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Received Date : 27-Oct-2016

Revised Date : 09-Feb-2017

Accepted Date : 22-Feb-2017

Article type : Original Paper

LONG-TERM OUTCOMES OF DAAs IN POST-TRANSPLANT ADVANCED HCV RECURRENCE AND FIBROSING CHOLESTATIC HEPATITIS

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Running head: Sofosbuvir in severe post-transplant HCV recurrence: long-term outcomes

Conflict of interest statement: PA has served as speaker, consultant and advisory board member for AbbVie, BMS, Boehringer Ingelheim, Gilead Sciences, Janssen Cilag, MSD, Roche and Intercept and has received research funding from Gilead Sciences, MSD and Roche. SF has served as speaker for AbbVie, Bayer, BMS, Gilead Sciences, Janssen Cilag, MSD, Novartis and Roche. MFD has served as speaker and teacher for AbbVie, BMS, Gilead Sciences, Janssen Cilag and MSD. AMDA has served as speaker and advisory board member for AbbVie, BMS, Gilead Sciences and Janssen Cilag. RV[1], FC, MCM, LP, MC, FGF, SB, PP, MM[1], FM, SM, MT,

GM, LSB, RV[5], PC, PB, FPR, IL, PT, MM[10], LL, RI, AR, AP and MR do not declare any conflict of interests.

No financial support has been received with concern to this study.

ABSTRACT

Long-term functional outcomes of sofosbuvir-based antiviral treatment were evaluated in a cohort-study involving 16 Italian centers within the international compassionate-use program for post-transplant HCV-recurrence. Seventy-three patients with cirrhosis (n=52) or fibrosing cholestatic hepatitis (FCH, n=21) received 24-weeks sofosbuvir with ribavirin±pegylated interferon or interferon-free sofosbuvir-based regimen with daclatasvir/simeprevir+ribavirin. The patients were observed for a median time of 103 (82-112) weeks. Twelve of 73 (16.4%) died (10 non-FCH, 2 FCH) and 2 underwent re-LT. Sustained virological response was achieved in 46/66 (69.7%): 31/47 (66%) non-FCH and 15/19 (79%) FCH patients. All relapsers were successfully retreated. Comparing the data of baseline with last follow-up, MELD and Child-Turcotte-Pugh scores improved both in non-FCH (15.3±6.5 vs. 10.5±3.8, p<0.0001 and 8.4±2.1 vs. 5.7±1.3, p<0.0001, respectively) and FCH (17.3±5.9 vs. 10.1±2.8, p=0.001 and 8.2±1.6 vs. 5.5±1, p=0.001, respectively). Short-treatment mortality was higher in patients with baseline MELD≥25 than in those with MELD<25 (42.9% vs. 4.8%, p=0.011). Long-term mortality was 53.3% among patients with baseline MELD≥20 and 7.5% among those with MELD<20 (p<0.0001). Among deceased patients 75% were CTP class C at baseline while among survivors 83.9% were class A or B (p<0.0001). DAAs-based treatments for severe post-transplant hepatitis C recurrence, comprising fibrosing cholestatic hepatitis, significantly improve liver function, even

without viral clearance and permit an excellent long-term survival. The setting of severe HCV-recurrence may require the identification of 'too-sick-to-treat patients' to avoid futile treatments.

Keywords: antiviral therapy; fibrosing cholestatic hepatitis; liver transplant; long-term outcome; severe HCV recurrence

INTRODUCTION

The recurrence of hepatitis C virus (HCV) infection is universal in HCV-RNA positive liver transplants (LT) [1-3]. Patients with severe HCV recurrence progress rapidly to end-stage illness and, if re-LT cannot be performed, to graft loss and/or death [4,5]. Moreover, the progression of post-LT HCV-recurrence can be particularly fast in patients with features of fibrosing cholestatic hepatitis (FCH) [6-9]. Successful antiviral therapy of HCV recurrence has been shown to allow longer survival and better clinical outcome [10]. In recent years, therapeutic management of HCV recurrence has changed [11-13] with excellent virological results of direct acting antivirals (DAAs) [14-22]. Nevertheless, data on their long-term outcomes are lacking in the actual literature.

The aim of this study was to evaluate the long-term outcomes of sofosbuvir (SOF)-based treatment in patients with severe post-LT HCV recurrence.

METHODS

Patients

From April 2013 to July 2014, consecutive patients with post-LT HCV recurrence were enrolled in 16 Italian hepatology centers to receive antiviral treatment with DAAs upon individual authorizations for compassionate use from local Ethical Committees. The inclusion criteria were: age ≥18 years, severe hepatitis C recurrence, no access to experimental treatment and estimated

life expectancy ≤6 months. The exclusion criteria were: inability or refusal to give informed consent, pregnancy, unstable immunosuppressive regimen.

Seventy-three LT recipients with advanced HCV recurrence (52 with cirrhosis and 21 with FCH) were treated for 24 weeks with SOF (400 mg daily) in combination with ribavirin (RBV) (n=54), pegylated interferon (PegIFN)+RBV (n=14), daclatasvir (DCV) (n=4) or simeprevir (SMV)+RBV (n=1).

Sustained virological response (SVR12) was defined as negative HCV-RNA according to lower limit of detection (<25 IU/mL) 12 weeks after end of treatment (EOT). Laboratory analyses included HCV-RNA, blood count, alanine transaminases (ALT), aspartate transaminases (AST), alkaline phosphatase (ALP), γ-glutammyl transferases (γGT), albumin, total bilirubin, serum creatinine and international normalized ratio (INR). Child-Turcotte-Pugh (CTP) and Model for End-Stage Liver Disease (MELD) scores were reported. Each center confirmed the diagnosis of FCH according to the following criteria (8): a) prominent ductular reaction in the portal tracts, b) cholestasis defined as canalicular bile plugs and/or intracellular bile pigment, c) prominent hepatocyte ballooning with lobular disarray, d) any degree of periportal sinusoidal/pericellular fibrosis, e) >1-month after transplantation, f) total bilirubin >2.0 mg/dL, e) γGT >150 U/L. In patients showing these histological features, surgical biliary obstruction and thrombosis of hepatic artery were excluded. Finally, high serum HCV-RNA levels were confirmed (Table 2).

Statistical Analysis

Categorical variables are expressed as number (%), and quantitative variables are shown as mean±standard deviation or as median (interquartile range, IQR). Chi-square or Fisher's exact test were used to compare categorical variables, while for quantitative variables the t test or Mann Whitney's test (unpaired data) or the t test or Wilcoxon's test (paired data) were used.

Survival analyses were evaluated by the Kaplan Meier method. Statistical significance was established at a two-tailed *p* level <0.05. Data handling and analysis were performed with SPSS 21.0 statistical package (®SPSS inc., Chicago, IL, USA) for Windows® XP (Microsoft Corp.).

RESULTS

Study population

Demographic and clinical characteristics of the 73 enrolled patients are provided in Table 1. Figure 1 shows the disposition of patients throughout the study. Starting from the enrolment, the median follow-up was 724 (574-788) days. Twelve patients died (4 before EOT, 2 during the first 12 weeks of follow-up and 6 after), 2 underwent re-LT (1 before EOT and 1 afterwards). Finally, 2 patients were lost on follow-up. Overall SVR12 rate was 63% (46/73) according to intention-to-treat and 69.7% (46/66) according to per-protocol analysis. SVR12 patients differed from non-SVR12 ones in terms of treatment schedule and CTP class (Supplementary Table 1). Among non-SVR12 patients, 19/20 survived and all 19 were successfully re-treated.

Clinical outcomes

All liver function tests improved significantly during and after therapy. The MELD score was improved from baseline to last follow-up (15 [11-19] vs. 10 [7-13], p<0.0001, Supplementary Figure 1A). Also the CTP score improved from baseline to last follow-up (8 [7-10] vs. 5 [5-6] p<0.0001, Supplementary Figure 1B). This improvement was confirmed also after subdividing the patients in those who obtained SVR12 and those who did not.

After the observation period, 59/73 (80.8%) subjects were alive (Figure 1). Four patients (5.5%) died during treatment (2 kidney failure, 1 sepsis and 1 respiratory failure), and 8 during follow-up (4 liver failure, 1 HCC, 1 graft rejection, 1 sepsis and 1 severe biliary complication). Table 2 shows the comparison of the patients who died with those who were alive at last follow-up.

Nine out of 59 (15.3%) with available data on last follow-up presented relevant hepatic complications: 1 ascites requiring TIPS placement, 1 liver failure (currently awaiting re-LT), 1 hepatic encephalopathy, 2 HCC, 2 variceal bleedings, 1 sepsis and 1 portal vein thrombosis. Two patients had extrahepatic complications (1 stroke and 1 Parkinson's disease).

Survival analyses

The overall survival of the study population is represented in the Figure 2A. Furthermore, we compared the survival curves of patients divided according to baseline MELD cut-off values of 20 (median value in patients who died during long-term follow-up) and 25 (median value in patients who died during treatment or shortly after EOT) (Figures 2B and 2C). The survival was lower in both MELD≥20 compared to MELD<20 patients (Log rank test, $\chi2(1)=17.506$, $p <.0001$) and in MELD≥25 compared to MELD<25 patients (Log rank test, $\chi2(1)=12.551$, $p <.0001$). Finally, we found a similar overall cumulative survival of FCH patients compared to cirrhotic ones (Log rank test, $\chi2(1)=1.313$, $p=0.252$, Figure 2D).

Outcomes in patients with FCH and in cirrhotics

Baseline characteristics and outcomes of FCH and non-FCH patients are presented in Table 2. One FCH died short after starting treatment and one underwent re-LT at week 16. Fifteen of 19 obtained SVR12 (79%, per-protocol analysis). The virological relapsers were all successfully re-treated afterwards. FCH patients showed a significant improvement from baseline to last follow-up: bilirubin (6.3 [2.8-11.5] vs. 1.1 [0.6-2.5], $p<0.0001$), γ-GT (546 [77-1100] vs. 67 [35-244], $p<0.0001$), albumin (3.4 [3-3.8] vs. 4.2 [3.7-4.3], $p=0.001$) and MELD (17 [14-20] vs. 10 [8-13], $p<0.0001$).

Among 52 cirrhotics, the SVR12 rate was 66%. Also in this sub-group all relapsers were successfully re-treated and experienced an improvement of baseline vs. long-term observation MELD (13 [11-18] vs. 9 [7-13], p<0.0001) and CTP score (9 [7-10] vs. 5 [5-6], p<0.0001).

DISCUSSION

Data about efficacy of DAA-based treatments in post-LT setting have been promising [14-22], but to our knowledge there are no data available on long-term impact in end-stage cirrhosis and FCH cohorts. In two studies on LT recipients treated with SOF+SMV [17-18], SVR12 ranged from 90% to 93% but most of the patients had not an advanced disease and FCH was underrepresented. A phase-2 study on the LT cohort treated with SOF+ledipasvir showed SVR12 rates of 80% for CTP-B and ~60% for CTP-C patients [20]. A phase-3 open label study with SOF+DCV+RBV in 55 patients with post-LT HCV-recurrence showed SVR rate of 94% [22]. Notably, this cohort had no patients with FCH. In a recent study utilizing SOF+DCV in FCH, 22/23 (96%) patients reached SVR12 with significant clinical improvement [19]. None of these studies reports on long-term outcomes.

Finally, recently published data on 126 LT patients, showing long-term functional impact and fibrosis regression after SOF-based treatment, had no FCH subjects included and described a fairly shorter follow-up respect to our data (23).

Our results show that DAAs-based treatments are able to induce a durable clinical improvement in severe HCV-recurrence, including FCH. The satisfactory clinical outcomes allow successful re-treatments in patients with virological failure.

The limitations of this study, starting from the retrospective collection of the information on follow-up, are also the small sample size, a non-centralized evaluation of virological, histological and laboratory data and the heterogeneity of the population in terms of treatment schedule.

To our knowledge, our data are the first to show that clinical attainment of DAAs-based post-LT therapy is maintained over a long period of observation. Patients with FCH had apparently higher SVR12 rate and cumulative survival than patients with cirrhosis, although these differences did not reach statistical significance. The MELD, mostly resulting from high bilirubin values in FCH subjects, was similar between these two sub-populations. Still, the median overall survival was significantly longer in FCH patients. This probably implicates that in FCH, characterized by extremely high baseline HCV-RNA, the viral clearance itself brings a substantial benefit even in severe cholestatic hepatitis setting, thus prolonging survival. On the other hand, cirrhotic patients with very advanced disease might not benefit from the treatment, even though achieving SVR12.

The mortality is presumably due to the context of an advanced HCV recurrence wherefore both baseline MELD and CTP scores were higher in deceased patients compared to the ones who survived.

The appropriate patients' selection is a demanding issue since those with extremely advanced disease seem not to benefit even from the virological response and are, moreover, more fragile towards possible adverse events. In our cohort the baseline MELD≥25 and baseline MELD≥20 emerged as valid thresholds for the prediction of short-term and long-term mortality, respectively. Patients with baseline MELD≥25 had an extremely poor survival with almost all events of death registered early during treatment. On the other hand, a lower threshold as MELD≥20 can help identifying those patients who are not as sick as not to survive the treatment but who, despite HCV clearance, do not survive long afterwards. Nevertheless, it should be prospectively explored whether and which cut-off MELD value could effectively detect a "too-sick-to-be-treated" population.

Our results show the long-term functional effectiveness of DAAs-based treatments for severe HCV-recurrence comprising FCH. The treatment might be futile in certain patients; therefore, future studies are necessary to identify a valid selection strategy in extremely advanced settings.

ACKNOWLEDGMENTS

The data of the present study were presented in abstract form at 65th Annual Meeting of the American Association for the Study of Liver Diseases, 7-11 November 2014, Boston, and at 50th International Liver Congress of the European Association for the Study of Liver Diseases, 22-26 April 2015, Vienna.

Besides for the drug supply, the Authors are thankful to Gilead Sciences, Inc. for the constant technical and scientific high-quality endorsement and for a sensitive human approach in this compassionate use program.

Dr Marco Marzioni and the Coordinating Liver Transplantation Committee of AISF are also gratefully acknowledged.

Authorship statement

Professor Pietro Andreone, MD, is the corresponding author and the guarantor of this article.

The study was conceived in collaboration with Gilead Sciences and Italian Association for the Study of the Liver (AISF). Study design: PA and MR; provision of data: all Authors; acquisition of data: RV[1] and FC; analysis and interpretation of data: PA, RV[1] and FC; drafting of the manuscript: RV[1]; critical revision of the manuscript for important intellectual content: all Authors; statistical analysis: RV[1]; study supervision: PA and MR.

All Authors approved the final version of the article.

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TABLES

Table 1. Baseline characteristics in overall population and according to treatment regimen

	Overall (n=73)	**SOF +RBV** (n=54)	**SOF +PegIFN+RBV** (n=14)	**SOF +DCV/SMV+RBV** (n=5)
Male gender	54 (74%)	41 (76%)	11 (79%)	1 (20%)
Age (years)	53 (49-62)	53 (49-62)	52 (49-56)	55 (40-66)
Time from LT (months)	26 (12-53)	26 (13-55)	21 (9-78)	27 (15-41)
FCH	21 (28.8%)	16 (29.6%)	5 (35.7%)	0
Previous antiviral treatment	46 (63%)	32 (59%)	11 (79%)	3 (60%)
Starting RBV dose (mg)	600 (400-800)	600 (400-800)	900 (600-1000)	600 (600-600)
Starting RBV dose (mg/Kg)	10.5 (6.9-13)	9.5 (6.8-12.5)	12.2 (9.9-13.7)	9.2 (9.2-9.2)
HCV Genotype 1a/1b/2/3/4	20/37/1/6/9	15/27/1/6/5	3/7/0/0/4	2/3/0/0/0
HCV-RNA (Log_{10} IU/mL)	6 (5.2-6.4)	6 (5.3-6.5)	6 (4.9-6.3)	6 (5-6.2)
ALT (IU/L)	70 (49-108)	71 (45-116)	74 (56-92)	51 (41-103)
AST (IU/L)	100 (66-147)	98 (64-162)	104 (78-128)	127 (34-175)
FA (IU/L)	162 (103-247)	156 (103-234)	204 (102-275)	186 (96-324)
γGT (IU/L)	131 (50-284)	123 (47-265)	217 (82-649)	77 (53-208)
Total bilirubin (mg/dL)	2.6 (1.5-6.1)	2.7 (1.4-5.6)	2.6 (1.6-7.2)	2.6 (2.2-9.9)
Albumin (g/dL)	3.3 (3-3.6)	3.3 (2.9-3.6)	3.4 (3.2-3.8)	3.1 (2.6-3.3)
INR	1.2 (1.1-1.4)	1.2 (1.1-1.4)	1.2 (1.1-1.3)	1.6 (1.4-1.7)
Creatinine clearance (mL/min)	66.8 (51.5-88.4)	66.5 (52-84.3)	74 (63.5-96.8)	33 (30.1-80.8)
Platelets ($1x10^3$/μL)	82 (56-126)	82 (61-131)	75 (54-112)	68 (46-88)
MELD score*	15 (11-19)	15 (11-18)	12 (11-17)	20 (20-23)
CTP Class A/B/C, %	14/59/27	14/61/25	22/64/14	0/20/80
CTP score*	8 (7-10)	8 (7-10)	7 (7-8)	10 (9-12)

Values are expressed as median (IQR) or number (%)
*Data are calculated after excluding 2 patients in anticoagulant oral therapy

Table 2. Comparison of baseline characteristics and outcomes between cirrhotic and FCH patients

	Cirrhosis (n=52)	**FCH** (n=21)	P value
Male gender	38 (73%)	16 (76%)	1
Age (years)	55 (51-64)	50 (48-56)	**0.011**
BMI	23 (21-26)	23 (21-24)	0.235
Time from LT (months)	39 (20-65)	11 (4.5-12)	**<0.001**
Previous antiviral treatment	33 (64%)	13 (62%)	1
Starting RBV dose (mg)	600 (400-800)	800 (500-800)	0.550
Starting RBV dose (mg/Kg)	10.3 (6.8-13)	11.6 (8-13.2)	0.393
Genotype 1-4	47 (90.4%)	19 (90.5%)	1
SOF+RBV/SOF+RBV+PegIFN/SOF+DCV or SMV, n	38/9/5	16/5/0	0.383
HCV-RNA (Log_{10} IU/mL)	5.9 (5-6.3)	6.3 (2.9-9)	**0.010**
Total bilirubin (mg/dL)	2 (1.3-3.3)	6.3 (2.8-11.5)	**<0.001**
γ - glutammyltransferase (IU/L)	91 (49-174)	546 (77-1100)	**0.001**
Albumin (g/dL)	3.2 (2.9-3.6)	3.3 (3-3.8)	0.234
INR	1.3 (1.1-1.4)	1.1 (1-1.4)	**0.021**
Creatinine clearance (mL/min)	66 (49-88)	69 (64-97)	0.352
Platelets ($1x10^3/\mu L$)	77 (53-116)	93 (64-128)	0.195
MELD score*	13 (11-18)	17 (14-20)	0.109
MELD≥25	5 (10%)	2 (10%)	1
MELD≥20	11 (22%)	6 (30%)	0.543
CTP Class A/B/C, %	16/56/28	10/65/25	0.739
CTP score*	9 (7-10)	8 (7-10)	0.726
SVR (per-protocol analysis)	31/47 (66%)	15/19 (79%)	0.383
Patients with SAE	16 (30.8%)	4 (19.2%)	0.393
Complications at last follow-up**	8 (19.1)	1 (5.3)	0.251
Deaths at last follow-up	10 (19.2%)	2 (9.6%)	0.488
Overall survival time after treatment cessation (days)	650 (480-770)	769 (599-808)	**0.047**

Values are expressed as median (IQR) or number (%); categorical variables were compared using the χ^2 and Fischer's exact test and quantitative variables were compared by the Mann-Whitney test
*Data are calculated in 71 patients (after excluding 2 patients in anticoagulant oral therapy)
**Data are calculated in patients alive at last follow-up

FIGURE LEGENDS

Fig 1. Enrolment and study completion

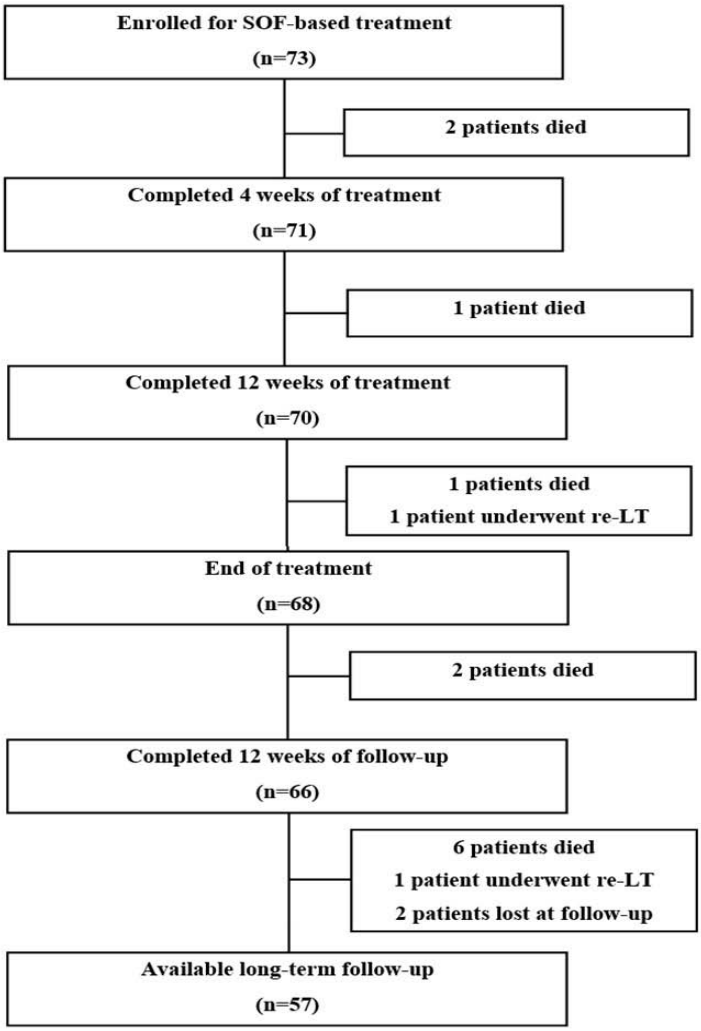
The distribution of the patients during the study is represented in a flow-chart showing the number of subjects at each time-point: baseline, weeks 4, 12 and 24 of treatment, week 12 of follow-up and last available long-term follow-up. The reasons of drop-outs are briefly depicted.

Fig. 2 Survival curves

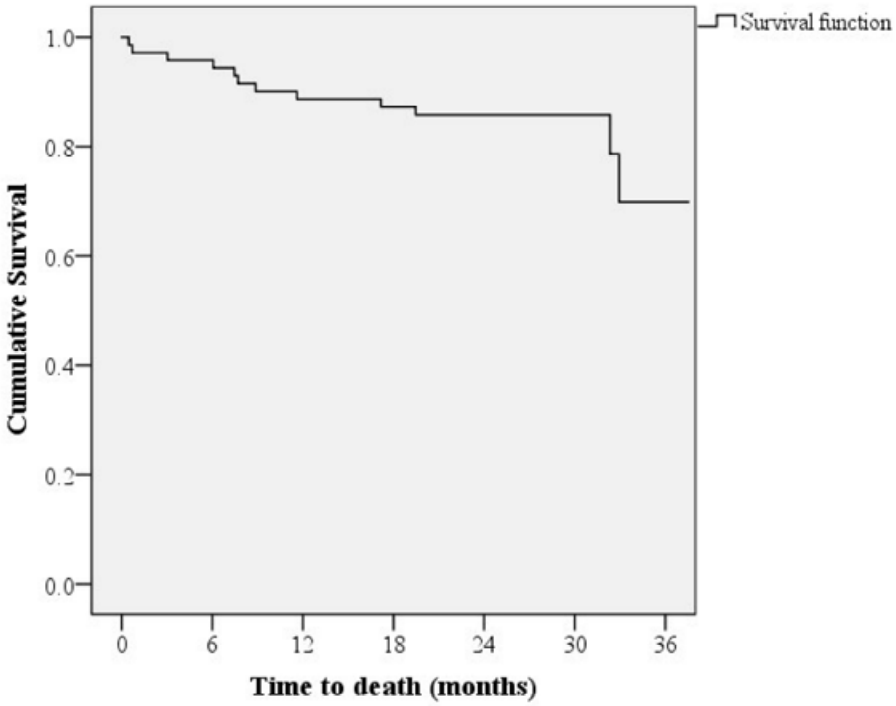
Kaplan-Meier survival curves of **A)** overall study population, **B)** patients stratified according to baseline MELD cut-off 20, **C)** patients stratified according to baseline MELD cut-off 25, **D)** patients with cirrhosis compared to patients with FCH.

Supplementary Fig. 1 Liver function outcomes

The comparison of mean values of **A)** MELD and **B)** CTP scores at baseline, after 12 weeks of follow-up and after long-term observation

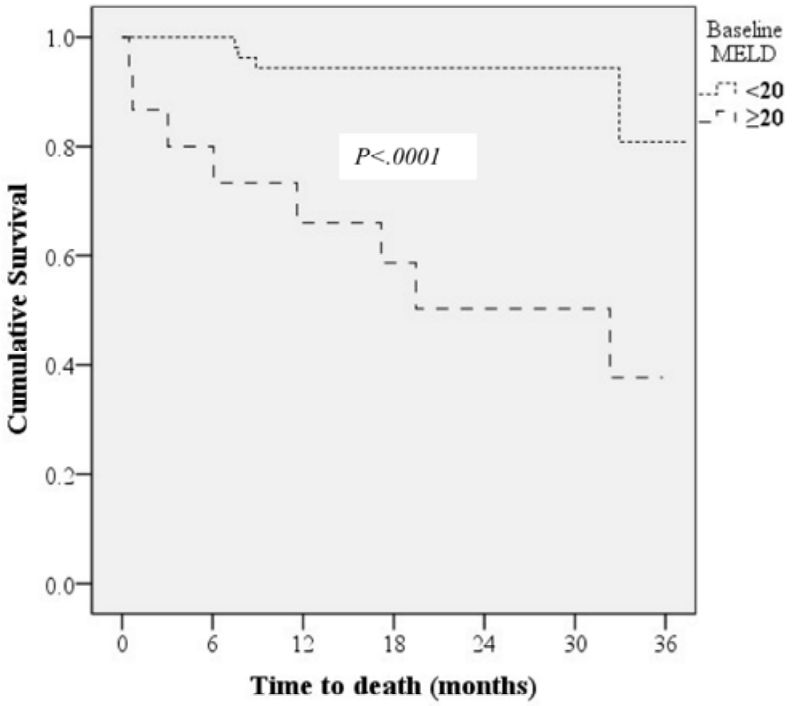


A)



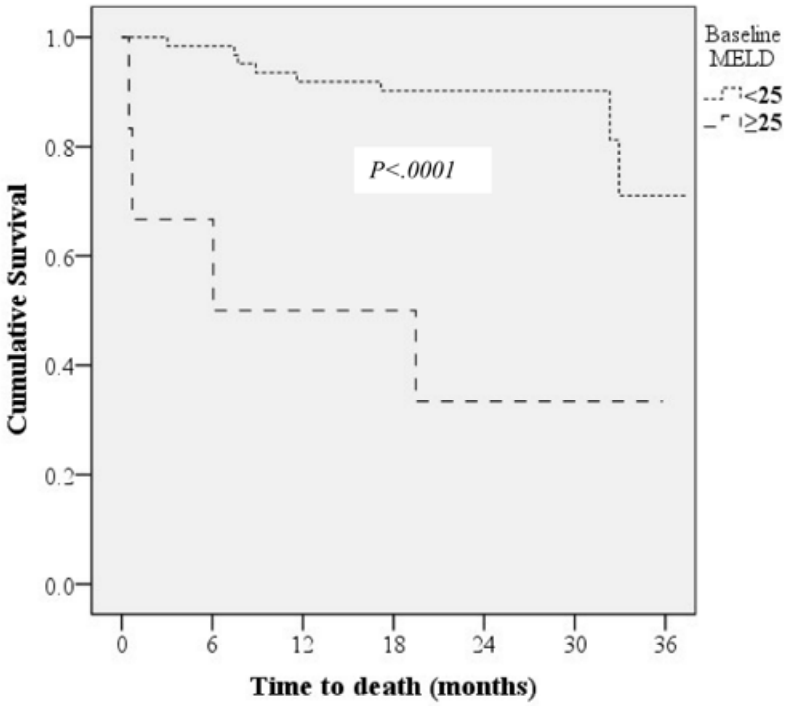
Patients at risk	71	68	64	63	61	61	59

B)



Patients at risk							
<20MELD	53	53	50	50	50	50	49
≥20MELD	15	12	10	9	8	8	7

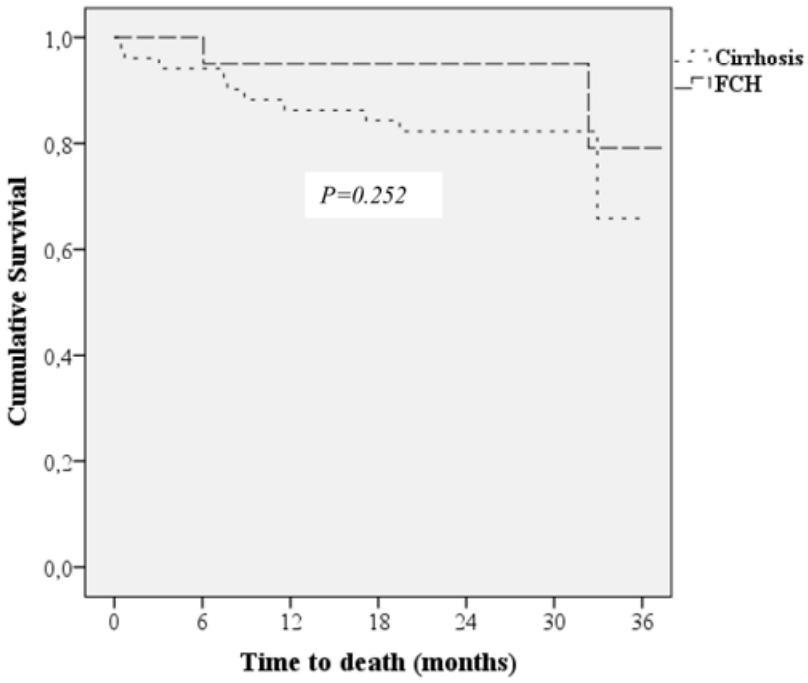
C)



Patients at risk

<25MELD	62	61	57	56	56	56	54
≥25MELD	6	3	3	3	2	2	2

D)



Patients at risk

Cirrhosis	50	47	43	42	41	41	40
FCH	21	21	20	20	20	20	19