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Natural history of grade 1 ascites in patients with liver cirrhosis

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Abstract

Background No evidence is available on the natural history of grade 1 ascites and its progression to grade 2/3 in patients with liver cirrhosis. The aim of the current study was to address this issue, to assess the development of main comorbid disorders closely related to ascites progression, and to identify the predictive factors for survival in this setting.

Methods Consecutive Caucasian cirrhotic patients with grade 1 ascites were retrospectively analyzed. None of patients was under treatment with diuretics at diagnosis. Control groups consisted of 145 cirrhotics with grade 2/3 ascites and 175 cirrhotics without ascites.

Results Diuretics were initiated in 58 patients with grade 1 ascites at baseline by the attending physician. At the last follow up, 29 patients had no ascites, 33 patients had grade 1 and 38 patients had grade 2/3 ascites. No variable was found to be an independent predictor of grade 2/3 ascites. Seven patients developed spontaneous bacterial peritonitis while under treatment with diuretics; at that time only 1 patient had grade 1 ascites. The mortality rate was similar among all examined groups.

Conclusions This study suggests that the presence of grade 1 ascites does not constitute a precursor of grade 2/3 ascites in patients with cirrhosis. Thus, patients with grade 1 ascites do not require specific treatment with diuretics.

Keywords Ascites, grade 1, natural history, liver cirrhosis

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Introduction

The presence of ascites is considered to be a significant landmark in liver cirrhosis, as it is associated with decompensation and 50% mortality over 2 years [1,2]. In addition, the evolution of ascites is connected to a poor quality of life, higher risk of infection, and renal failure [3,4]. The classification of ascites is based on the amount of fluid in the abdominal cavity: grade 1 ascites, or mild ascites, detectable by ultrasound examination; grade 2 ascites, or moderate ascites, characterized by a mild symmetrical abdominal distension; and grade 3 ascites, or large ascites, with significant abdominal distension [5,6]. Cirrhotic patients with ascites are at high risk of developing various complications of liver disease, including spontaneous bacterial peritonitis (SBP) and hepatorenal syndrome (HRS) [5,7]. It has been shown that the 1-year probability of survival in patients with uncomplicated ascites is 85%, compared to 25.6%, 31.6% and 38.5%, in patients with hyponatremia, refractory ascites and HRS, respectively [8].

The International Club of Ascites has documented that patients with ascites grade 1 do not require specific treatment, but should be followed-up carefully and advised to reduce their sodium intake, since they usually progress to the development of grade 2 ascites [5]. European Association for the Study of the Liver (EASL) guidelines have reported that there is no data on the evolution of grade 1 ascites, nor it is known whether its treatment modifies its natural history [6]. Furthermore, there

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are no data on how frequently patients with grade 1 develop grade 2/3 ascites [6,9]. Therefore, there is a great need for a better understanding of the natural history of ascites grade 1 in liver cirrhosis.

To this end, the current study aimed to assess grade 1 ascites as a representative risk factor for the development of grade 2/3 ascites in patients with cirrhosis, to evaluate the main comorbid disorders which come along with ascites progression, and to identify the predictive factors for survival in this setting.

Patients and methods

Study population

One hundred consecutive Caucasian patients with grade 1 ascites were enrolled in this retrospective study. One hundred forty-five consecutive Caucasian patients with grade 2/3 ascites and 175 without ascites served as control groups. The study population was composed of hospitalized medical patients or outpatients from 3 university hospitals in Greece (University Hospital of Patras, n=315; University Hospital of Ioannina, n=59; and University Hospital of Heraklion, n=46). The recruitment of the patients was performed between November 1993 and July 2014. Blood samples were collected from patients throughout the year.

Definitions

The diagnosis of liver cirrhosis was based on clinical, laboratory, histological and ultrasonographic findings [10,11]. The severity of liver cirrhosis was assessed by the Child-Pugh (CP) score, CP stage, and by model for end-stage liver disease (MELD) score [12]. The evaluation of ascites was based on medical history, physical examination, abdominal ultrasound, assessment of laboratory parameters and analysis of the ascitic fluid [6]. The diagnosis of SBP was defined as suggested by the International Club of Ascites diagnostic criteria, hepatic encephalopathy (HE) was defined as suggested by the EASL and the American Association for the Study of Liver Diseases practice guidelines, and HRS was defined as suggested by the revised consensus recommendations of the International Club of Ascites [5,13-15]. Patients with human immunodeficiency virus infection and severe cardiopulmonary disease or renal failure were excluded from enrolment. Alcoholic patients ceased alcohol abuse according to the guidelines [16]. Sodium intake restriction was applied, according to guidelines [9] and the physician's intuitive judgment.

Follow up

The study population was followed-up over a mean period of 18.93±30.74 (range: 1-241) months until death or liver transplantation. Diagnostic and therapeutic criteria were applied uniformly during the follow-up period. Patients underwent clinical evaluation in the hepatology clinic at regular intervals according to current guidelines [10]. The initiation of diuretics during follow up in patients with ascites grade 1 was based on the physician's intuitive judgment.

Statistical analysis

All patients' characteristics were presented separately by ascites status (no ascites, ascites grade 1, ascites grade 2/3) and were compared using chi-square test for categorical characteristics, or the Kruskal-Wallis test for continuous characteristics. Both univariate and multivariate Cox models were used to evaluate potential risk factors for patients' survival. This analysis was repeated in the subgroup of patients with ascites grade 1. Univariate and multivariate logistic regression models were used for binary outcomes. Life-table analysis with the Kaplan-Meier method was used to estimate proportional outcomes. All comparisons were performed at the 5% level of significance. Analysis was conducted using Stata (StataCorp, College Station, Texas) version 13.1.

Ethical guidelines

The study protocol was reviewed and approved by the Ethics Committee of the University Hospital of Patras. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki for medical research involving human subjects.

Results

The patients' baseline demographic, clinical and laboratory characteristics are summarized in Table 1. Patients with grade 1 ascites presented at baseline with CP stage A 18%, CP stage B 60% and CP stage C 22%; patients with grade 2/3 ascites presented with CP stage A 12.9%, CP stage B 65.2% and CP stage C 22%; and lastly, patients with no ascites presented with CP stage A 76%, CP stage B 22.6% and CP stage C 1.4%. The median MELD score at baseline was 12.5 for those patients with grade 1 ascites, 14.0 for those with grade 2/3 ascites and 9.0 for those with no ascites. At baseline, infection was observed in 6 patients (6%)—SBP in 1 patient (1%)—hepatocellular carcinoma (HCC) in 9 patients (9%), pleural effusion in 6 patients (6%), portal gastropathy bleeding in 10 patients (10%), acute variceal bleeding in 7 patients (7%) and portal vein thrombosis in 5 patients (5%) of the grade 1 ascites group. Moreover, at baseline 50 (50%) of the 100 patients with grade 1 ascites had varices (23 small and 27 large varices). The development of the main clinical manifestations related to ascites progression in each group of patients during the follow-up period is presented in Table 2.

Table 1 Patients' baseline demographic, clinical and laboratory characteristics

Characteristics	Grade 1 ascites	Grade 2/3 ascites	No ascites	Overall	P-value
	N (%)	N (%)	N (%)	N (%)	
Sex					0.004
Male	88 (88.0)	109 (75.2)	123 (70.3)	320 (76.2)	
Female	12 (12.0)	36 (24.8)	52 (29.7)	100 (23.8)	
Cause of liver cirrhosis					<0.001
Alcohol	62 (62.0)	105 (71.4)	82 (47.1)	249 (59.2)	
HBV	21 (21.0)	25 (17.3)	42 (24.2)	88 (20.9)	
HCV	14 (14.0)	8 (6.0)	28 (15.3)	50 (11.8)	
Autoimmune	2 (2.0)	5 (3.8)	23 (13.4)	30 (7.3)	
NASH	1 (1.0)	2 (1.5)	0 (0.0)	3 (0.8)	
Smoking					0.767
Yes	57 (57.0)	86 (59)	97 (55.6)	240 (57.2)	
No	43 (43.0)	59 (41)	78 (44.4)	180 (42.8)	
Nutritional status					0.003
Obese	13 (13.0)	11 (7.6)	31 (17.7)	55 (13.1)	
Normal	71 (71.0)	112 (77.2)	135 (77.1)	318 (75.7)	
Malnourished	16 (16.0)	22 (15.2)	9 (5.1)	47 (11.2)	
CP stage					<0.001
A	18 (18.0)	18 (12.9)	134 (76.0)	170 (38.6)	
B	60 (60.0)	95 (65.2)	39 (22.6)	194 (47.4)	
C	22 (22.0)	32 (22.0)	2 (1.4)	56 (14)	
Intrinsic renal disease					0.046
Yes	3 (3.0)	10 (6.9)	3 (1.7)	16 (3.8)	
No	97 (97.0)	135 (93.1)	172 (98.3)	403 (96.2)	
Diabetes mellitus					0.746
Yes	18 (18.0)	32 (22.1)	36 (20.6)	86 (20.5)	
No	82 (82.0)	113 (77.9)	139 (79.4)	334 (79.5)	
Non-HCC malignancy					0.024
Yes	3 (3.0)	6 (4.1)	18 (10.3)	27 (6.4)	
No	97 (97.0)	139 (95.9)	157 (89.7)	393 (93.6)	
Hepatic encephalopathy					0.042
Yes	9 (9.0)	7 (4.8)	4 (2.3)	20 (4.8)	
No	91 (91.0)	138 (95.2)	171 (97.7)	400 (95.2)	
	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)	
Age (years)	59.0 (50.0-70.0)	59.0 (50.0-67.5)	64.0 (50.0-71.0)	60.0 (50.0-69.0)	0.318
Plt (cells/μL)	112.0 (68.0-167.0)	124.5 (95.0-176.0)	131.0 (80.0-190.0)	125.0 (81.0-180.0)	0.054
PT (sec)	16.1 (14.6-19.4)	15.9 (14.2-18.4)	13.7 (12.6-15.4)	14.9 (13.1-17.0)	<0.001
INR	1.3 (1.2-1.5)	1.4 (1.2-1.5)	1.2 (1.0-1.4)	1.3 (1.1-1.5)	<0.001
Bilirubin (mg/dL)	2.1 (1.3-4.0)	2.1 (1.4-3.4)	1.0 (0.7-1.8)	1.6 (0.9-2.8)	<0.001
Albumin (g/dL)	3.1 (2.7-3.7)	3.1 (2.8-3.6)	3.8 (3.3-4.2)	3.4 (3.0-3.9)	<0.001

(*Contd...*)

Table 1 (*Continued*)

Characteristics	Grade 1 ascites	Grade 2/3 ascites	No ascites	Overall	P-value
	N (%)	N (%)	N (%)	N (%)	
Urea (mg/dL)	31.0 (21.0-39.0)	32.0 (22.0-43.0)	33.0 (24.0-42.0)	32.0 (22.0-42.0)	0.543
Creatinine (mg/dL)	0.9 (0.8-1.0)	0.9 (0.7-1.1)	0.9 (0.8-1.0)	0.9 (0.7-1.0)	0.473
Sodium (mmol/L)	138.0 (135.0-140.0)	137.0 (134.2-139.0)	139.0 (136.4-142.0)	138.0 (135.1-140.0)	<0.001
CP score	8.0 (7.0-9.0)	8.0 (7.0-9.0)	5.0 (5.0-6.0)	7.0 (6.0-9.0)	<0.001
CP creatinine score	8.0 (7.0-10.0)	8.0 (7.0-10.0)	5.0 (5.0-7.0)	7.0 (5.0-9.0)	<0.001
MELD score	12.5 (10.0-17.0)	14.0 (11.0-16.0)	9.0 (8.0-12.0)	12.0 (9.0-15.0)	<0.001
MELD-Na score	14.0 (11.0-18.0)	16.0 (13.0-19.0)	11.0 (8.5-14.0)	14.0 (10.0-18.0)	<0.001

N, number of patients; HBV, hepatitis B virus; HCV, hepatitis C virus; NASH, non-alcoholic steatohepatitis, CP, Child-Pugh; HCC, hepatocellular carcinoma; Plt, platelets; PT, prothrombin time; INR, international normalized ratio; MELD, model for end-stage liver disease; IQR, interquartile range

Table 2 The development of main clinical manifestations related to ascites progression during follow up

Characteristics	Overall	Grade 1 ascites vs. Grade 2/3 ascites			Grade 1 ascites vs. No ascites		
		Grade 1 ascites	Grade 2/3 ascites	P-value	Grade 1 ascites	No ascites	P-value
	N (%)	**N (%)**	**N (%)**		**N (%)**	**N (%)**	
Hepatic encephalopathy				0.742			<0.001
No	351 (83.6)	77 (77.0)	109 (75.2)		77 (77.0)	165 (94.3)	
Yes	69 (16.4)	23 (23.0)	36 (24.8)		23 (23.0)	10 (5.7)	
Hepatorenal syndrome				0.481			<0.001
No	398 (94.8)	90 (90.0)	134 (92.4)		90 (90.0)	174 (99.4)	
Yes	22 (5.2)	10 (10.0)	11 (7.6)		10 (10.0)	1 (0.6)	
HCC				0.054			0.287
No	372 (88.6)	93 (93.0)	123 (84.8)		93 (93.0)	156 (89.1)	
Yes	48 (11.4)	7 (7.0)	22 (15.2)		7 (7.0)	19 (10.9)	
Pleural effusion				0.225			<0.001
No	374 (89.0)	86 (86.0)	117 (80.7)		86 (86.0)	171 (97.7)	
Yes	46 (11.0)	14 (14.0)	28 (19.3)		14 (14.0)	4 (2.3)	
Portal gastropathy bleeding				0.924			0.030
No	382 (90.8)	88 (88.0)	127 (87.5)		88 (88.0)	167 (95.4)	
Yes	38 (9.2)	12 (12.0)	18 (12.6)		12 (12.0)	8 (4.6)	
New variceal bleeding				0.030			0.129
No	367 (87.5)	89 (89.0)	113 (78.1)		89 (89.0)	165 (94.3)	
Yes	53 (12.5)	11 (11.0)	32 (31.8)		11 (11.0)	10 (5.7)	
Portal vein thrombosis				0.304			0.116
No	396 (94.2)	94 (94.0)	131 (90.4)		94 (94.0)	171 (97.7)	
Yes	24 (5.7)	6 (6.0)	14 (9.7)		6 (6.0)	4 (2.3)	
Infection				0.633			0.002
No	310 (73.5)	68 (68.0)	94 (64.8)		68 (68.0)	148 (84.5)	
Yes	110 (26.5)	32 (32.0)	51 (35.2)		32 (32.0)	27 (15.5)	

N, number of patients; HCC, hepatocellular carcinoma

Ascites outcome

At the last follow up, 29 patients (29%) had no ascites, 33 patients (33%) had grade 1, 17 patients (17%) had grade 2 and 21 patients (21%) had grade 3 ascites. A univariate analysis was performed in the grade 1 ascites group to explore the factors associated with ascites outcome (regression, stability or deterioration) at the last follow up. Patients' advanced age (P=0.041) and HCC (P=0.042) were the only factors related to ascites outcome. In the multivariate analysis, no variable was found to be an independent predictor of ascites outcome. A separate analysis was conducted for the identification of risk factors for grade 2/3 ascites development. In the univariate analysis, advanced age (P=0.012) and HCC (P=0.044) were found to be potential predictors of grade 2/3 ascites. In the multivariate analysis, no variable was found to be an independent predictor of grade 2/3 ascites.

Diuretics

Treatment with diuretics was initiated in 58 patients with grade 1 ascites (58%) at baseline. During follow up, 78 patients with grade 1 (78%), 89 patients with grade 2/3 (61%) and 30 patients with no ascites (17.2%) were treated with diuretics. Treatment with diuretics at baseline (odds ratio [OR] 0.534, 95% confidence interval [CI] 0.214-1.336; P=0.177) or during follow up (OR 1.887, 95%CI 0.571-6.229; P=0.292) was not correlated with regression of ascites. Twenty-five patients with grade 1 ascites treated with diuretics had regression of ascites, 20 patients had stable ascites and 33 patients had worsening ascites at the last follow up.

HE

Twenty-three patients with ascites grade 1 (23%), 36 patients with ascites grade 2/3 (24.8%), and 10 patients with no ascites (5.7%) presented HE during follow up (P<0.001). The univariate analysis of factors correlated with HE development is presented in Supplementary Table 1. Multivariate analyses were performed between 2 sets of variables for the total population to avoid collinearity errors (Table 3). The use of diuretics, HE at baseline and international normalized ratio in the first analysis, and the use of β-blockers, diuretics, and CP stage B and C in the second, were independently associated with HE development. The same analyses were conducted in the group of patients with ascites grade 1 (Supplementary Table 2); in the multivariate analysis no variable was found to be independently associated with HE development.

HRS

Ten patients with ascites grade 1 (10%), 11 patients with ascites grade 2/3 (7.6%) and 1 patient with no ascites (0.6%) developed HRS during follow up (P=0.001). Fourteen patients with HRS (63.6%) had developed concomitant SBP infection. The factors

Table 3 Multivariate analyses of factors correlating with the main comorbid disorders that accompany ascites progression in the total population

Hepatic encephalopathy development		
MODEL 1		
Parameters	OR (95%CI)	P-value
Group		
No ascites*	1	
Grade 1 ascites	2.12 (0.86-5.24)	0.102
Grade 2-3 ascites	2.27 (0.96-5.40)	0.064
β-blockers		
No*	1	
Yes	1.87 (0.96-3.64)	0.067
Diuretics		
No*	1	
Yes	4.05 (1.36. 13.03)	0.019
Hepatic encephalopathy		
No*	1	
Yes	5.22 (1.77-15.40)	0.003
Albumin		
Per unit	0.80 (0.51-1.27)	0.350
INR		
Per unit	2.75 (1.08-7.04)	0.034
Bilirubin		
Per unit	1.02 (0.94-1.10)	0.668
MODEL 2		
Parameters	OR (95%CI)	P-value
Group		
No ascites*	1	
Grade 1 ascites	1.27 (0.50-3.20)	0.615
Grade 2-3 ascites	1.26 (0.51-3.12)	0.613
β-blockers		
No*	1	
Yes	1.94 (1.01-3.74)	0.048
Diuretics		
No*	1	
Yes	3.48 (1.13-10.75)	0.030
CP stage		
A*	1	
B	2.98 (1.15-7.68)	0.024
C	6.79 (2.31-19.90)	<0.001

(*Contd...*)

Table 3 (*Continued*)

Hepatorenal syndrome development		
MODEL 1		
Parameters	OR (95%CI)	P-value
Group		
No ascites*	1	
Grade 1 ascites	4.59 (0.48-43.60)	0.184
Grade 2-3 ascites	3.68 (0.39-35.07)	0.257
Sex		
Female*	1	
Male	6.19 (0.79-48.20)	0.082
Diuretics		
No*	1	
Yes	2.14 (0.77-6.01)	0.147
CP stage		
A*	1	
B	2.21 (0.44-11.10)	0.335
C	2.63 (0.45-15.43)	0.284
β-blockers		
No*	1	
Yes	11.98 (1.57-91.53)	0.017
MODEL 2		
Parameters	OR (95%CI)	P-value
Group		
No ascites*	1	
Grade 1 ascites	6.74 (0.4-61.43)	0.091
Grade 2-3 ascites	4.80 (0.52-44.37)	0.167
Diuretics		
No*	1	
Yes	2.06 (0.73-5.77)	0.171
β-blockers		
No*	1	
Yes	11.95 (1.57-91.06)	0.017
CP score		
per unit	1.07 (0.82-1.40)	0.630
Infection development		
Parameters	OR (95%CI)	P-value
Group		
No ascites*	1	
Grade 1 ascites	1.58 (0.83-3.04)	0.166
Grade 2-3 ascites	2.22 (1.22-4.06)	0.009

(*Contd...*)

Table 3 (*Continued*)

Infection development		
Sex		
Female*	1	
Male	1.81 (0.96-3.41)	0.069
Hepatic encephalopathy		
No*	1	
Yes	6.30 (2.12-18.78)	0.001
MELD		
Per unit	1.05 (0.99-1.10)	0.094
SBP Development		
Parameters	OR (95%CI)	P-value
Group		
No ascites*	1	
Grade 1 ascites	7.13 (0.81-62.88)	0.077
Grade 2-3 ascites	23.07 (2.87-185.18)	0.003
Sex		
Female*	1	
Male	2.56 (0.82-7.98)	0.106
β-blockers		
No*	1	
Yes	0.60 (0.25-1.44)	0.254
Diuretics		
No*	1	
Yes	0.96 (0.44-2.09)	0.918
Albumin		
Per unit	0.77 (0.42-1.40)	0.387
MELD		
Per unit	1.01 (0.93-1.11)	0.761
Sodium		
Per unit	0.96 (0.87-1.05)	0.371

* Reference category

OR, odds ratio; INR, International normalized ratio; CI, confidence interval; CP, Child-Pugh; MELD, model for end-stage liver disease

related to HRS development are presented in Supplementary Table 1. Multivariate analysis for the total population (Table 3) determined that the use of β-blockers was the only independent prognostic factor for HRS development. The same analyses were performed in the group of patients with ascites grade 1 (Supplementary Table 2); in the multivariate analysis no variable was found to be associated with HRS development.

Infection

Thirty-two patients with ascites grade 1 (32%), 51 patients with ascites grade 2/3 (35.2%) and 26 patients

with no ascites (14.9%) developed infection during follow up (P<0.001). In the group of patients with ascites grade 1, 7 patients (24.1%) developed SBP. Patients who developed SBP were under treatment with diuretics. At the time of SBP infection, 6 of them had grade 2/3 ascites and 1 patient had grade 1 ascites. At the last follow up, 6 SBP infected patients had grade 2/3 ascites, 1 patient had no ascites and none of them had grade 1 ascites (P=0.023). The factors associated with the development of infection are presented in Supplementary Table 1. In the multivariate analysis (Table 3), ascites grade 2/3 and the presence of HE at baseline were independently correlated with infection development and ascites grade 2/3 was the only predictor for SBP development (Table 3).

Survival analysis

Total population

During follow up, 166 of 420 patients died, with a cumulative mortality rate of 39.5%. In the univariate analysis, the factors associated with patients' survival are presented in the Supplementary Table 3. In the multivariate analysis, age (hazard ratio [HR] 1.03, 95%CI 1.02-1.05; P<0.001), diabetes mellitus (DM) (HR 1.53, 95%CI 1.03-2.28; P=0.036), and the CP stage C (HR 2.30, 95%CI 1.37-3.85; P=0.002) were demonstrated as significant independent prognostic factors for patients' survival (Table 4).

Ascites 1 group

During follow up, 36 of 100 patients died, with a cumulative mortality rate of 36%. In the multivariate analysis, 2 models were constructed (Table 4). The first model included creatinine, CP stage, HCC, and age. HCC (HR 4.84, 95%CI 1.08-21.70; P=0.040), age (HR 1.04, 95%CI 1.00-1.08; P=0.048), and creatinine (HR 1.39, 95%CI 1.11-1.75; P=0.005) were found to be significantly related to patients' survival. The second model included MELD score, albumin, HCC, and age. Age (HR 1.05, 95%CI 1.01-1.09; P=0.014) and albumin (HR 0.46, 95%CI 0.23-0.93; P=0.031) were independently correlated with patients' survival.

Ascites 2-3 group

During follow up, 73 of 145 patients died of all causes, with a cumulative mortality rate of 50%. For the multivariate analysis, 2 models, including DM, age and CP score and DM, age and MELD score, were constructed (Table 4). In the first model, only age (HR 1.04, 95%CI 1.01-1.06; P=0.002) was demonstrated as a predictor of mortality. In contrast, the second model, apart from age (HR 1.04, 95%CI 1.02-1.06; P=0.001), also demonstrated that MELD score (HR 1.09, 95%CI 1.03-1.16; P=0.006) was an independent predictor of survival.

Table 4 Multivariate cox regression analysis for patients' survival

Total population		
Parameters	HR (95%CI)	P-value
Intrinsic renal disease		
No*	1	
Yes	2.02 (0.86-4.74)	0.107
HCC		
No*	1	
Yes	1.16 (0.51-2.63)	0.729
Ischemic heart disease		
No*	1	
Yes	1.66 (0.74-3.70)	0.218
Diabetes mellitus		
No*	1	
Yes	1.53 (1.03-2.28)	0.036
Age		
per unit	1.03 (1.02-1.05)	<0.001
CP stage		
A*	1	
B	1.15 (0.78-1.69)	0.491
C	2.30 (1.37-3.85)	0.002
ASCITES 1 GROUP		
MODEL 1		
Parameters	HR (95%CI)	P-value
HCC		
No*	1	
Yes	4.84 (1.08-21.70)	0.040
Age		
per unit	1.04 (1.00-1.08)	0.048
Creatinine		
per unit	1.39 (1.11-1.75)	0.005
CP stage		
A*	1	
B	1.97 (0.62-6.33)	0.253
C	2.66 (0.66-10.70)	0.168
MODEL 2		
Parameters	HR (95%CI)	P-value
HCC		
No*	1	
Yes	3.78 (0.96-14.89)	0.057

(*Contd...*)

Table 4 (*Continued*)

MODEL 2		
Parameters	HR (95%CI)	P-value
Age		
per unit	1.05 (1.01-1.09)	0.014
Albumin		
per unit	0.46 (0.23-0.93)	0.031
MELD score		
per unit	1.03 (0.94-1.13)	0.499
ASCITES 2/3 GROUP		
MODEL 1		
Parameters	HR (95%CI)	P-value
Diabetes mellitus		
No*	1	
Yes	1.67 (0.93-2.98)	0.086
Age	1.04 (1.01-1.06)	0.002
per unit		
CP score		
per unit	1.13 (0.95-1.34)	0.162
MODEL 2		
Parameters	HR (95%CI)	P-value
Diabetes mellitus		
No*	1	
Yes	1.52 (0.89-2.60)	0.127
Age		
per unit	1.04 (1.02-1.06)	0.001
MELD score		
per unit	1.09 (1.03-1.16)	0.006
NO ASCITES GROUP		
Parameters	HR (95%CI)	P-value
Ischemic heart disease		
No*	1	
Yes	1.97 (0.46-8.74)	0.370
Age		
per unit	1.04 (1.01-1.06)	0.008
Albumin		
per unit	0.74 (0.53-1.06)	0.100

* Reference category

HR, hazard ratio; CI, confidence interval; HCC, hepatocellular carcinoma; CP, Child-Pugh; MELD, model for end-stage liver disease

No ascites group

During follow up, 57 of 175 patients died of all causes, with a cumulative mortality rate of 32.8%. In the multivariate analysis, only age (HR 1.04, 95%CI 1.01-1.06; P=0.008) was independently correlated with survival (Table 4). The probability of overall survival in patients with ascites grade 1, ascites grade 2/3 and no ascites is presented in Fig. 1. There was no difference in overall survival among the 3 groups (log-rank = 1.408, P=0.484).

Discussion

To our knowledge, this study constitutes the first report on the natural history and clinical course of cirrhotic patients with ascites grade 1, compared to patients with ascites grade 2/3 or no ascites, followed-up for a mean period of 18.93 months. EASL guidelines have reported that there is no evidence regarding the natural history of ascites grade 1 and its progression to grade 2/3 in patients with liver cirrhosis [6,9]. The present study shows that at the last follow up, 62% of patients with grade 1 ascites had regression or stability of ascites, while 38% of patients had worsening ascites. Grade 1 ascites was not found to be an independent predictor of grade 2/3 ascites. The initiation of diuretics was not correlated with regression of ascites at baseline or during follow up. The risk for SBP infection was low and occurred mainly in patients who developed worsening ascites. The mortality risk was similar to that of non-ascitic patients. These results indicate that the existence of grade 1 ascites in patients with liver cirrhosis does not represent a risk factor for the development of worsening ascites and suggest that there is no need for treatment with diuretics.

Development of ascites is the most common complication in patients who have liver cirrhosis, with approximately 60% of patients developing ascites within 10 years. Ascites' emergence and progression indicate a poor prognosis for patients, with a mortality of approximately 40% after 1 year [17-19]. Numerous reports have evaluated the natural history of liver disease of various etiologies [20-24]. Two studies have examined the natural history of patients hospitalized for the management of ascites in a cirrhotic population and have identified the prognostic factors associated with ascites progression [8,25]. Nevertheless, both studies included patients with clinically significant ascites (grade 2/3) [8,25].

The current study evaluated the development of the main comorbid disorders closely associated with ascites progression. HRS developed in 10% of ascites grade 1 patients, in 7.6% of those with ascites grade 2/3 and in 0.6% of patients with no ascites during follow up. Studies have shown variation among HRS rates in patients with ascites (11.4% in 5 years [8] and 3% at 8.1 months [25]). These discrepancies could be explained by the variation in ascites severity and duration of follow up between these studies. Our study revealed that the use of β-blockers was the only independent predictive factor of

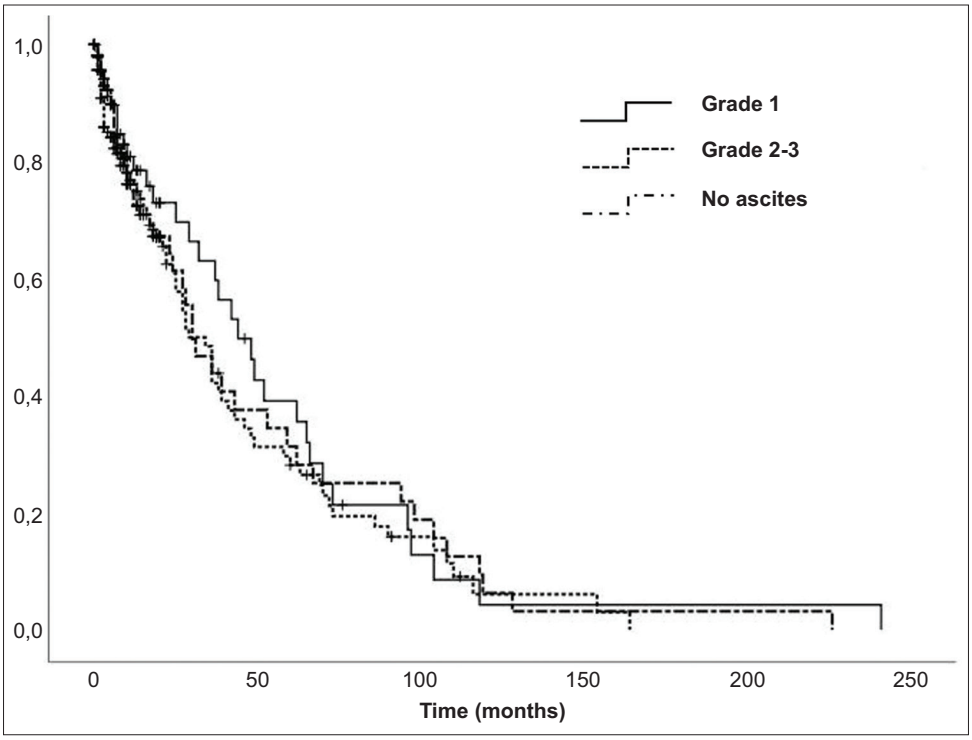

Figure 1 Kaplan-Meier curves for the cumulative probability of survival in patients with grade 1, 2/3 and no ascites

HRS development during follow up. A possible explanation of this finding could be the presence of concomitant SBP infection (63.6%) in a high percentage of HRS patients in this cohort. The progression from cirrhosis with ascites to HRS development represents a pathophysiologic continuity driven by the existence of sinusoidal portal hypertension and systemic arterial vasodilation. Consequently, one explanation for the association between β-blocker intake and HRS development could be the severity of the underlying portal hypertension (grade of varices, etc.) as reflected by the clinical portal hypertension-related clinical events in Table 2.

The development of infection during follow up was also assessed in this cohort: 32% of patients with ascites grade 1, 35.2% of patients with ascites grade 2/3 and 14.9% of patients with no ascites were found to develop infection during the follow-up period. Patients with cirrhosis are at increased risk of developing bacterial infections [26,27]. In patients with liver cirrhosis and ascites, one of the most serious complications is the development of SBP, as it is associated with a high 1-year mortality rate (30% to 90%) [28,29]. Several studies have examined the prevalence of SBP in patients with liver cirrhosis and ascites, which ranged between 10% and 30% [30-31]. However, one study reported a significantly higher prevalence of SBP infection (67.7%), in part explained by the small number and the advanced CP stage of the included patients [32]. In the present study, 7% of cirrhotic patients with ascites 1 developed SBP infection during follow up. However, at the time of infection only 1 patient had grade 1 ascites; the remaining 6 patients had grade 2/3. Moreover, the multivariate analysis demonstrated that the development of SBP was independently associated with grade 2/3 ascites, in contrast to grade 1. These results strengthen the suggestion that there is no requirement for specific treatment in patients with ascites grade 1.

The significance of HE as a prognostic marker in cirrhotic patients with ascites has been demonstrated, as it is associated with short survival in this population [33]. In this study, 23% of patients with ascites grade 1, 24.8% of those with ascites grade 2/3 and 5.7% of patients with no ascites developed HE during follow up. A previous report revealed a greater degree of HE development, at a rate of 32.1%, in cirrhotic patients [25]; however, that study concerned patients with moderate or severe ascites [25].

It is worth noting the high infection and HE rate of ascites grade 1 patients, which is comparable to ascites 2/3 patients, but significantly higher than in patients without ascites; this is in contrast to the other complications investigated in this study. Although this finding did not reach statistical significance in the multivariate analysis, it may indicate that patients need particular attention in that direction and should be made a subject of investigation by future studies. Moreover, the similar risk of developing complications such as HE, HRS or infections between patients with grade 1 and grade 2/3 ascites may indicate that the presence and not the grade of ascites could impact specific outcomes.

Ascites appearance indicates a poor prognosis, as the 5-year survival decreases from about 80% in patients with compensated cirrhosis to about 30% in decompensated patients with ascites [2]. The overall survival rate in the total population of this study was 60.5%. Previous studies reported lower survival rates (18.7-56.5%) compared to the present

results [8,25,34]. However, those studies included patients with clinically significant ascites [8,25,34]. Survival analysis in our patients demonstrated similar survival rates among all examined groups (P>0.05): grade 1 patients (64%) vs. grade 2/3 patients (50%) vs. non-ascites group (67.2%).

Some limitations of the current study should be acknowledged. First, the fact that the cessation of alcohol intake was based on the patients' medical record; second, the retrospective nature of the study; and last, the omission of urine sodium measurement. The patients' compliance with the sodium restriction could have been monitored by measurement of urinary sodium excretion. However, considering the physician-imposed salt restriction, the patients' compliance was taken for granted.

In conclusion, these results suggest that the presence of grade 1 ascites does not constitute a precursor of grade 2/3 ascites in patients with cirrhosis; therefore, patients with grade 1 ascites do not require specific treatment.

Summary Box

What is already known:

- Ascites is the most common major complication of cirrhosis and constitutes a critical landmark in the natural history of chronic liver disease
- Patients with ascites grade 1 do not require specific treatment, but should be followed up carefully and advised to reduce their sodium intake, since they usually progress to the development of grade 2 ascites, according to the International Club of Ascites
- There are no data on the evolution of grade 1 ascites, nor it is known whether its treatment modifies its natural history, according to the European Association for the Study of the Liver (EASL) guidelines
- No data exist on how frequently patients with grade 1 will develop grade 2 or 3 ascites, according to the EASL guidelines

What the new findings are:

- Grade 1 ascites does not constitute an independent predictor of grade 2 or 3 ascites in patients with liver cirrhosis
- There is no need for treatment with diuretics in cirrhotic patients with grade 1 ascites

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Supplementary material

Supplementary Table 1 Univariate analyses of factors correlating with the main comorbid disorders that accompany ascites progression in the total population

Characteristics	HE		HRS		Infection		SBP	
	OR (95%CI)	P-value	OR (95%CI)	P-value	OR (95% CI)	P-value	OR (95%CI)	P-value
Group								
No ascites*	1		1		1		1	
Grade 1 ascites	4.87 (2.21-10.73)	<0.001	19.32 (2.43-153.39)	0.005	2.53 (1.40-4.59)	0.002	4.29 (1.08-16.98)	0.038
Grade 2/3 ascites	5.38 (2.57-11.30	<0.001	14.02 (1.79-109.90)	0.012	2.89 (1.69-4.96)	<0.001	14.13 (4.21-47.46)	<0.001
Sex								
Female*	1		1		1		1	
Male	0.63 (0.33-1.24)	0.181	7.00 (0.93-52.71)	0.059	1.94 (1.09-3.46)	0.024	2.95 (1.02-8.51)	0.046
Intrinsic renal disease								
No*	1		1		1		1	
Yes	0.52 (0.16-1.70)	0.281	0.78 (0.10-6.18)	0.810	1.28 (0.43-3.77)	0.655	0.66 (0.08-5.11)	0.687
Diabetes mellitus								
No*	1		1		1		1	
Yes	0.67 (0.37-1.22)	0.187	1.17 (0.39-3.55)	0.784	1.13 (0.66-1.92)	0.656	0.86 (0.36-2.01)	0.719
Non-HCC malignancy								
No*			1		1		1	
Yes	NA		1.50 (0.19-11.56)	0.700	0.47 (0.16-1.38)	0.169	0.37 (0.05-2.77)	0.329
Lung disease								
No*	1		1		1		1	
Yes	0.59 (0.24-1.44)	0.247	0.45 (0.13-1.62)	0.222	1.51 (0.68-3.37)	0.309	0.72 (0.17-3.16)	0.666
Smoking								
No*	1		1		1		1	
Yes	0.98 (0.58-1.68)	0.948	0.91 (0.38-2.19)	0.836	1.30 (0.83-2.06)	0.254	1.32 (0.66-2.63)	0.435
Hypertension								
No*	1		1		1		1	
Yes	2.04 (0.93-4.45)	0.074	2.48 (0.57-10.82)	0.228	0.64 (0.35-1.17)	0.146	0.45 (0.15-1.29)	0.497
Hepatic encephalopathy								
No*	1		1		1		1	
Yes	8.97 (3.51-22.92)	<0.001	0.48 (0.10-2.20)	0.341	6.70 (2.48-18.12)	<0.001	3.59 (1.23-10.48)	0.019
Diuretics								
No*	1		1		1		1	
Yes	8.27 (2.94-23.25)	<0.001	4.97 (1.90-12.98)	0.001	2.09 (1.34-3.26)	0.001	2.43 (1.25-4.74)	0.009
CP stage								
A*	1		1		1		1	
B	5.63 (2.44-13.01)	<0.001	9.13 (1.78-46.77)	0.008	2.66 (1.52-4.67)	0.001	2.45 (0.94-6.34)	0.067
C	12.84 (5.03-32.81)	<0.001	1.50 (0.55-4.11)	0.435	6.03 (2.97-12.27)	<0.001	6.83 (2.41-19.32)	<0.001
β-blockers								
No*	1		1		1		1	
Yes	3.35 (1.84-6.09)	<0.001	19.46 (2.59-146.05)	0.004	2.89 (1.79-4.66)	<0.001	0.38 (0.18-0.79)	0.010

(*Contd...*)

Supplementary Table 1 (*Continued*)

Characteristics	HE		HRS		Infection		SBP	
	OR (95%CI)	P-value	OR (95%CI)	P-value	OR (95% CI)	P-value	OR (95%CI)	P-value
PVT								
No*			1		1		1	
Yes	NA		5.82 (1.94-17.46)	0.002	0.39 (0.05-3.22)	0.383	1.41 (0.17-11.73)	0.753
HCC								
No*			1		1		1	
Yes	NA		0.88 (0.11-6.99)	0.907	0.36 (0.08-1.60)	0.178	0.60 (0.08-4.65)	0.625
Age (years)								
per unit	1.00 (0.98-1.02)	0.979	0.98 (0.95-1.01)	0.193	0.99 (0.97-1.01)	0.207	1.00 (0.97-1.02)	0.890
Plt								
per unit	1.00 (0.99-1.00)	0.106	1.00 (1.00-1.01)	0.334	1.00 (1.00-1.00)	0.439	1.00 (0.99-1.00)	0.231
PT								
per unit	1.10 (1.03-1.16)	0.003	0.98 (0.91-1.05)	0.532	1.03 (0.99-1.08)	0.144	1.02 (0.97-1.08)	0.406
INR								
per unit	5.61 (2.45-12.83)	<0.001	1.00 (0.48-2.08)	0.998	1.43 (0.89-2.30)	0.145	1.22 (0.83-1.81)	0.318
Sodium								
per unit	5.61 (2.45-12.83)	<0.001	1.04 (0.94-1.15)	0.482	0.97 (0.92-1.03)	0.336	0.91 (0.84-0.99)	0.023
Bilirubin								
per unit	1.10 (1.03-1.19)	0.008	1.00 (0.87-1.14)	0.943	1.11 (1.03-1.19)	0.007	1.07 (0.99-1.16)	0.090
Albumin								
per unit	0.57 (0.40-0.80)	0.001	0.60 (0.36-1.01)	0.053	0.61 (0.45-0.83)	0.001	0.57 (0.37-0.088)	0.010
Creatinine								
per unit	1,02 (0.73-1.42)	0.899	0.84 (0.58-1.22)	0.360	0.86 (0.57-1.29)	0.465	1.00 (0.64-1.57)	0.994
CP score								
per unit	1.56 (1.35-1.81)	<0.001	1.34 (1.08-1.66)	0.008	1.40 (1.24-1.59)	<0.001	1.49 (1.24-1.78)	<0.001
MELD score								
per unit	1.18 (1.11-1.25)	<0.001	0.94 (0.87-1.02)	0.114	1.08 (1.03-1.14)	0.001	1.08 (1.01-1.15)	0.026

* Reference category

The indication NA concerns associations in which no patient or small sample size met the examined criteria and thus the association between these variables could not be evaluated by means of regression

HE, hepatic encephalopathy; HRS, hepatorenal syndrome; SBP, spontaneous bacterial peritonitis; OR, odds ratio; CI, confidence interval; HCC, hepatocellular carcinoma; NA, not applicable; CP, Child-Pugh; PVT, portal vein thrombosis; Plt, platelets; PT, prothrombin time; INR, international normalized ratio; MELD, model for end-stage liver disease

Supplementary Table 2 Univariate analyses of factors correlating with the main comorbid disorders that accompany ascites progression in the group of patients with ascites grade 1

Characteristics	HE		HRS	
	OR (95%CI)	P-value	OR (95%CI)	P-value
Sex				
Female*			1	
Male	NA		1.27 (0.15-11.01)	0.829
Intrinsic renal disease				
No*			1	
Yes	NA		4.78 (0.39-58.02)	0.220

(*Contd...*)

Supplementary Table 2 (*Continued*)

Characteristics	HE		HRS	
	OR (95%CI)	P-value	OR (95%CI)	P-value
Diabetes mellitus				
No*	1		1	
Yes	1.00 (0.29-3.42)	>0.99	2.27 (0.52-9.83)	0.275
Non-HCC malignancy				
No*			1	
Yes	NA		4.67 (0.38-56.68)	0.227
Lung disease				
No*	1		1	
Yes	0.60 (0.12-2.94)	0.528	1.75 (0.33-9.33)	0.512
Smoking				
No*	1		1	
Yes	1.10 (0.42-2.89)	0.846	0.74 (0.20-2.73)	0.645
Hypertension				
No*	1		1	
Yes	0.87 (0.26-2.94)	0.823	1.06 (0.21-5.44)	0.945
Hepatic encephalopathy				
No*	1		1	
Yes	2.55 (0.30-21.54)	0.390	1.13 (0.13-10.05)	0.916
Diuretics				
No*	1		1	
Yes	2.98 (0.63-13.97)	0.167	3.04 (0.61-15.15)	0.175
CP stage				
A*	1		1	
B	0.27 (0.05-1.50)	0.134	0.59 (0.05-7.07)	0.676
C	0.65 (0.22-1.92)	0.437	1.35 (0.26-7.04)	0.725
β-blockers				
No*	1			
Yes	3.17 (0.98-10.23)	0.054	NA	
PVT				
No*				
Yes	NA		NA	
HCC				
No*				
Yes	NA		NA	
Age (years)				
per unit	0.97 (0.93-1.00)	0.079	1.00 (0.95-1.05)	0.985
Plt				
per unit	0.99 (0.99-1.00)	0.183	1.00 (0.99-1.01)	0.880
PT				
per unit	1.21 (1.03-1.43)	0.019	0.97 (0.72-1.31)	0.842

(*Contd...*)

Supplementary Table 2 (*Continued*)

Characteristics	HE		HRS	
	OR (95%CI)	P-value	OR (95%CI)	P-value
INR				
per unit	2.96 (0.66-13.33)	0.156	0.28 (0.02-4.30)	0.360
Sodium				
per unit	0.98 (0.86-1.12)	0.814	1.00 (0.83-1.20)	0.995
Bilirubin				
per unit	1.11 (0.99-1.25)	0.064	0.95 (0.76-1.18)	0.617
Albumin				
per unit	0.74 (0.33-1.64)	0.454	0.55 (0.17-1.79)	0.32
Creatinine				
per unit	0.78 (0.27-2.31)	0.659	1.11 (0.70-1.76)	0.670
CP score				
per unit	1.31 (0.99-1.73)	0.053	1.04 (0.71-1.52)	0.859
MELD score				
per unit	1.11 (1.00-1.23)	0.043	0.98 (0.85-1.14)	0.796

* Reference category

The indication NA concerns associations in which no patient or small sample size met the examined criteria and thus the association between these variables could not be evaluated by means of regression

HE, hepatic encephalopathy; HRS, hepatorenal syndrome; OR, odds ratio; CI, confidence interval; HCC, hepatocellular carcinoma; CP, Child-Pugh; PVT, portal vein thrombosis; Plt, platelets; PT, prothrombin time; INR, international normalized ratio; MELD, model for end-stage liver disease

Supplementary Table 3 Univariate Cox regression analysis for patients' survival

Characteristics	Total population		Ascites 1 group		Ascites 2/3 group		No ascites group	
	HR (95%CI)	P-value	HR (95%CI)	P-value	HR (95%CI)	P-value	HR (95%CI)	P-value
Group								
per unit	1.09 (0.86-1.28)	0.639	NA		NA		NA	
Sex								
per unit	0.96 (0.63-1.46)	0.849	1.43 (0.33-6.19)	0.633	1.26 (0.63-2.54)	0.512	0.75 (0.41-1.38)	0.355
Intrinsic renal disease								
per unit	2.25 (1.04-4.84)	0.039	25.96 (4.26-158.08)	<0.001	1.84 (0.65-5.16)	0.248	0.96 (0.13-7.03)	0.968
Diabetes mellitus								
per unit	1.63 (1.15-2.32)	0.006	1.57 (0.64-3.86)	0.325	1.68 (1.02-2.78)	0.043	1.48 (0.81-2.72)	0.201
Ischemic heart disease								
per unit	2.61 (1.26-5.41)	0.010	3.76 (0.47-30.00)	0.211	1.99 (0.71-5.61)	0.192	3.77 (1.13-12.62)	0.031
Non-HCC malignancy								
per unit	1.18 (0.58-2.41)	0.653	NA		3.16 (0.72, 13.80)	0.126	1.02 (0.43, 2.39)	0.970
Lung disease								
per unit	1.60 (0.88-2.89)	0.121	1.31 (0.49-3.45)	0.589	1.56 (0.48-5.02)	0.457	2.13 (0.76-5.99)	0.150
Smoking								
per unit	0.79 (0.58-1.09)	0.152	0.50 (0.24-1.02)	0.057	1.13 (0.68-1.89)	0.640	0.63 (0.36-1.09)	0.095
Hypertension								
per unit	1.24 (0.86-1.78)	0.247	1.33 (0.66-2.66)	0.427	1.08 (0.57-2.07)	0.811	1.28 (0.72-2.30)	0.400

(*Contd...*)

Supplementary Table 3 (*Continued*)

Characteristics	Total population		Ascites 1 group		Ascites 2/3 group		No ascites group	
	HR (95%CI)	P-value	HR (95%CI)	P-value	HR (95%CI)	P-value	HR (95%CI)	P-value
Hepatic encephalopathy								
per unit	0.65 (0.35-1.21)	0.174	0.73 (0.29-1.83)	0.504	0.32 (0.10-1.05)	0.061	0.48 (0.12-2.01)	0.317
Diuretics								
per unit	1.06 (0.74-1.51)	0.769	2.40 (0.95-6.06)	0.065	1.04 (0.30-3.70)	0.946	0.95 (0.56-1.62)	0.854
CP stage								
per unit	1.34 (1.03-1.74)	0.030	1.54 (0.85-2.79)	0.150	1.31 (0.77-2.22)	0.326	1.27 (0.63-2.55)	0.506
Varices								
per unit	1.19 (0.82-1.74)	0.359	1.68 (0.62-4.53)	0.304	1.06 (0.52-2.14)	0.877	1.33 (0.75-2.37)	0.328
PVT								
per unit	0.12 (0.03-0.44)	0.001	0.12 (0.03-0.44)	0.001	NA		NA	
HCC								
per unit	4.45 (1.21-16.37)	0.025	4.45 (1.21-16.37)	0.025	NA		NA	
β-blockers								
per unit	1.33 (0.97-1.82)	0.074	2.20 (0.96-5.04)	0.063	NA		NA	
Age (years)								
per unit	1.04 (1.02-1.05)	<0.001	1.05 (1.02-1.09)	0.005	1.03 (1.01-1.05)	0.003	1.04 (1.02-1.07)	0.001
Plt								
per unit	1.00 (1.00-1.00)	0.591	1.00 (0.99-1.00)	0.829	1.00 (1.00-1.01)	0.246	1.00 (1.00-1.00)	0.802
PT								
per unit	1.03 (0.99-1.06)	0.127	1.07 (0.95-1.20)	0.255	1.02 (0.95-1.11)	0.563	0.99 (0.90-1.09)	0.857
INR								
per unit	1.21 (0.89-1.65)	0.231	3.23 (0.93-11.22)	0.065	1.24 (0.52-2.93)	0.631	1.07 (0.55-2.06)	0.851
Sodium								
per unit	0.98 (0.94-1.02)	0.263	0.97 (0.88-1.07)	0.523	0.95 (0.89-1.02)	0.146	1.01 (0.95-1.08)	0.716
Bilirubin								
per unit	1.03 (0.98-1.09)	0.273	0.99 (0.89-1.10)	0.797	1.05 (0.97-1.13)	0.203	1.09 (0.95-1.25)	0.231
Albumin								
per unit	0.74 (0.59-0.93)	0.011	0.45 (0.23-0.88)	0.020	0.92 (0.62-1.35)	0.664	0.70 (0.50-0.99)	0.043
Creatinine								
per unit	1.16 (1.00-1.36)	0.057	1.35 (1.09-1.68)	0.007	1.20 (0.68-2.13)	0.528	1.06 (0.82-1.38)	0.641
CP score								
per unit	1.08 (0.99-1.18)	0.089	1.13 (0.90-1.41)	0.307	1.04 (0.88-1.23)	0.638	1.10 (0.87-1.41)	0.415
MELD score								
per unit	1.05 (1.01-1.09)	0.017	1.04 (0.96-1.13)	0.344	1.06 (1.00-1.13)	0.056	1.02 (0.95-1.09)	0.632

The indication NA concerns associations in which no patient or small sample size met the examined criteria and thus the association between these variables could not be evaluated by means of regression

HR, hazard ratio; CI, confidence interval; HCC, hepatocellular carcinoma; CP, Child-Pugh; PVT, portal vein thrombosis; Plt, platelets; PT, prothrombin time; INR, international normalized ratio; MELD, model for end-stage liver disease