DR. SIMONA ONALI (Orcid ID : 0000-0002-5735-928X)

DR. EMMANUEL TSOCHATZIS (Orcid ID : 0000-0001-5069-2461)

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Non-selective beta-blockers are not associated with increased mortality in cirrhotic patients with ascites

Simona Onali[1], Maria Kalafateli[1], Avik Majumdar[1], Rachel Westbrook[1], James O'Beirne[1], Gioacchino Leandro[2], David Patch[1], Emmanuel A. Tsochatzis[1]

1. UCL Institute for Liver and Digestive Health and Sheila Sherlock Liver Unit, Royal Free Hospital and UCL, London, UK

2. Gastroenterology I Department, IRCCS De Bellis Hospital, Castellana Grotte, Italy

Short Title: NSBBs and survival in cirrhosis with ascites

Correspondence: Emmanuel A. Tsochatzis, Sheila Sherlock Liver Unit and UCL Institute of Liver and Digestive Health, Royal Free Hospital and UCL, Pond Street, NW3 2QG, London, UK, Phone: (0044)2077940500 ext 31142, Fax: (0044)2074726226, email: e.tsochatzis@ucl.ac.uk

List of abbreviations:

NSBBs: non-selective beta-blockers

HRS: hepato-renal syndrome

SBP: spontaneous bacterial peritonitis

BMI: body mass index

HCC: hepatocellular carcinoma

MELD: Model for End-Stage Liver Disease

UKELD: UK Score for Patients with End-Stage Liver Disease

GFR: Glomerular filtration rate

MDRD: modification of diet in renal disease

IQR: interquartile range

CI: confidence interval

HR: hazard ratio

TIPSS: Transjugular intrahepatic portosystemic shunt

Statement of interests

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Abstract

Background & Aims: Controversy exists on the impact of non-selective beta-blockers (NSBBs) on survival in patients with ascites. We assessed whether NSBB treatment affects survival in a cohort of 316 consecutive patients with ascites undergoing evaluation for liver transplantation.

Methods: Consecutive patients with cirrhosis and ascites assessed for liver transplantation between 2011-2014 were retrospectively evaluated. Cox regression and competing risk analysis were performed to identify predictors of survival.

Results: 316 patients were evaluated: males 229 (73%), mean age 54 years, median follow-up: 7 months. Refractory ascites was diagnosed in 124 (39%) patients. Patients receiving NSBBs (n=128, 40.5%) had a higher frequency of previous spontaneous bacterial peritonitis (27% vs. 17%, p=0.025), lower frequency of refractory ascites (32% vs. 44%, p=0.03) but similar MELD and UKELD scores. Overall 80 (25%) patients died: 20 (16%) in the NSBB group vs. 60 (32%) in the non-NSBB group (p=0.002). In multivariate competing risk Cox regression analysis, NSBB use was associated with reduced mortality (HR=0.55, 95%CI=0.33-0.94) along with prophylactic antibiotic use (HR=0.33, 95%CI=0.14-0.74), MELD score (HR=1.10, 95%CI= 1.06-1.14) and sodium levels (HR=0.94, 95%CI 0.89-0.98).. No impact on survival was found when considering only patients with refractory ascites (NSBB use: HR=0.43, 95%CI=0.20-1.11).

Conclusions: Patients with ascites on NSBBs didn't have impaired survival compared to those not receiving NSSBs and interestingly this observation was also confirmed in the subgroup with refractory ascites. Our results suggest that NSBBs are not detrimental, but instead seem safe even in more advanced stages of cirrhosis in patients on a transplant waiting list.

Keywords: prognosis, propranolol, carvedilol, spontaneous bacterial peritonitis.

Key points

- Non-selective beta blockers (NSBB) are widely used in patients with cirrhosis for primary and secondary prevention of variceal bleeding. Controversial data exist on their role in advanced cirrhosis.
- Our study showed that NSBBs do not affect survival in patients with cirrhosis and ascites in a transplant waiting list
- NSBB use was not associated with impaired survival in patients with refractory ascites
- A thorough evaluation should be carried out before discontinuing these drugs in advanced cirrhosis

Introduction

Non-selective beta-blockers (NSBBs) are currently recommended for the primary and secondary prophylaxis of variceal haemorrhage in cirrhotic patients [1-3]. Traditionally they have been associated with improved survival [4-6] and reduced incidence of portal hypertension-related complications [7-9]. However, their benefits have been recently questioned after a poor survival rate has been reported in patients with refractory ascites treated with NSBBs [10]. Use of NSBBs in patients with advanced stage of cirrhosis has been associated with deleterious effects, such as an increased incidence of paracentesis-induced circulatory dysfunction, hepato-renal syndrome (HRS) and acute kidney injury [11, 12]. Therefore it has been suggested that cirrhotic patients with portal hypertension may only benefit from NSBBs

use within a well-defined phase of the natural history of the disease, starting with the development of esophageal varices and ending with the occurrence of refractory ascites or a severe complication such as spontaneous bacterial peritonitis (SBP) or HRS [13]. However no universal consensus exists on this topic, particularly as NSBBs have also been shown to lower the risk of SBP in patients with ascites through a possible decrease in gut permeability and bacterial translocation [8, 14, 15]. Moreover improved transplant-free survival has been recently reported in cirrhotic patients with ascites awaiting liver transplantation and taking NSBBs [16], thus supporting the use of these drugs even in advanced stages of cirrhosis. Finally, no impact of NSBBs on survival was observed in a post-hoc analysis of three randomised control trials including cirrhotic patients with ascites [17].

In this setting, we assessed whether NSBB treatment could affect survival in a cohort of patients with ascites, undergoing evaluation for potential liver transplantation in our centre.

Patients and methods

This was a single-centre retrospective audit including consecutive patients with cirrhosis and ascites, who were assessed for liver transplant suitability between January 2011 and October 2014 at the Royal Free Hospital following recent concerns on their use in such patients. As such, ethical approval and consent was not required. The following variables at the time of transplant assessment were recorded: age, gender, blood group, body mass index (BMI), heart rate, blood pressure, aetiology of cirrhosis, presence of hepatocellular carcinoma (HCC), diabetes mellitus, nutritional status, previous episodes of variceal bleeding, hepatic encephalopathy, spontaneous bacterial peritonitis, hepato-renal syndrome, and laboratory data.

Patients were divided in two groups according to whether they were receiving NSBBs or not at the time of transplant assessment. The type of NSBB and the duration of treatment were recorded, as well as the prescription of diuretics and long-term antibiotic prophylaxis for spontaneous bacterial peritonitis. Presence of ascites was defined on the basis of clinical and/or radiological findings, and its severity was graded according to the International Ascites Club criteria [18]. Child-Pugh score, Model for End-Stage Liver Disease (MELD) score and UK Score for Patients with End-Stage Liver Disease (UKELD) were calculated as per published equations [19, 20] at the time of transplant assessment. Glomerular filtration rate was estimated (eGFR) using the modification of diet in renal disease (MDRD) study formula [21].

Statistical analysis

Categorical variables were expressed as counts and percentages, and compared using the Chi Square test. Continuous variables were reported as median and interquartile ranges IQR (or mean and standard deviations when appropriate) and compared with the Wilcoxon/Mann Whitney test or student-T test when appropriate.

A competing risk Cox regression model was used to analyze the independent risk of two failure types, namely death and transplantation. Patients that stopped NSBB during the follow-up period were censored at the time of drug discontinuation. Variables with $p \leq 0.10$ at univariate analysis were entered in the multivariate model, using a stepwise forward approach. The results are reported as hazard ratios (HRs) with 95% confidence interval (CIs) and the significance was set at a 0.05 level. A simple Cox regression model is reported in the Supplementary material.

A propensity analysis using logistic regression was carried out to create a score for patients who were receiving NSBBs and those that were not receiving NSBBs. The model for Propensity Score (PS) included HCC, age, gender, MELD, sodium, prophylactic antibiotic use, previous variceal bleeding as well as the interaction term (prophylactic antibiotic use, previous variceal bleeding) with $p \leq 0.1$. We used the nearest neighbour method with no replacement to match NSBB patients and non-NSBB patients, with a caliper width of 0.2 of the standard deviation of the logit of the PS. After matching, appropriated paired tests were used (Wilcoxon signed-rank test for continuous variables, McNemar test for 2×2 tables and McNemar-Bowker test for tables with more than two response categories).

All analyses were performed using SPSS version 22.0 (IBM, New York, NY, USA), except for the competing risk analyses, which were performed using Stata version 12.1 (Statacorp, College Station, Texas, USA).

Results

Patient characteristics

A total of 316 patients were evaluated with a median follow up of 7 months (±12). Clinical characteristics, biochemical values and treatment at inclusion are summarised in Table 1. Mean age was 54 years. Alcohol and viral hepatitis were the most common causes of cirrhosis, accounting for almost the 70% of cases. The frequency of previous variceal bleeding, spontaneous bacterial peritonitis and hepatic encephalopathy were 32.3%, 20.3% and 45.3%, respectively. Median MELD score was 15 (6-40), while median UKELD was 55 (43-85). Only 6% of the population was classified as Child-Pugh A class and these patients had HCC. Refractory ascites was diagnosed in 124 (39%) patients, the majority of patients

with grade III ascites. Only 6 patients with severe ascites did not fulfil the criteria for refractory ascites. One hundred and twenty-eight patients (40.5%) received NSBB for prevention of variceal bleeding: 92% used propranolol (median daily dose 80 mg, IQR 40), while only 8% received carvedilol (median daily dose 6.25 mg). Twenty-two (6%) patients discontinued NSBBs during follow-up. The reasons for discontinuation were: drug intolerance (n=11), transjugular intrahepatic portosystemic shunt (TIPSS) (n=6), HRS (n=3) and SBP (n=2). Treatment with furosemide or spironolactone were documented in 114 (36.6%) and 215 (69%) patients respectively. Use of antibiotics for SBP prophylaxis was recorded in 57 (19%) patients. During follow-up 26 (8%) patients underwent TIPSS placement for the management of ascites (8 in NSBB group and 18 in no-NSBB group).

Comparison between NSBB and non-NSBB group

The comparison between NSBB and non-NSBB group is shown in Table 1. Patients receiving NSBB had a higher frequency of previous variceal bleeding (NSBB 50% vs. no-NSBB 20.7%, $p<0.001$) and spontaneous bacterial peritonitis (NSBB 27.4% vs. no-NSBB 16.8%, $p=0.025$). In no-NSBB group, patients with a history previous bleeding did not receive NSBBs due to the presence of TIPSS (n=11) or drug intolerance (n=27). More patients had varices (98% vs. 58%, $p<0.001$), while the proportion of patients with grade III and refractory ascites was significantly lower in the NSBB group (46.3% and 44% vs. 36.6% and 32% $p=0.013$ and 0.03 respectively). All patients on NSBBs had varices, except from two who had portal hypertensive gastropathy. Of the patients with varices not on NSBBs, 53 (48%) had previous endoscopic band ligation, 49 (45%) had small varices and 8 (7%) had medium size varices. As expected, heart rate was significantly lower in NSBB group (70 vs. 81 bpm, $p=0.001$), as well as mean arterial blood pressure (MAP: 80 vs. 86 mmHg, $p=0.012$). Other

significant differences were found in platelet count (87 $x10^9$ in NSBB vs. 96 $x10^9$/l in non-NSBB, p=0.016), white blood cell count (5.04 vs 5.8 $x10^6$/l, p=0.037), haemoglobin levels (11.1 vs. 10.7 g/dl, p=0.034) and sodium (137 vs. 135 mmol/L, p=0.002). MELD and UKELD score were similar between the two groups. There was no difference in MAP and GFR in patients with Child-Pugh C in the NSBBs and non-NSBBs group. Diuretics were more frequently prescribed in NSBB group with 47% of patients receiving furosemide and 82% spironolactone, compared to 29% and 60% in non-NSBB group. This was due to the fact that more patients with refractory ascites who were not on diuretics were included in the non-NSBB group. The median daily dose of diuretics did not differ between the two groups.

Outcome in whole population

Overall 80 (25.3%) patients died after a median follow up of 4 months (range 0-37) or 125 days (5-1123): 20 (16%) in NSBB group vs. 60 (32%) in no-NSBB group (p=0.002). Causes of death were: liver failure (n=28, 35%), infection (n=16, 20%), haemorrhage (n=7, 9%), non-liver related (n=5, 6%), multiple-organ failure (n=4, 5%) and hepatocellular carcinoma (n=3, 4%). The exact cause was not reported in 17 (21%) cases. No difference was found between NSBB and no-NSBB patients regarding the cause of death.

Two hundred and sixteen (68%) patients were listed for liver transplantation: 98 (76%) among NSBB patients compared to 118 (63%) among no-NSBB patients, p=0.01). Of them, 146 (46.2%) were transplanted (62 (48%) in NSBB group versus 84 (45%) in no-NSBB group, p=NS) after a median time of 150 days (8-920).

Twenty-six (8.6%) patients developed SBP, while 22 (7.3%) experienced an episode of hepatorenal syndrome without significant difference between NSBB and non-NSBB group. Variceal bleeding occurred in 22 patients (7.3%) with similar prevalence between NSBB and non-NSBB group (10 (8%) in NSBB versus 12 (7%) in no-NSBB group, p=0.723).

Predictors of mortality in the whole population

Variables associated with mortality in the univariate and multivariate competing risk Cox regression analyses are shown in Table 2. In the multivariate analysis use of NSBB was associated with reduced mortality (HR=0.55, 95% CI=0.33-0.94 p=0.03). Other factors significantly associated with mortality were prophylactic antibiotic use (HR=0.33, 95% CI=0.14-0.74, p=0.007) MELD score (HR=1.1, 95% CI=1.06-1.14, p<0.001) and sodium (HR= 0.94, 95% CI= 0.89-0.98, p=0.004).

In the multivariate Cox regression analysis on propensity-risk score matched patients no association between NSBBs and mortality was found (Table 3). The only factors associated with mortality were severe malnutrition at the time of liver transplant work-up (HR=2.84, 95% CI= 1.45-5.54, p=0.002), MELD score (HR=1.08, 95% CI= 1.04-1.12, p<0.001) and sodium (HR=0.92, 95% CI= 0.86-0.99, p=0.021). Characteristics of propensity-risk score matched patients are shown in Supplementary Table 1.

In standard multivariate Cox-regression analysis, NSBB use was again associated with reduced mortality (HR=0.56, 95%CI=0.33-0.96, p=0.036, Supplementary Table 2 and Supplementary Figure 1). No significant difference was observed in all analyses when we excluded patients who had TIPSS (data not shown).

Outcomes and predictors of mortality in patients with refractory ascites.

Refractory ascites was diagnosed in 124 (39%) patients (Supplementary Table 3). Patients taking NSBB (41, 33%) had more frequently a history of variceal bleeding (61% vs. 19.3%, p<0.001) and spontaneous bacterial peritonitis (44% vs. 25%, p=0.033). Mean systolic and diastolic arterial pressures were lower in NSBB group (82 vs. 83 mmHg, p=0.012 and 65 vs. 68 mmHg, p=0.014, respectively), as well as white blood cell count (5.4 vs. 6.8, p=0.024). Serum sodium levels were significantly higher in patients taking NSBBs (137 vs. 133 mmol/l, p=0.004).

Overall forty-nine (39%) patients underwent liver transplantation after a median time of 4 (±7) months, while 34 (27%) died after a median follow-up of 2.5 (±4) months. Of them, 6 (17.6%) were in NSBB group and 28 (82.4%) in non-NSBB group (p=0.005). Causes of death were liver failure (50%), infections (23.5%), haemorrhage (11.8%), multi-organ failure (3%), non-liver related (3%) and unknown (8.8%). There was no difference in the cause of death between the two groups.

Variables associated with mortality on competing risk Cox regression analysis are shown in Table 4. No association was found between NSBB use and mortality in multivariate analysis (HR=0.47, 95%CI=0.2-1.11, p=0.086). When propensity-score matched patients were analysed, NSBBs was associated with reduced mortality (HR=0.09, 95%CI=0.01-0.54, p=0.009) (Table 5). Characteristics of propensity-risk score matched patients are shown in Supplementary Table 4. Similar results were obtained from Cox regression analysis. (HR=0.285, 95% CI=0.11-0.70, p=0.006) (Supplementary Table 5 and Supplementary Figure 2).

Influence of NSBBs on SBP incidence.

NSBB group had a lower frequency of SBP (5.6% vs. 10.9%), however this difference did not reach statistical significance (p=0.106). Kaplan Meier analysis showed a trend toward a protective effect of NSBBs against SBP, although it was not statistically significant (log rank test p=0.128). The same results were found when considering only patients with refractory ascites (data not shown).

Discussion

In this large single-centre retrospective study, we assessed whether NSBB use could affect survival in patients with cirrhosis and ascites undergoing evaluation for potential liver transplantation. In our cohort, NSBB use was not associated with impaired survival in patients with ascites or refractory ascites and appeared safe even in more advanced stages of cirrhosis. Although our data suggest improved survival in patients with ascites on NSBBs, causality cannot be established from observational studies and this will need further confirmation in prospective studies. None of the analyses showed a detrimental effect of NSBBs on survival.

Our findings conflict with those by Serstè et al. who were the first to question the beneficial role of NSBBs in advanced cirrhosis, showing an increased mortality among patients with refractory ascites treated with these drugs [10, 11]. The authors concluded that NSBBs should be contraindicated in this population, triggering a lively debate within the hepatology community on whether NSBBs should be stopped or not in end-stage cirrhosis. Close monitoring is currently recommended for patients with end-stage liver disease receiving NSBBs and dosage reduction or drug discontinuation may be considered in the presence of

low blood pressure and renal impairment [1]. However no universal consensus exists on this topic since opposite results supporting the beneficial role of NSBBs have recently been reported. Leithead et al. showed that patients receiving NSBBs while on LT waiting list had a reduced transplant-free mortality compared to those not on beta blockers [16]. Similarly, Mandorfer et al [12] observed a 25%-reduction in mortality risk for patients with cirrhosis and ascites treated with NSBBs, while an impaired survival was only found after the development of SBP. This observation reinforced the so-called "window hypothesis", which considers the beneficial effect of beta blockers as limited to a specific period of the natural history of cirrhotic disease [13]. Finally, a recent study conducted on cirrhotic patients developing acute-on-chronic liver failure, reported an improved 28-day survival in patients taking NSBBs, further supporting the benefit of these drugs even in the acutely ill cirrhotic population [22] .

The reason for such a controversial results might be related to the different characteristics of the studied populations concerning the disease severity and beta-blockers dosage. In our cohort, the two groups were well-matched with regards to possible confounding factors that could affect survival, such as the presence of hepatocellular carcinoma, hepatic encephalopathy and malnutrition. As expected, patients taking NSBBs had a higher frequency of varices and previous variceal bleeding, while refractory ascites was more common in the non-NSBB group. However no significant difference was observed in the markers of hepatic synthetic function, as documented by the similar MELD score (14 in NSBB and 15 in non-NSBB group). When compared to the population studied by Serstè et al [10], our patients were younger and with a more compensated liver disease. In fact, we had a lower proportion of Child-Pugh C patients (49% vs. 67.5%), HCC (8% vs. 27%) and lower MELD score (15 vs. 18.8). Moreover, renal dysfunction, defined as a serum creatinine level greater than 1.5mg/dl, was documented at entry only in 16% of patients compared to a third of French patients. By contrast, the overall frequency of varices was higher than in Serstè et

al. cohort (80% vs. 49%) and less different between NSBB and non NSBB group (94% and 69% vs. 100% and 4% in NSSB and non-NSBB group, respectively). Finally, in our population propranolol was administered at a lower daily dose with only 8% of patients taking 160 mg compared to 46.7% in the French cohort. This is also in line with previous studies by Leithead et al, whose median propranolol dose was 80 mg/day [16], and Mandorfer et al, where only 5% of patients received a higher dose of 100-120 mg/day [12]. We must therefore acknowledge that all these factors could have contributed to the lower mortality rate observed in our study and therefore counterbalanced in some way the potential negative effect of NSBBs use. However it should be noted that patients taking NSBBs did not have impaired survival despite having a significantly lower heart rate and mean arterial blood pressure, which are considered poor prognostic markers in cirrhotic patients with ascites[23].

No difference was found in the cause of death between NSBB and non-NSBB group, as well as in the incidence of SBP or HRS, although the number of events reported during the follow-up period was limited. The improved survival we observed in NSBB cohort is in line with the increased transplant-free survival reported by Mandorfer et al [12] in cirrhotic patients with ascites who were taking NSBBs. However, due to the limited number of SBP episodes, we could not evaluate the impact on survival of NSBBs after the occurrence of SBP.

The benefits of beta-blockers extend over and above primary and secondary prophylaxis of variceal bleeding[24]. Indeed, longitudinal follow up of patients randomised to endoscopic band ligation or NSBBs for secondary prophylaxis of variceal bleeding showed increased survival in the NSBB group despite a higher rate of re-bleeding, demonstrating an additive therapeutic benefits of NSBBs[25]. This could be due to reduction of bacterial translocation and subsequent infection[14].

The paper by Serste and colleagues has introduced the "window" hypothesis in relation to the use of NSBBs in patients with cirrhosis. According to this hypothesis, refractory ascites should be an indication for discontinuing NSBBs. We believe that this data adds to the substantial evidence published since the Serste paper that argue against this hypothesis. Although the use of NSBBs should be cautious in these patients, we should not deprive them of their potential beneficial effects. Systolic blood pressure, serum sodium and renal function should be evaluated in patients in every outpatient visit or hospitalization, particularly in the presence of SBP, in accordance with the recent Baveno guidelines[1] and consideration given to dose reduction. Until further prospective data are available, a thorough evaluation should be carried out before discontinuing these drugs in advanced cirrhosis and such decisions should be revisited.

Our study has limitations that need to be taken into account. Firstly, we could not assess how many patients had already been taken off NSBBs at the entry of the study, since we started collecting data from the date of liver transplant suitability assessment. Secondly, the relative short follow-up due to transplantation might have affected our findings preventing the occurrence of detrimental events in patients with more advanced liver disease. Therefore, we acknowledge that the applicability of our results to patients not listed for liver transplantation should be further explored. Although patients included in this study were followed up when the first studies suggesting deleterious effects of NSBBs were published, the departmental policy regarding their use did not change. [15]

Although retrospective, our cohort included consecutive well-characterized patients with detailed baseline information such as the presence of varices that were lacking in similar studies [17] and thorough follow-up. We showed that the use of NSBBs does not harm and might actually benefit patients with cirrhosis and ascites. We could not assess the impact of NSBBs on survival after an episode of SBP due to the limited number of cases. The lack of

significant association between NSBBs and survival observed in the propensity-score matched patients could be due to a type II error due to the reduced number of patients included in that analysis.

In conclusion, our data suggest that NSBB use is safe and potentially beneficial in patients with cirrhosis and ascites in the liver transplant waiting list. As such patients have a very narrow window of opportunity to be transplanted, discontinuation of NSBBs should only occur in the events of hypotension, hyponatremia or acute kidney injury.

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Table 1. Baseline patients' characteristics

	All (n=316)	NSBB (n=128)	No-NSBB (n=188)	P value
Gender, male	229 (72.5)	94 (73.4)	135 (71.8)	0.75
Age, years	54 ±10	53.8±10	54.3±10	0.65
Aetiology of cirrhosis				0.005
Alcoholic	134 (42)	48 (37)	86 (46)	
Viral hepatitis	82 (26)	44 (34)	38 (20)	
Non-alcoholic steatohepatitis	30 (10)	12 (9)	18 (10)	
Other	70 (22)	24 (19)	46 (24)	
Hepatocellular carcinoma	39 (12)	18 (14)	21 (11)	0.443
Varices small medium large previous endoscopic band ligation	236 (75) 101 (32) 13 (4) 2 (1) 121 (38)	126 (98) 51 (40) 5 (4) 2 (1) 68 (53)	110 (58) 49 (26) 8 (4) 0 (0) 53 (28)	<0.001
Hepatic encephalopathy	98 (31)	46 (36)	52 (28)	0.118
Severity of ascites				0.013
Mild	74 (23.4)	40 (31.2)	34 (18.1)	
Moderate	112 (35.4)	45 (35.2)	67 (35.6)	
Severe	130 (41.1)	43 (33.6)	87 (46.3)	
Refractory ascites	124 (39)	41 (32)	83 (44)	0.03
TIPSS	23 (7.3)	3 (2.3)	20 (11)	0.005
Diabetes	91 (28.8)	44 (34.4)	47 (25.8)	0.094

Malnutrition	156 (49.4)	57 (50.4)	99 (60.4)	0.102
Mild	7 (2.2)	5 (4.5)	2 (1.2)	
Moderate	93 (29.4)	36 (32.1)	57 (35.6)	
Severe	51 (16.1)	15 (13.4)	36 (22.5)	
Previous variceal bleeding	102 (32.3)	64 (50)	38 (20.7)	<0.001
Previous spontaneous bacterial peritonitis	64 (20.3)	34 (27.4)	30 (16.8)	0.025
Previous hepatic encephalopathy	143 (45.3)	61 (48)	82 (44.8)	0.576
Previous hepato-renal syndrome	11 (3.5)	2 (1.6)	9 (4.4)	0.118
Body mass index, kg/m^2	27±6	27±6	27±7	0.992
Heart rate, bpm	79 (17)	70 (18)	81 (15)	<0.001
Systolic arterial pressure, mmHg	114 (20)	110 (17)	115 (19)	0.073
Diastolic arterial pressure, mmHg	67 (15)	64 (12)	70 (15)	0.014
Mean arterial pressure, mmHg	83 (15)	80 (15)	86 (14)	0.012
Child-Pugh class				0.016
A	18 (6)	12 (9.4)	6 (3.2)	
B	177 (56)	76 (59.3)	101 (53.7)	
C	121 (38)	40 (31.2)	81 (43.1)	
MELD score	15 (7)	14 (6)	15 (8)	0.125
UKELD score	55 (7)	54 (6)	55 (7)	0.156
Platelet count ($x10^9/L$)	93 (62)	87 (53)	96 (65)	0.016
White blood cell count	5.3 (3.2)	5 (3.1)	5.8 (3.3)	0.037

($x10^9$/L)				
Haemoglobin (g/dl)	10.9 (2.9)	11.1 (3)	10.7 (3)	0.034
Bilirubin (mg/dl)	2.34 (2.8)	1.99 (2.11)	2.48 (3)	0.133
Albumin (g/dl)	3.1 (0.7)	3.2 (0.8)	3.1 (0.8)	0.06
INR	1.4 (0.5)	1.3 (0.4)	1.4 (0.5)	0.053
Creatinine (mg/dl)	0.93 (0.38)	0.97 (0.36)	0.91 (0.41)	0.414
eGFR (ml/min), MDRD	82 (45)	81.5 (42)	84 (49)	0.48
Sodium (mmol/L)	136 (7)	137 (6)	135 (7)	0.002
Prophylactic antibiotic	57 (19)	26 (20.3)	31 (17.4)	0.521
Diuretic treatment				
Furosemide - dosage	114 (36%) 40 (0)	60 (47) 40 (0)	54 (29) 40 (5)	0.002
Spironolactone - dosage	215 (69) 100 (100)	105 (82) 100 (100)	110 (60) 100 (100)	<0.001

Values are expressed as number (per cent), mean ±standard deviation and median (interquartile range) when appropriate.

TIPSS, Transjugular intrahepatic portosystemic shunt; NSBB, non-selective beta blocker; MELD, Model for End-stage Liver Disease; UKELD, UK score for Patients with End-Stage Liver Disease; INR, international normalized ratio; eGFR, estimated glomerular filtration rate; MDRD, modification of Diet in Renal Disease;

Table 2. Competing risk Cox regression analysis of variables associated with mortality in all patients.

	Univariate			Multivariate		
	HR	95% CI	P	HR	95% CI	P
Gender, female	1.11	0.68-1.79	0.687			
Age, years	1.03	1.00-1.06	0.097			
Aetiology of cirrhosis	1.02	0.83-1.26	0.850			
Hepatocellular carcinoma	0.70	0.33-1.49	0.352			
Varices	1.17	0.61-2.23	0.633			
Hepatic encephalopathy	1.52	0.95-2.42	0.077			
Severity of ascites						
Moderate vs mild	1.34	0.72-2.49	0.356			
Severe vs mild	1.56	0.85-2.86	0.155			
Refractory ascites	1.31	0.83-2.08	0.247			
TIPSS	1.52	0.75-3.05	0.242			
Diabetes	0.97	0.57-1.62	0.859			
Malnutrition	1.21	0.73-2.04	0.455			
Severe	2.26	1.30-3.92	0.004			
Previous variceal bleeding	0.90	0.55-1.47	0.670			
Previous spontaneous bacterial peritonitis	0.70	0.37-1.34	0.283			
Previous hepatic encephalopathy	1.13	0.71-1.78	0.612			
Previous hepato-renal syndrome	0.76	0.19-3.00	0.696			
Body mass index	1.00	0.96-1.05	0.901			
Heart rate, bpm	1.02	1.00-1.04	0.074			

Systolic arterial pressure, mmHg	0.97	0.97-1.00	0.115			
Diastolic arterial pressure, mmHg	0.98	0.95-1.01	0.125			
Mean arterial pressure, mmHg	0.98	0.95-1.00	0.070			
Child-Pugh score	1.28	1.12-1.46	<0.001			
MELD score	1.09	1.06-1.13	<0.001	1.10	1.06-1.14	<0.001
UKELD score	1.11	1.08-1.14	<0.001			
Platelet count ($x10^9$/L)	1.00	0.99-1.00	0.654			
White blood cell count ($x10^9$/L)	1.03	0.96-1.11	0.444			
Haemoglobin ($x10^9$/L)	0.86	0.78-1.00	0.050			NS
Bilirubin (mg/dl)	1.07	1.05-1.09	<0.001			
Albumin (g/dl)	0.96	0.92-1.01	0.083			
INR	1.82	1.23-2.68	0.003			
Creatinine (mg/dl)	1.02	0.69-1.52	0.902			
eGFR (ml/min), MDRD	1.00	0.99-1.00	0.565			
Sodium (mmol/L)	0.93	0.89-0.97	0.001	0.94	0.89-0.98	0.004
Prophylactic antibiotics	0.45	0.21-1.00	0.049	0.33	0.14-0.74	0.007
Diuretic treatment						
Furosemide	0.65	0.39-1.06	0.083			
Spironolactone	0.48	0.30-0.77	0.002			
NSBB use	0.48	0.29-0.79	0.004	0.55	0.33-0.94	0.030

TIPSS, Transjugular intrahepatic portosystemic shunt; MELD, Model for End-stage Liver Disease; UKELD, UK score for Patients with End-Stage Liver Disease; INR, international normalized ratio; eGFR, estimated glomerular filtration rate; MDRD, modification of Diet in Renal Disease; NSBB, non-selective beta blocker.

Table 3. Competing risk Cox regression analysis of variables associated with mortality in 212 propensity risk score matched patients with ascites

	Univariate			Multivariate		
	HR	95% CI	P	HR	95% CI	P
Gender, female	1.29	0.70-2.36	0.414			
Age, years	1.03	0.99-1.07	0.204			
Aetiology of cirrhosis	0.96	0.73-1.27	0.769			
Hepatocellular carcinoma	0.43	0.14-1.38	0.158			
Varices	0.99	0.45-2.15	0.974			
Hepatic encephalopathy	1.70	0.95-3.04	0.072			
Severity of ascites						
Moderate vs mild	1.17	0.54-2.53	0.697			
Severe vs mild	1.65	0.79-3.48	0.184			
Refractory ascites	1.45	0.80-2.66	0.223			
TIPSS	1.81	0.80-4.09	0.155			
Diabetes	0.83	0.42-1.64	0.575			
Malnutrition	1.55	0.78-3.09	0.216			
Severe	3.45	1.73-6.87	<0.001	2.84	1.45-5.54	0.002
Previous variceal bleeding	1.19	0.66-2.14	0.570			
Previous spontaneous bacterial peritonitis	0.89	0.40-2.00	0.775			
Previous hepatic encephalopathy	1.54	0.86-2.76	0.143			
Body mass index	0.97	0.92-1.02	0.263			
Heart rate, bpm	1.01	0.99-1.04	0.198			
Systolic arterial pressure,	0.99	0.97-1.01	0.336			

mmHg						
Diastolic arterial pressure, mmHg	0.99	0.97-1.02	0.705			
Mean arterial pressure, mmHg	0.99	0.96-1.02	0.499			
Child-Pugh score	1.22	1.04-1.42	0.013			
MELD score	1.09	1.04-1.14	<0.001	1.08	1.04-1.12	<0.001
UKELD score	1.11	1.08-1.14	<0.001			
Platelet count ($x10^9$/L)	1.00	0.99-1.00	0.200			
White blood cell count ($x10^9$/L)	1.00	0.90-1.11	0.955			
Haemoglobin (g/dl)	0.89	0.77-1.03	0.110			
Bilirubin (mg/dl)	1.06	1.02-1.09	0.002			
Albumin (g/dl)	0.98	0.92-1.04	0.418			
INR	1.65	1.06-2.57	0.026			
Creatinine (mg/dl)	1.44	0.83-2.51	0.197			
eGFR (ml/min), MDRD	0.99	0.98-1.00	0.260			
Sodium (mmol/L)	0.92	0.86-0.97	0.005	0.92	0.86-0.99	0.021
Prophylactic antibiotics	0.78	0.26-2.17	0.605			
Diuretic treatment						
Furosemide	0.58	0.31-1.10	0.095			
Spironolactone	0.57	0.31-1.06	0.075			
NSBB use	0.62	0.34-1.12	0.114			

TIPSS, transjugular intrahepatic portosystemic shunt; MELD, Model for End-stage Liver Disease; UKELD, UK score for Patients with End-Stage LIver Disease; INR, international normalized ratio; eGFR, estimated glomerular filtration rate; MDRD, modification of Diet in Renal Disease; NSBB, non-selective beta blocker.

Table 4. Competing risk Cox regression analysis of variables associated with mortality in patients with refractory ascites

	Univariate			Multivariate		
	HR	95% CI	P	HR	95% CI	P
Gender, female	0.97	0.42-2.22	0.939			
Age, years	1.02	0.97-1.06	0.472			
Aetiology of cirrhosis	1.35	0.99-1.82	0.055			
Hepatocellular carcinoma	1.13	0.37-3.51	0.829			
Varices	1.05	0.34-3.20	0.933			
Hepatic encephalopathy	1.61	0.80-3.27	0.184			
TIPSS at baseline	1.69	0.71-4.02	0.234			
Diabetes	1.22	0.58-2.56	0.592			
Malnutrition - severe	0.92 2.85	0.41-2.07 1.37-5.97	0.844 0.005			
Previous variceal bleeding	0.85	0.39-1.83	0.671			
Previous spontaneous bacterial peritonitis	0.72	0.32-1.64	0.436			
Previous hepatic encephalopathy	1.54	0.76-3.13	0.234			
Previous hepato-renal syndrome	0.77	0.20-2.95	0.702			
Body mass index	0.99	0.93-1.06	0.799			
Heart rate, bpm	1.03	0.99-1.06	0.114			
Systolic arterial pressure, mmHg	0.99	0.97-1.01	0.206			
Diastolic arterial pressure, mmHg	0.97	0.93-1.01	0.092			
Mean arterial pressure, mmHg	0.97	0.94-1.00	0.091			
Child-Pugh score	1.19	0.99-1.44	0.066			
MELD score	1.12	1.08-1.16	<0.001	1.12	1.08-1.16	<0.001

UKELD score	1.12	1.08-1.16	<0.001			
Platelet count (x10^9/L)	1.00	0.99-1.01	0.844			
White blood cell count (x10^9/L)	1.06	0.95-1.19	0.282			
Haemoglobin (x10^9/L)	0.96	0.77-1.19	0.701			
Bilirubin (mg/dl)	1.08	1.06-1.10	<0.001			
Albumin (g/dl)	1.01	0.94-1.08	0.828			
INR	3.40	1.80-6.41	<0.001			
Creatinine (mg/dl)	1.09	0.72-1.65	0.684			
eGFR(ml/min), MDRD	1.00	0.99-1.01	0.496			
Sodium (mmol/L)	0.93	0.88-0.99	0.022			NS
Prophylactic antibiotics	0.58	0.23-1.44	0.242			
Diuretic treatment						
furosemide	0.45	0.20-1.02	0.057			
spironolactone	0.30	0.13-0.72	0.006	0.43	0.20-1.11	0.053
NSBB use	0.48	0.20-1.14	0.097	0.47	0.20-1.11	0.086

TIPSS, Transjugular intrahepatic portosystemic shunt; MELD, Model for End-stage Liver Disease; UKELD, UK score for Patients with End-Stage Liver Disease; INR, international normalized ratio; eGFR, estimated glomerular filtration rate; MDRD, modification of Diet in Renal Disease; NSBB, non-selective beta blocker;

Table 5. Competing risk Cox regression analysis of variables associated with mortality in 58 propensity risk score matched patients with refractory ascites.

	Univariate			Multivariate		
	HR	95% CI	P	HR	95% CI	P
Gender, female	1.42	0.51-3.97	0.507			
Age, years	1.01	0.97-1.06	0.561			
Aetiology of cirrhosis	1.08	0.70-1.73	0.763			
Hepatocellular carcinoma	0.60	0.08-4.25	0.610			
Varices	0.60	0.11-3.27	0.559			
Hepatic encephalopathy	1.04	0.39-2.80	0.933			
TIPSS	2.15	0.64-7.28	0.218			
Diabetes	1.39	0.53-3.62	0.499			
Malnutrition	1.21	0.43-3.39	0.715			
Severe	2.84	1.11-7.27	0.030	3.91	1.08-14.20	0.038
Previous variceal bleeding	0.65	0.24-1.74	0.393			
Previous spontaneous bacterial peritonitis	0.84	0.28-2.49	0.752			
Previous hepatic encephalopathy	2.84	1.00-8.08	0.050			NS
Body mass index	1.01	0.92-1.11	0.844			
Heart rate, bpm	1.04	0.99-1.09	0.066			NS
Arterial systolic pressure, mmHg	0.99	0.97-1.02	0.526			
Arterial diastolic pressure, mmHg	1.01	0.96-1.05	0.805			
Arterial mean pressure, mmHg	1.00	0.96-1.03	0.884			
Child-Pugh score	1.18	0.90-1.55	0.241			

MELD score	1.16	1.08-1.24	<0.001	1.18	1.10-1.27	<0.001
UKELD score	1.16	1.07-1.25	<0.001			
Platelet count ($x10^9$/L)	1.00	0.98-1.00	0.224			
White blood cell count ($x10^9$/L)	1.10	0.86-1.39	0.456			
Haemoglobin ($x10^9$/L)	0.71	0.50-1.01	0.056			NS
Bilirubin (mg/dl)	1.06	1.03-1.10	<0.001			
Albumin (g/dl)	1.06	0.99-1.14	0.071			NS
INR	18.00	4.41-73.41	<0.001			
Creatinine (mg/dl)	2.29	1.01-5.19	0.046			
eGFR (ml/min), MDRD	0.98	0.97-1.00	0.024			NS
Sodium	0.95	0.87-1.04	0.261			
Prophylactic antibiotics	0.20	0.02-1.61	0.137			
Diuretic treatment						
Furosemide	0.48	0.17-1.33	0.156			
Spironolactone	0.37	0.12-1.10	0.074			NS
NSBB use	0.34	0.11-1.03	0.057	0.09	0.01-0.54	0.009

TIPSS, Transjugular intrahepatic portosystemic shunt; MELD, Model for End-stage Liver Disease; UKELD, UK score for Patients with End-Stage Liver Disease; INR, international normalized ratio; eGFR, estimated glomerular filtration rate; MDRD, modification of Diet in Renal Disease; NSBB, non-selective beta blocker