However, there were no significant differences in mortality between patients with different degrees of AKI.

Patients diagnosed with SBP who have impaired kidney function (serum creatinine level of 1 mg/dl or higher) or hyperbilirubinemia (serum bilirubin level higher than 4

mg/dl) are currently considered to be candidates for volume expansion with SA (15). Eighty-seven per cent of patients in our series received SA, which was according to the EASL (European Association for the Study of the Liver) guidelines in the vast majority of cases (15). There were no significant differences in mortality between treated or non-treated patients with SA. Our study shows that patients treated with volume expansion, despite the absence of a clear indication, had a longer survival as compared to patients not given SA or with no indication for volume expansion. These results may suggest a benefit of SA in all patients with SBP, regardless of kidney function or hyperbilirubinemia. Failure of antibiotic treatment only influenced 30-day survival, probably due to the increased risk of bacteremia.

Primary prophylaxis with norfloxacin decreased SBP incidence (22) and improved prognosis (23). According to the results of our study, primary bowel decontamination may have beneficial effects on long-term survival of patients with SBP. In the multivariate study, the use of rifaximin was an independent protective factor at two years. As previously reported (24), rifaximin modifies intestinal bacterial flora and is probably associated with lower endotoxemia and thus, better liver function.

Although this is a controversial subject, recent studies related the use of PPIs to an increased incidence of ascitic fluid infections (25-28). This study showed a significant increase in one-year mortality in patients treated with PPIs, probably due to a decreased gastric acidity that promoted bacterial growth (29). However, there is no adequate evidence to advise against the use of PPIs in patients with cirrhosis (30).

Only 11% of patients in this study had bacteremia at diagnosis, as compared to 30%-50% in other published studies (31). However, our data support the study by Cho et al. (32) that showed that bacteremia was an independent variable of in-hospital mortality, being a prognostic factor of short-term mortality in our study.

Hospitalization unit is another independent risk factor for mortality. This was to be expected as almost all patients who were not admitted to a gastroenterology department were in an intensive care unit, which suggests a hemodynamic instability or organ failure that required specific support.

In patients that did not receive secondary prophylaxis, SBP relapse rate was close to 70%, while treatment with norfloxacin may lower this rate to 20% (33). All patients in

our study were discharged with prophylactic treatment and the relapse rate of SBP was 22% according to the literature.

A novel aspect of our study was the inclusion of CCI among prognostic factors of patients with SBP. Survival does not depend only on liver function (MELD and BPT) alone but also on comorbidities. These results offer a new interpretation of indices routinely used in clinical practice. Thus, MELD is a good predictor of short- and long-term survival in patients with SBP. The CCI is of value as a long-term prognostic scale. By contrast, CPT has no adequate statistical precision to be used as prognostic index in episodes of SBP. A new prognostic index specifically designed for patients with SBP that includes these different variables is required.

The limitations of our study stem from its design. However, the comprehensive case review, multicenter nature and sample size compensate for this limitation. In addition, the lack of a common treatment protocol at all three hospitals was also a study limitation.

Furthermore, potential delays in diagnosis of admitted patients could not be assessed.

In conclusion, our study shows that despite improvements in diagnosis and treatment, SBP results in high short- and long-term mortality, and liver and kidney function impairment are the main prognostic factor for mortality.

Volume expansion with SA may represent a benefit for all patients with SBP, irrespective of kidney and liver function. MELD and CCI may be used as prognostic indices of mortality in patients with SBP.

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Table 1. Clinical and laboratory characteristics of the study patients

Variables	*Mean (± SD) or n (%)*
Demographic variables	
– Sex	
• Male	→ 114 (71.7)
• Female	→ 45 (28.3)
– Age (years)	→ 63.53 (± 13.288)
Cause of cirrhosis	
– Alcohol	→ 76 (47.8)
– Chronic hepatitis C	→ 41 (25.8)
– HCV + OH	→ 16 (10.1)
– Chronic hepatitis B	→ 5 (3.1)
– HBV + OH	→ 3 (1.9)
– Other	→ 18 (11.3)
Associated comorbidities	
– Diabetes mellitus	→ 41 (25.8)
– Chronic kidney failure	→ 33 (20.8)
– Hepatocarcinoma	→ 29 (18.2)
– HIV	→ 5 (3.1)
Treatment at admission	
– Diuretics	→ 92 (57.9)
– Proton pump inhibitors	→ 83 (52.2)
– Beta-blockers	→ 63 (39.5)
– Rifaximin	→ 22 (13.8)
– Norfloxacin	→ 12 (7.5)
Unit of hospitalization	
– Hepatology/other	132/27 (83/27)
Place where infection was acquired	
– Nosocomial/community-acquired	40/119 (25.2/74.8)
Scores	
– Child-Pugh (A/B/C)	→ 23/68/68

	(14.5/42.8/42.8)
– MELD	→ 19.37 (± 9.4)
– CCI	→ 6.12 (± 2.54)
Complications at admission	
– HE	→ 50 (31.4)
– UGB	→ 16 (10)
– AKI	→ 50 (31.4)
Mean blood pressure	80 (± 22.47)
Temperature > 37.5 °C	33 (20.8)
Laboratory tests	
– WBCs (mm/^{3})	→ 9,649.31 (± 6,912.74)
– Serum creatinine (mg/dl)	→ 1.45 (± 1.19)
– BUN (mg/dl)	→ 73.09 (± 52.01)
– Na+ (mEq/l)	→ 133.46 (± 5.4)
– PT (ratio)	→ 9.64 (± 23.14)
– Serum albumin (g/dl)	→ 6.22 (± 9.14)
– Total bilirubin (mg/dl)	→ 4.46 (± 6.34)
Positive AF cultures (n/%)	59 (37.1)
– *E. coli*	→ 18 (11.3)
– *Enterococcus* spp	→ 6 (3.8)
– *K. pneumoniae*	→ 4 (2.5)
– *S. aureus*	→ 3 (1.9)
– *P. aeruginosa*	→ 2 (1.2)
– ESBLs	→ 2 (1.25)
– Other	→ 24 (15.1)
Positive blood cultures (n/%)	→ 18 (11.3)
– *E. coli*	→ 8 (5)
– *Enterococcus* spp	→ 2 (1.3)
– *P. aeruginosa*	→ 1 (0.6)
– *S. aureus*	→ 1 (0.6)
– Other	→ 7 (4.4)

Antibiotic prescribed (n/%)	
– Cefalosporin	→ 127 (79.9)
– Carbapenem	→ 15 (9.4)
– Piperacillin-tazobactam	→ 4 (2.5)
– Amoxicillin-clavulanic ac.	→ 2 (1.3)
– Other	→ 11 (6.9)
Resistance (n)	
– Amoxicillin-clavulanic ac.	→ 6
– Ciprofloxacin	→ 1
– Ceftriaxone	→ 3
– Other	→ 7
– Multiple	→ 17

Summary of results of the descriptive study of demographic, laboratory, clinical and microbiological variables. OH: Alcohol; HCV: Hepatitis C virus; HBV: Hepatitis B virus; DM: Diabetes mellitus; CKF: Chronic kidney failure; HCC: Hepatocellular carcinoma; HIV: Human immunodeficiency virus; PPI: Proton pump inhibitor; HE: Hepatic encephalopathy; UGB: Upper gastrointestinal bleeding; AKI: Acute kidney injury; MBP: Mean blood pressure; WBC: White blood cells.

Table 2. Univariate study of prognostic factors of mortality

Variables	*30 days*		*90 days*		*1 year*		*2 years*	
	p	*OR (95% CI)*	*p*	*OR (95% CI)*	*p*	*OR (95% CI)*	*p*	*OR (95% CI)*
Demographic variables								
– Sex (male/female)	0.67	NS	0.54	NS	0.014	2.43 (1.19-4.94)	0.14	NS
– Age (years)	0.22	NS	0.001	1.05 (1.02-1.08	0.001	1.05 (1.02-1.08)	0.003	1.04 (1.01-1.07)
Cause of cirrhosis	0.1	NS	0.75	NS	0.53	NS	0.34	NS
Associated comorbidities								
– DM	0.124	NS	0.26	NS	0.6	NS	0.66	NS
– HIV	0.96	NS	0.58	NS	0.8	NS	0.58	NS
– CKF	0.004	3.44 (1.47-8.02)	0.001	4.15 (1.86-9.26)	0.022	2.66 (1.15-6.18)	0.07	NS
– HCC	0.62	NS	0.09	NS	0.002	5.1 (1.83-14.2)	0.07	NS
Treatment at admission								
– Beta-blockers	0.44	NS	0.14	NS	0.25	NS	0.18	NS
– PPI	0.48	NS	0.51	NS	0.016	2.18 (1.15-4.12)	0.016	2.32 (1.16-4.61)
– Norfloxacin	0.25	NS	0.88	NS	0.15	NS	0.7	NS
– Rifaximin	0.8	NS	0.96	NS	0.07	NS	0.027	0.18 (0.042-0.82)
– Diuretics	0.97	NS	0.98	NS	0.23	NS	0.5	NS
Unit of hospitalization								
– Hepatology/other	0.001	5.2 (2.13-12.69)	0.001	4.19 (1.77-9.91)	0.17	NS	0.49	NS
Place where infection was acquired	0.22	NS	0.18	NS	0.74	NS	0.82	NS
–Nosocomial/community-acquired								
Complications at admission								
– HE	0.001	4.34 (1.94-	0.04	2.09 (1.03-	0.003	3.14 (1.48-	0.02	2.56 (1.12-

		12.02)		4.24)		6.05)		5.89)
– UGB	0.28	NS	0.58	NS	0.89	NS	0.56	NS
– AKI	0.002	3.52 (1.59-7.79)	0.001	5.78 (2.77-12.08)	0.014	2.49 (1.2-5.19)	0.05	2.24 (1-5.03)
Positive AF cultures	0.89	NS	0.85	NS	0.07	NS	0.02	2.27 (1.12-4.56)
Positive blood cultures	0.007	4.32 (1.49-12.54)	0.07	NS	0.32	NS	0.36	NS
MBP	0.77	NS	0.57	NS	0.59	NS	0.81	NS
Temperature (> 37.5 °C)	0.37	NS	0.029	3.11 (1.12-8.61)	0.11	NS	0.36	NS
Laboratory – WBCs (mm/^{3})	0.012		0.1	NS	0.9	NS	0.43	NS
– Serum creatinine (mg/dl)	0.001	1.76 (1.26-2.48)	0.001	1.92 (1.33-2.79)	0.03	1.46 (1.03-2.08)	0.27	NS
– BUN (mg/dl)	0.001	1.01 (1.00-1.02)	0.001	1.02 (1.01-1.02)	0.003	1.01 (1.00-1.02)	0.04	1.01 (1.01-1.02)
– Na+ (mEq/l)	0.9	NS	0.8	NS	0.36	NS	0.16	NS
– PT (ratio)	0.24	NS	0.12	NS	0.008	0.97 (1.01-1.02))	0.61	NS
– Serum albumin (g/dl)	0.95	NS	0.75	NS	0.69	NS	0.36	NS
– Total bilirubin (mg/dl)	0.03	1.05 (1-1.11)	0.06	NS	0.86	NS	0.63	NS

Summary of the results of the univariate study of short- and long-term prognostic factors of mortality in demographic, laboratory, clinical and microbiological variables. NS: Not significant; DM: Diabetes mellitus; HIV: Human immunodeficiency virus; CKF: Chronic kidney failure; HCC: Hepatocellular carcinoma; PPI: Proton pump inhibitor; HE: Hepatic encephalopathy; UGB: Upper gastrointestinal bleeding; AKI: Acute kidney injury; AF: Ascitic fluid; WBCs: White blood cells; BUN: Blood urea nitrogen; PT: Prothrombin time.

Table 3. Multivariate study of short- and long-term mortality

			95% CI for EXP(B)	
	Sig.	OR	Lower	Upper
30 days				
Leukocytosis/leukopenia	0.004	5.016	1.685	14.929
HE	0.002	4.942	1.835	13.307
BUN	0.002	1.014	1.005	1.024
Unit of hospitalization	0.004	4.692	1.646	13.373
90 days				
Age	0	1.088	1.042	1.135
Unit of hospitalization	0	9.261	2.709	31.661
T > 37.5 °C	0.026	4.914	1.211	19.948
Creatinine	0.029	0.513	0.282	0.932
BUN	0	1.03	1.014	1.046
1 year				
Age	0.025	1.04	1.005	1.077
Male sex	0.002	4.65	1.797	12.031
HCC	0.004	6.652	1.859	23.797
PPI	0.004	3.574	1.52	8.405
AKI	0.026	2.798	1.13	6.932
HE	0	6.38	2.437	16.706
2 years				
Age	0.003	1.045	1.015	1.076
Rifaximin	0.034	0.174	0.034	0.874
HE	0.008	3.496	1.387	8.809

HCC: Hepatocellular carcinoma; PPI: Proton pump inhibitor; AKI: Acute kidney injury; HE: Hepatic encephalopathy; PT: Prothrombin time.

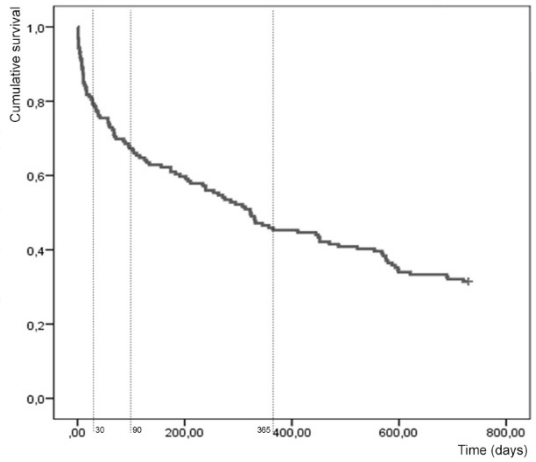

Fig. 1. Cumulative overall survival of the patient cohort after two years of follow-up.

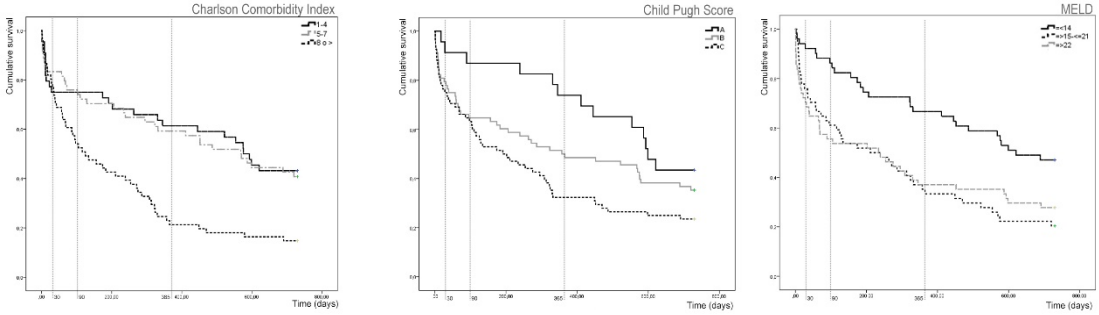

Fig. 2. Cumulative survival after two years of follow-up categorized by MELD, Charlson Comorbidity Index and Child Pugh Score.