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

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
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.
| 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)                         |                |                  |           |         |         |
| 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 |

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Table 1 (Continued)

| Characteristics       | Overall | Grade 1 ascites vs. Grade 2/3 ascites | Grade 1 ascites vs. No ascites |
|-----------------------|---------|---------------------------------------|-------------------------------|
|                       | 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 (7.0-10.0) | 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 |
|-----------------------|---------|---------------------------------------|-------------------------------|
|                       | N (%)   | N (%)                                 | N (%)                         | N (%)                         | P-value |
| 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

| 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...)
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

### Table 3 (Continued)

| Hepatorenal syndrome development | Parameters | OR (95%CI) | P-value |
|----------------------------------|------------|------------|---------|
| **MODEL 1**                      |            |            |         |
| **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**                      |            |            |         |
| **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      |
| **CP STAGE**                     |            |            |         |
| **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      |
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

| Parameters | HR (95%CI) | P-value |
|------------|------------|---------|
| **Total population** | | |
| 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...)
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

**Table 4 (Continued)**

| Parameters                  | MODEL 2 |   |
|-----------------------------|---------|---|
| Parameters                  | HR (95%CI) | P-value |
| Diabetes mellitus           | HR (95%CI) | P-value |
| No*                         | 1       |   |
| Yes                         | 1.67 (0.93-2.98) | 0.086 |
| Age per unit                | 1.04 (1.01-1.06) | 0.002 |
| CP score per unit           | 1.13 (0.95-1.34) | 0.162 |
| 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           | HR (95%CI) | P-value |
| 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      | HR (95%CI) | P-value |
| 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
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. In 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 Table 1

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

| Characteristics          | HE OR (95% CI) | P-value | HRS OR (95% CI) | P-value | Infection OR (95% CI) | P-value | SBP 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                     |         | 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 | 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 (0.37-0.88) | 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...)
| Characteristics            | HE               | P-value | HRS               | P-value |
|----------------------------|------------------|---------|-------------------|---------|
|                            | OR (95%CI)       |         | OR (95%CI)        |         |
| 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                |         | 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                |         | 1                 |         |
| Yes                        | 3.17 (0.98-10.23)| 0.054   | NA                |         |
| PVT                        |                  |         |                   |         |
| No*                        | NA               |         | NA                |         |
| HCC                        |                  |         |                   |         |
| No*                        | NA               |         | NA                |         |
| 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.

**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 | 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                  |
| **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.