Risk stratification in cirrhosis and acute-on-chronic liver failure : exploration of invasive and non-invasive prognostic markers

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Hepatic encephalopathy is an independent risk factor for mortality at the liver transplant waiting list: a propensity score analysis

Submitted

ABSTRACT

Background: Hepatic encephalopathy (HE) is associated with poor survival, but is not reflected in the MELD score. We assessed the independent impact of HE on mortality in cirrhotic patients awaiting liver transplantation using a propensity score analysis. Furthermore, we aimed at validating the results in two independent cohorts.

Methods: 262 Cirrhotic patients registered at the liver transplant waiting list between 2007 and 2012 in two Dutch centres, were retrospectively analysed. A propensity score was assigned to each patient based on the likelihood of HE development at time of enlistment and was then entered in a competing-risk Cox-regression model. Two independent cohorts of cirrhotic patients from another Dutch (n=226) and Spanish (n=279) centre were used as validation cohorts.

Results: HE was found to predict one-year survival at the waiting list, independently of the propensity score, MELD score and the presence of HCC (SHR=2.4, 95%CI=1.2-5.0, p=0.01). These results were confirmed in the Dutch validation cohort. In the Spanish cohort, with fundamental differences in composition and clinical approach, HE was not a risk factor for waitlist mortality.

Conclusions: HE at time of registration at the liver transplant waiting list is an independent risk factor for mortality, but its impact seems to be attenuated in settings with significantly higher transplantation rates and a shorter waiting time until transplantation.

INTRODUCTION

Liver transplantation (LT) is a curative treatment option for patients with end-stage chronic liver disease and has a 5-year survival rate of 70-80%.[1] Prioritization of patients for LT is currently determined by the Model for End-Stage Liver Disease (MELD) score. This score was initially designed as a prognostic scoring system in patients undergoing a transjugular intrahepatic portosystemic shunt (TIPS) procedure and incorporates objective markers of liver function, namely serum bilirubin and creatinine concentration and the international normalized ratio (INR).[2,3] However, a limitation of this liver specific prognostic scoring system is that it does not account for other sequelae of hepatic decompensation, such as ascites or hepatic encephalopathy (HE). HE is a severe complication of advanced liver cirrhosis, manifested by neuropsychological abnormalities ranging from subclinical alterations to coma.[4] The presence of HE is a symptom of the decompensated phase of the underlying liver disease, associated with poor survival and high recurrence rates.[5-7] Prognosis of cirrhotic patients with HE has been found to depend on the severity of the underlying liver disease and features of precipitating factors.[8] The subjectivity and interobserver variability in diagnosing and grading of HE is the main reason for not incorporating HE in the MELD score. However, several previous studies reported that the MELD score underestimates the risk of mortality in cirrhotic patients with HE[9-11], who may therefore not receive LT in a timely manner. Furthermore, the severity of HE appeared not to be correlated to the MELD score.[8-9] In addition, the presence of high HE grades at time of registration at the waiting list has been found to increase 90-day waitlist mortality, independently of the MELD-score.[12]

A challenging aspect of retrospective studies regarding the impact of HE on mortality is the inadvertent bias that may be created by the presence of confounding factors, such as infections, ascites, variceal bleeding or a TIPS procedure.[4] Therefore, we aimed at exploring the impact of HE on mortality at the LT waiting list, independently of the MELD score and presence of comorbidities related to HE development using a propensity score analysis. Furthermore, we externally validated our findings in two independent cohorts from centres with different lengths of LT waiting list.

PATIENTS AND METHODS

Study design

Cirrhotic patients (age> 18 years), who were registered at the waiting list for LT between 2007 and 2012, were retrospectively enrolled in the study. Exclusion criteria were enlistment for re-transplantation, combined liver and kidney transplantation and acute liver failure.

Demographics, clinical characteristics and laboratory values at time of registration at the waiting list for LT were retrieved from patient files. A window of minus 2 weeks was applied for the presence of decompensation of cirrhosis (i.e. HE, ascites, spontaneous bacterial peritonitis (SBP), variceal bleeding). Grading of HE severity reported in patient files was based on the West Haven Criteria.[13] If no information on the presence of HE was reported, patients were considered as not having HE. Patients were followed-up until death or LT with a maximum follow-up period of 12 months.

Study population

The study consisted of 3 cohorts of cirrhotic patients who were all registered at the waiting list for LT between 2007 and 2012: 1 reference cohort from 2 Dutch tertiary referral centres (n=262), a validation cohort from a tertiary referral centre in the Netherlands (n=226) and a validation cohort from Spain (n=279). Primary indications for enlistment were advanced liver cirrhosis or hepatocellular carcinoma (HCC) in the setting of liver cirrhosis.

Statistical analysis

Comparisons between patients with and without HE at time of registration at the waiting list were performed using the Chi-square test or Student's t-test when appropriate. Baseline characteristics of patients in the three different cohorts were compared using the Chi-square or ANOVA test when appropriate. Results are presented as frequencies and percentages or mean and standard deviation (SD). A $p \leq 0.05$ was considered statistically significant. Survival estimates at 12 months of follow-up, stratified according to the presence of HE, were performed using Kaplan Meier analysis. Univariate and multivariate analysis of prognostic factors for mortality was performed by means of a competing-risk regression analysis using the method of Fine and Gray.[14] Mortality at the waiting list was the outcome of interest and LT was considered as a competing risk, because it influences the probability of death and vice versa. Competing risk analysis provides event-specific hazard ratios that are adjusted for interdependence. To adjust for the bias inherent to the presence of other types of hepatic decompensation in patients with HE, propensity scores were assigned to each patient, based on the likelihood of developing HE at time of registration at the waiting list. The propensity score method is an effective method to adjust for confounding.[15-17] This method uses multivariate logistic regression to combine all confounding variables in the study into a single score. Depending on the presence of these variables, an individual score is calculated for each patient included in the study, defining the propensity of developing the outcome of interest. The propensity score is finally entered as a continuous variable into the competing risk regression model. The following basic risk parameters for the development of HE were included in the multivariate logistic regression model for propensity score calculation: prior HE, ascites, SBP, variceal bleeding and TIPS. In multivariate analysis, the impact of the

presence of HE on waitlist mortality was adjusted for the MELD score, propensity score and presence of HCC. Identical survival analysis was performed in the two validation cohorts.

RESULTS

Reference cohort

Patient characteristics

Patient demographics and clinical characteristics at time of registration at the waiting list for LT are shown in table 1. A total of 63 patients had HE at time of registration at the LT waiting list. Of them, 26 (41.3%) of these patients had previous episodes of HE. Patients with HE at time of registration at the LT waiting list had significantly more frequently features of clinical decompensation of the underlying liver disease (i.e., variceal bleeding, ascites and SBP) as compared to patients without HE. The MELD score was also significantly higher in this subgroup of patients. Severity of HE, as defined by the Westhaven criteria[13], was registered for 58 of the 63 patients (grade I: n=33, grade II: n=15, grade III: n=10). Mean MELD scores were significantly higher in patients with HE grade III as compared to patients with grade I (grade III: 21 points, grade I: 14 points, p=0.01). No significant difference in MELD score was found between grade I and grade II (grade II: 16 points) and grade II and grade III (both p=0.12).

Kaplan Meier survival analysis

At 12 months of follow-up, 23 (8.8%) patients had died while awaiting LT. Survival curves stratified according to the presence of HE at 12 months of follow-up are shown in figure 1. Patients without HE at time of registration at the LT waiting list showed a significantly better one-year transplant-free survival. As expected, patients with HE grade III displayed the worst survival, as compared to patients with HE grade I or II at time of registration at the waiting list (figure 2). Inspection of figure 2 clearly shows that the prognostic significance of HE was entirely due to the patients with HE grades II and III, as the transplant-free survival was superimposed to patients with no HE or with grade I HE.

Table 1. Patient characteristics at time of registration at the waiting list for liver transplantation of 262 cirrhotic patients included in the reference cohort.

Variable	All patients (n=262)	HE (n=63)	No HE (n=199)	p-value
Age (years), mean (±sd)	52.6 (±11.6)	55.3 (±8.5)	51.7 (±12.3)	0.03
Gender (male), n (%)	185 (70.6)	48 (76.2)	137 (68.8)	0.27
Etiology, n (%)				0.04
Alcohol	80 (30.5)	22 (34.9)	58 (29.1)	
Viral hepatitis	48 (18.3)	7 (11.1)	41 (20.6)	
PSC/PBC/AIH	80 (30.5)	14 (22.2)	66 (33.2)	
NASH	17 (6.5)	7 (11.1)	10 (5.0)	
other	37 (14.1)	13 (20.6)	24 (12.1)	
Clinical features, n (%)				
HCC	60 (22.9)	7 (11.1)	53 (26.6)	0.01
TIPS	9 (3.4)	3 (4.8)	6 (3.0)	0.45
Ascites	63 (24.0)	38 (60.3)	72 (36.2)	0.001
Variceal bleeding	110 (41.8)	6 (9.5)	7 (3.5)	0.056
SBP	13 (5.0)	7 (11.1)	6 (3.0)	0.01
Prognostic scores, mean (±sd)				
MELD	13.2 (±5.5)	12.4 (±4.8)	7.2 (±1.9)	0.008
Child-Pugh	8.0 (±243)	10.6 (±2.0)	10.6 (±2.0)	0.723
Laboratory data, mean (±sd)				
Creatinine (µmol/L)	83.6 (±56.8)	102.6 (±100.4)	77.5 (±30.8)	0.011
Sodium (mmol/L)	137.9 (±4.6)	137.2 (±5.7)	138.1 (±4.2)	0.017
INR	1.3 (±0.3)	1.3 (±0.3)	1.4 (±0.4)	0.006
Bilirubin (µmol/L)	74.6 (±125.3)	125.4 (±197.7)	58.6 (±86.0)	<0.001
Albumin (g/L)	34.6 (±6.4)	31.9 (±5.6)	35.5. (±6.5)	0.13
AF	183.9 (±139.4)	147.5 (±75.6)	195.2 (±152.3)	0.001
Leucocytes (x 10^9/L)	5.8 (±2.9)	6.0 (±3.3)	5.7 (±2.7)	0.163

Data are presented as numbers (percentage) or mean (± standard deviation).

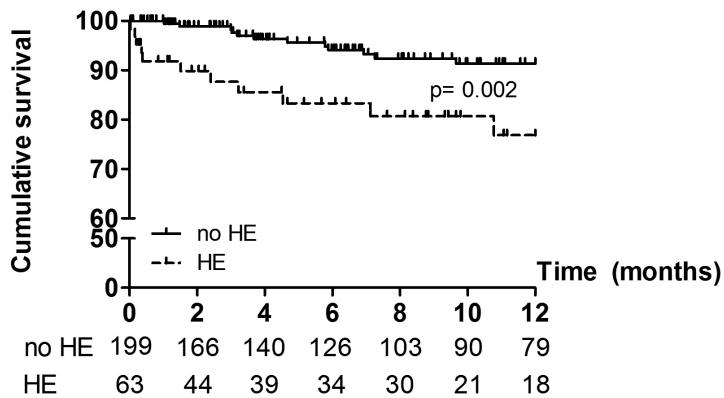

Figure 1. One-year transplant-free survival at 12 months of follow-up of 262 cirrhotic patients, stratified according to the presence of HE at time of registration at the liver transplant waiting list. Patients were censored at time of liver transplantation or last hospital visit.

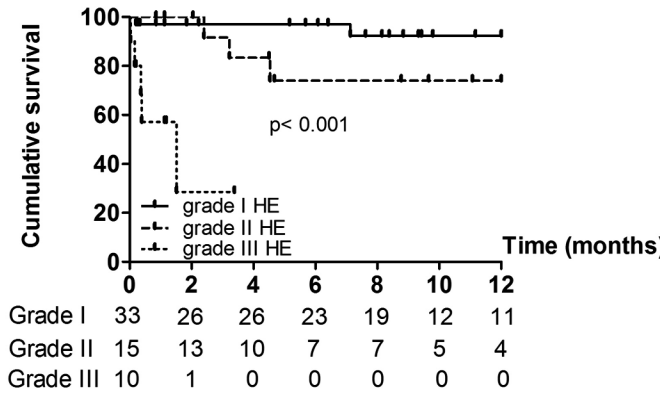

Figure 2. One-year transplant-free survival at 12 months of follow-up of 58 cirrhotic patients with HE, stratified according to the severity of HE as defined by the West Haven criteria. Patients were censored at time of liver transplantation or last hospital visit.

Competing-risk regression analysis

HE and other potential risk factors for one-year mortality were tested for significance in a univariate competing-risk regression model. Significant associations with mortality were found for MELD score and the presence of HE, ascites and SBP at time of registration at the LT waiting list (table 2).

In multivariate analysis adjusted for propensity scores (which already included ascites and variceal bleeding), MELD score and presence of HCC, the presence of HE at time of registration at the LT waiting list, was significantly and independently associated with one-year mortality at the LT waiting list (table 3).

Validation cohorts

Patient characteristics

Baseline characteristics of the Dutch and Spanish validation cohort are shown in Supplementary table 1. Except from the number of patients with HE at enlistment (reference cohort: 24.0% vs. Dutch validation cohort: 15.9%, p=0.03), baseline characteristics of the two Dutch cohorts were highly comparable. In the Spanish cohort, some fundamental differences in baseline characteristics were present as compared to the Dutch reference cohort. Mean age in the Spanish population was higher (56.4 vs. 52.5 years, p<0.001) and significantly more patients had HCC as compared to the reference cohort (46.2% vs. 22.9%, p<0.001). Furthermore, patients in the Spanish cohort had a much shorter median waiting time till LT (4.1 vs. 6.4 months, p<0.001) and higher one-year transplantation rates (74.6% vs. 54.9%, p<0.001). No significant differences were found, however, in one-year waitlist mortality between the Spanish and reference cohort (6.1% vs. 8.8%, p=0.233).

Table 2. Results of competing-risk univariate regression analysis of potential risk factors for 12-month mortality in A) the Dutch reference cohort, B) the Dutch validation cohort and C) the Spanish validation cohort.

A. Reference cohort (n=262)

Variable	All patients (n=262) SHR (95% CI)	p-value
Age	1.023 (0.98-1.07)	0.272
Gender (male)	1.64 (0.81-3.31)	0.167
HE	3.99 (2.02-7.90)	<0.001
HCC	0.86 (0.38-1.95)	0.719
Ascites	2.14 (1.00-4.58)	0.049
SBP	4.50 (1.92-10.60)	0.001
Variceal bleeding	2.22 (0.62-7.99)	0.223
MELD score	1.10 (1.03-1.17)	0.006
Propensity score	0.737 (0.15-3.74)	0.721

B. Dutch validation cohort (n=226*)

Variable	All patients (n=226) SHR (95% CI)	p-value
Age	1.07 (1.02-1.12)	0.004
Gender (male)	2.49 (1.12-5.52)	0.026
HE	2.22 (1.21-4.46)	0.005
HCC	0.63 (0.28-1.42)	0.271
Ascites	3.15 (1.40-7.06)	0.005
SBP[#]	-	-
Variceal bleeding	2.82 (0.48-16.7)	0.252
MELD score	1.10 (1.03-1.20)	0.03
Propensity score	6.37 (1.08-37.69)	0.041

C. Spanish validation cohort (n=279)

Variable	All patients (n=279) SHR (95% CI)	p-value
Age	0.99 (0.96-1.03)	0.776
Gender (male)	0.45 (0.05-3.81)	0.467
HE	1.97 (0.39-10.03)	0.413
HCC	0.86 (0.17-4.40)	0.852
Ascites	11.66 (1.40-97.4)	0.023
SBP[#]	-	-
Variceal bleeding[#]	-	-
MELD score	1.15 (1.00-1.31)	0.044
Propensity score	4.44 (0.061-319)	0.495

*Due to missing values on ascites in the Dutch validation cohort, propensity scores could not be calculated for 26 patients. Therefore, survival models in this cohort were based on 200 patients. [#]Competing-risk regression analysis could not be performed for this variable, because there were no events in this subgroup of patients.

Table 3. Results of multivariate competing-risk regression models for 12-month mortality in A) the reference cohort and B) the Dutch validation cohort.

A. Reference cohort (n=262)

	All patients (n=262)	
Variables	**SHR (95% CI)**	**p-value**
HE	2.44 (1.20-4.95)	0.014
HCC	3.29 (1.33-8.16)	0.010
MELD score	1.09 (1.02-1.15)	0.003
Propensity score	2.26 (0.31-16.53)	0.43

B. Dutch validation cohort (n=226*)

	All patients (n=200)	
Variables	**SHR (95% CI)**	**p-value**
HE	3.99 (1.61-9.87)	0.003
HCC	0.47 (0.10-2.27)	0.34
MELD score	1.16 (1.08-1.24)	0.001
Propensity score	0.40 (0.05-3.46)	0.41

*Due to missing values on ascites in the Dutch validation cohort, propensity scores could not be calculated for 26 patients. Therefore, survival models in this cohort were based on 200 patients.

Survival analysis

To validate the impact of HE on one-year mortality at the LT waiting list, identical competing-risk regression models were fitted in the two validation cohorts. Results of univariate analyses are shown in table 2.

In the Dutch validation cohort, it was confirmed that HE is a predictor for mortality at the waiting list, independently of propensity scores, MELD score and presence of HCC (table 3). However, in contrast to the findings in the two Dutch cohorts, HE and other complications of cirrhosis, except for ascites, were found not to be associated with mortality at the waiting list in the Spanish cohort, remaining solely MELD score as a prognostic factor (table 2).

DISCUSSION

In this study, we showed that the presence of HE at time of registration at the waiting list for LT is an independent risk factor for mortality. However, it was also found that HE seems not to be of prognostic significance in a setting with significantly higher transplantation rates and shorter waiting time until transplantation.

HE is a severe complication of advanced liver cirrhosis and is manifested by neuropsychological abnormalities ranging from subclinical alterations to coma.[4] It is of interest to observe that the negative waiting list survival significance of HE was limited to patients with grade II and grade III HE considering that there has been reluctance in including HE in modern cirrhosis

prognostic scores due to the fact that its diagnosis in initial steps is based in appreciating subtle changes in cognitive state that on one side are not specific and on the other are subjective and therefore, observer-dependent. Our finding that only obvious HE (as it is in patients with HE grades II and III) has a negative prognostic implication is therefore a robust finding, unlikely to be influenced by subjective judgment.

Pathogenesis of this complex syndrome relies on effects of substances that are metabolized by the liver under normal circumstances, such as ammonia, on the brain. Also increased levels of circulating inflammatory cytokines may play a role in the pathogenesis of HE in cirrhotic patients.[18] Most common precipitating factors for HE are infection and gastrointestinal bleeding.[4] Also the presence of ascites, TIPS placement and previous episodes of HE may increase the risk of HE development.[4,19] In the present study, in particular ascites, spontaneous bacterial infection and variceal bleeding were more frequently present in patients with HE at time of registration at the waiting list as compared to patients without HE. Presence of these risk factors for HE development may also affect prognosis in cirrhosis, irrespective of whether they lead to HE development.[20-22] To adjust for the bias inherent to the presence of these factors, we used a propensity score model reflecting the baseline risk of HE development. With this approach, we aimed to study the prognostic value of HE independently of other complications of cirrhosis. In consistence with findings in previous studies, we found an association between HE and an increased risk for mortality at the liver transplant waiting list.[10,12] However, previous studies did not adjust for the presence of other complications of cirrhosis as risk factors for mortality at the liver transplant waiting list in patients with HE. In addition, these studies did not perform competing-risk survival analysis, which is essential in the setting of waitlist mortality, because it provides event-specific hazard ratios, without censoring at time of LT. The results of the present study add to what is presently known that the presence of HE at time of registration at the waiting list appears to be a risk factor for mortality, independently of the MELD score and other complications of cirrhosis, such as HCC and a combined propensity score, in a large cohort of cirrhotic patients awaiting LT.

The results of the present study were validated in two independent cohorts of cirrhotic patients at the liver transplant waiting list, one in the Netherlands and one in Spain. The findings in the study population were confirmed in the Dutch validation cohort. However, in the Spanish cohort, HE was not a predictor for mortality at the waiting list. This might be explained by the presence of several important differences between the reference study population and the Spanish cohort. Firstly, LT candidates in the Spanish cohort were transplanted more frequently and on a shorter term than patients in the two Dutch cohorts. The presence of complications of cirrhosis may therefore have less impact on survival as compared to populations with a longer expected waiting time until LT. In addition, the

prevalence of HE at time of enlistment was significantly lower in the Spanish cohort as compared to the Dutch cohorts. This may partly be explained by the relatively high number of patients with HCC as primary indication for registration at the waiting list in the Spanish centre. In Spain, patients receive additional MELD points for the presence of HCC at time of registration at the waiting list, while in the Netherlands an exception MELD score is granted to HCC patients 6 months after enlistment. Differences in policy regarding exceptional MELD points allocation between the two countries may, together with the relatively high percentage of HCC patients at the waiting list and higher donor organ rates, explain the shorter waiting times until LT in the Spanish cohort.

Several previous studies have reported a significant association for the presence of HE with an increased risk for waitlist mortality.[10,12,23,24] Therefore, the hypothesis was raised that the lack of considering HE in the prioritizing criteria for LT may lead to underestimation of the severity of the underlying liver disease and prognosis. Indeed, subsequent studies have shown the additional prognostic value of considering HE next to the MELD score.[8,25,26] Although patients with HE in our study cohort had significantly higher MELD scores in association with lower one-year survival rates as compared to patients without HE, we found a significant association of HE with mortality at the waiting list independently of the MELD score and other well-known prognostic factors in cirrhosis.

Some limitations according to the present study are to be considered. The most important one is the retrospective study design. The presence of HE in the weeks prior to registration at the waiting list relied on documentation in patient files. The subjectivity and interobserver variability in diagnosing and grading of HE is a challenging aspect in research to this neuropsychological syndrome. In addition, the grade of HE severity was not reported in a small number of the HE patients. Nevertheless, mortality rates did significantly increase along with the reported grade of HE, which is in consistence with previously reported data.[8,12] Prospective studies in which clear definitions for diagnosing and grading of HE are used will be needed in order to validate the independent prognostic value of HE on mortality and to evaluate its reliability as a potential prognostic factor to be considered in the prioritizing criteria for LT. Due to the retrospective study design, we were not able to reliably investigate the impact of the use of medication for HE and the use of other potentially relevant co-medication, such as beta-blockers and diuretics, on survival of HE patients. Future studies with a prospective study design could provide more knowledge on the effect of these treatments on survival in this specific subgroup. Larger cohorts of cirrhotic patients registered at the liver transplant waiting list are needed to validate the impact of HE on short-term waitlist mortality. Also, the influence of differences in waiting time until transplantation on the impact of complications of cirrhosis on mortality needs further evaluation.

Based on the results of the present study, we conclude that HE is an independent risk factor for mortality awaiting LT. However, the prognostic impact of HE seems to be attenuated in settings with significantly higher transplantation rates and a shorter waiting time until transplantation.

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Supplementary table 1. Baseline characteristics of cirrhotic patients registered at the waiting list for liver transplantation in the Dutch reference cohort and in the Dutch and Spanish validation cohorts.

Variable	Reference cohort (n= 262)	Dutch validation cohort (n= 226)	Spanish validation cohort (n= 279)	p-value
Age (years), mean (±sd)	52.6 (±11.6)	52.4 (±10.1)	56.4 (±8.7)	< 0.001
Gender (male), n (%)	185 (70.6)	160 (70.8)	207 (74.2)	0.58
Etiology, n (%)				< 0.001
Alcohol	80 (30.5)	52 (23.0)	65 (23.3)	
Viral hepatitis	48 (18.3)	57 (25.2)	176 (63.1)	
PSC/PBC/AIH	80 (30.5)	70 (31.0)	18 (6.5)	
NASH	17 (6.5)	4 (1.8)	6 (2.2)	
other	37 (14.1)	43 (19.0)	14 (5.0)	
Clinical features, n (%)				
HCC	60 (22.9)	63 (27.9)	129 (46.2)	< 0.001
TIPS	9 (3.4)	9 (4.0)	18 (6.5)	0.22
HE	63 (24.0)	36 (15.9)	33 (11.8)	0.001
Ascites	110 (41.8)	86 (43.0)*	116 (41.6)	0.95
Variceal bleeding	13 (5.0)	4 (1.8)	6 (2.2)	0.07
SBP	13 (5.0)	8 (3.6)	8 (2.9)	0.44
Prognostic scores, mean (±sd)				
MELD	13.2 (±5.5)	15.4 (±5.5)	13.4 (±5.4)	< 0.001
Child-Pugh	8.0 (±243)	8.3 (±2.3)	8.0 (±2.3)	0.187
Laboratory data, mean (±sd)				
Creatinine (µmol/L)	83.6 (±56.8)	76.5 (±29.9)	83.0 (±24.1)	0.099
Sodium (mmol/L)	137.9 (±4.6)	137.8 (±5.6)	137.0 (±4.6)	0.057
INR	1.3 (±0.3)	1.4 (±0.4)	1.5 (±0.4)	< 0.001
Bilirubin (µmol/L)	74.6 (±125.3)	102.8 (±138.8)	55.9 (±62.3)	< 0.001
Albumin (g/L)	34.6 (±6.4)	34.7 (±7.9)	33.5 (±6.4)	0.068
AF (U/L)	183.9 (±139.4)	215.5 (±187.6)	340.1 (±317.1)	< 0.001
Leucocytes (x 10^9/L)	5.8 (±2.9)	6.0 (±3.2)	5.2 (±2.3)	0.003

Data are presented as numbers (percentage) or mean (± standard deviation).
*Information on the presence of ascites was available in 200 out of 226 patients in this cohort.