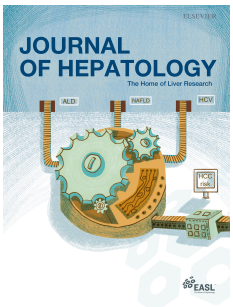
Journal Pre-proof



DAA therapy and long-term hepatic function in advanced/decompensated cirrhosis: Real-world experience from HCV-TARGET cohort

Elizabeth C. Verna, MD, MS, Giuseppe Morelli, MD, Assistant Professor, Norah A. Terrault, MD, Professor, Anna S. Lok, MD, Professor, Joseph K. Lim, MD, Adrian M. Di Bisceglie, MD, Professor, Stefan Zeuzem, MD, Charles S. Landis, MD, PhD, Associate Professor, Paul Kwo, MD, Mohamed Hassan, MD, Professor of Medicine, Michael P. Manns, MD, Professor, Monika Vainorius, MD, Director, Lucy Akushevich, MS, Senior Biostatistician, David R. Nelson, MD, Professor of Medicine, Michael W. Fried M, MD, Professor, K. Rajender Reddy, MD, Professor

PII: S0168-8278(20)30193-8

DOI: https://doi.org/10.1016/j.jhep.2020.03.031

Reference: JHEPAT 7679

To appear in: *Journal of Hepatology*

Received Date: 7 October 2019

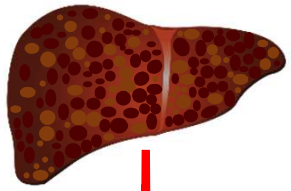
Revised Date: 27 February 2020

Accepted Date: 19 March 2020

Please cite this article as: Verna EC, Morelli G, Terrault NA, Lok AS, Lim JK, Di Bisceglie AM, Zeuzem S, Landis CS, Kwo P, Hassan M, Manns MP, Vainorius M, Akushevich L, Nelson DR, Fried M MW, Reddy KR, DAA therapy and long-term hepatic function in advanced/decompensated cirrhosis: Real-world experience from HCV-TARGET cohort, *Journal of Hepatology* (2020), doi: https://doi.org/10.1016/j.jhep.2020.03.031.

DAA HCV Therapy and Long-Term Hepatic Function in Advanced/Decompensated Cirrhosis: Real World Experience from the HCV-TARGET Cohort

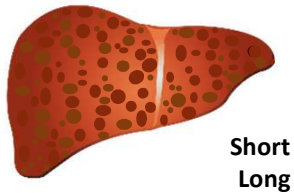
HCV Advanced/Decompensated Cirrhosis



DAAs

SVR

90.5%
(95% CI: 87.8-92.4)



F/U
158 patients

Short term: 9-26 weeks
Long term: 213 weeks
(IQ range: 174-224)

Endpoints

- Total Bilirubin
- Albumin
- MELD score

Baseline Characteristics

- 642 patients
- Median Age: 60 yrs
- 68% Men
- 68% Caucasian
- Median MELD: 12 [IQR 10-39]
- 48.1% CTP B
- 64% prior hepatic decompensations

Negative Predictors of MELD Improvement
(Multivariable analysis)

Short Term	*Long Term*
Male Sex	
ALT <60 u/l	ALT <60 u/l
CTP A	CTP C
MELD <16	MELD ≥16
Age ≥ 60	

Conclusions

- 24% achieved a clinically significant decrease in MELD by ≥3 points during short term follow-up
- In long term follow up, a clinically meaningful decrease in MELD of ≥ 3 occurred in 29% and a final MELD score of < 10 was achieved in 25%.
- In long-term follow up mean changes in MELD (-0.30 points), total bilirubin (+0.23 mg/dl) and albumin (+0.36 g/dl) were marginal.
- Fifty-one patients died and 22 underwent liver transplant.
- Patients with advanced/decompensated cirrhosis need ongoing and close follow up as a majority remain at risk for hepatic decompensation over the long term

DAA therapy and long-term hepatic function in advanced/decompensated cirrhosis: Real-world experience from HCV-TARGET cohort

Short Title: HCV Therapy in Advanced/Decompensated Liver Disease

Elizabeth C. Verna, MD, MS; Assistant Professor of Medicine, Columbia University, New York, NY

Giuseppe Morelli, MD; Assistant Professor, Division of Gastroenterology, Hepatology, and Nutrition, University of Florida, Gainesville, FL

Norah A. Terrault, MD; Professor, School of Medicine, University of Southern California, Los Angeles, CA

Anna S. Lok, MD; Professor, Division of Gastroenterology and Hepatology, University of Michigan, Ann Arbor, MI

Joseph K. Lim, MD; Professor of Medicine, Viral Hepatitis Program, Yale University School of Medicine, New Haven, CT

Adrian M. Di Bisceglie, MD; Professor, Department of Internal Medicine, Chief of Hepatology, Division of Gastroenterology and Hepatology, Saint Louis University School of Medicine, Saint Louis, MO

Stefan Zeuzem, MD; Professor of Medicine and Chief of the Department of Medicine, Goethe University Hospital, Frankfurt, Germany

Charles S. Landis, MD, PhD; Associate Professor, Department of Gastroenterology, University of Washington, Seattle, WA

Paul Kwo, MD; Professor of Medicine and Director of Hepatology, Stanford University, Stanford, CA

Mohamed Hassan, MD; Professor of Medicine, Division of Gastroenterology Hepatology and Nutrition, University of Minnesota, Minneapolis, MN

Michael P. Manns, MD; Professor, Department of Gastroenterology, Hepatology and Endocrinology, Hannover Medical School, Hannover, Germany

Monika Vainorius, MD; Director, Biometrics and Data Quality HCV-TARGET Data Coordinating Center, University of North Carolina at Chapel Hill, Chapel Hill, NC

Lucy Akushevich, MS; Senior Biostatistician, University of North Carolina at Chapel Hill, Chapel Hill, NC

David R. Nelson, MD; Professor of Medicine, Department of Medicine, University of Florida, Gainesville, FL

Michael W. Fried M, MD; Professor, Division of Gastroenterology and Hepatology, University of North Carolina at Chapel Hill, Chapel Hill, NC

K. Rajender Reddy, MD; Professor, Division of Gastroenterology and Hepatology, University of Pennsylvania, Philadelphia, PA

Grant Support:

HCV-TARGET is an investigator-initiated study jointly sponsored by The University of Florida, Gainesville, FL (PI: Nelson), and The University of North Carolina at Chapel Hill, Chapel Hill, NC (PI: Fried) and is funded in part by AbbVie, Bristol Myers Squibb, Gilead, GlaxoSmithKline, Janssen, Kadmon, and Merck.

Abbreviations:

AE: Adverse Event; CTP: Child-Turcotte-Pugh; DAA: Direct-acting Antiviral; HCC: Hepatocellular Carcinoma; HCV: Hepatitis C Virus; LASSO: Least Absolute Shrinkage and Selection Operator; MELD: Model for End-Stage Liver Disease; PPI: Proton Pump Inhibitor; REDCap: Research Electronic Data Capture; SAE: Serious Adverse Event; SVR: Sustained Virologic Response

Corresponding author:

K. Rajender Reddy MD

Professor of Medicine

University of Pennsylvania

2 Dulles, 3400 Spruce Street, HUP

Philadelphia, PA 19104

Phone : 215-662-4311

Fax : 215-615-1601

E-mail : ReddyR@pennmedicine.upenn.edu

Keywords: Decompensated Liver Disease; HCV therapy; MELD score

Main Document: Word Count: 5992

Tables and figures: 8

Supplemental Figures: 4

Disclosures:

RR: AbbVie, Gilead, BMS, Intercept, Conatus, Exact Sciences, HCC-TARGET, HCV-TARGET, NASH-TARGET, Mallinckrodt, Grifols, Merck, Spark Therapeutics, Dova, Shionogi

EV: Gilead

GM: Nothing to disclose

NAT: Gilead, Intercept, EXIGO Management Consultants LLC

ASL: BMS, Gilead

JKL:BMS, Genfit, Gilead, Hologic, Intercept, Prometheus

AMD: Gilead, Abbvie

SZ: AbbVie, Gilead, Intercept, Janssen, Merck

CSL: AbbVie, Gilead

PK: AbbVie, BMS, Gilead, Merck, Ribavirin pregnancy registry, Target Registries, Eiger, Aligos, Johnson and Johnson, Dova, Shionogi, Edigene, Durect, Ferring, Surrozen, Mallinckrodt, Allergan, PPD development, Conatus, Eisai, Quest

MH: Nothing to disclose

MPM: BMS, Gilead, Merck (MSD), AbbVie

MV: Nothing to disclose

LA: Nothing to disclose

DRN: AbbVie, Gilead, Merck, Target Pharma Solutions

MWF: AbbVie, Altavant, BMS, Gilead, Merck, Roche, Target Pharma Solutions

Author Contributions:

Study concept and design: EV, RR

Acquisition of data: MV, LA

Analysis and interpretation of data: EV, RR, MV, LA

Drafting of manuscript: EV, RR

Critical revision of manuscript: GM, NAT, ASL, JKL, AMD, SZ, CSL, PK, MH, MPM, DRN, MWF, MV, LA

ClinicalTrials.gov: NCT01474811

Abstract:

Background and Aims: Direct-acting antiviral (DAA) HCV therapy is used in decompensated cirrhosis with the expectation of improvement in hepatic function. Little is known about the long-term benefit of successful treatment.

Methods: Patients with advanced/decompensated cirrhosis (MELD ≥10) in HCV-TARGET who initiated NS5A-containing DAA therapy prior to September, 2018, were included. Treatment outcomes and the impact of treatment on short-term and long-term hepatic function were examined.

Results: 642 patients were analyzed. The mean age was 60 years, 68% were male. The median baseline MELD was 12 (range 10-39) and 64% had prior decompensation. Among patients with available virologic outcomes, 90.5% achieved SVR12. Twenty-four % achieved a clinically significant decrease in MELD by ≥3 points during short term follow-up (9-26 weeks after the end of treatment). However, in long-term follow up (median of 4 years after treatment), mean changes in MELD (-0.30 points), total bilirubin (+0.23 mg/dl) and albumin (+0.36 g/dl) were marginal. Fifty-one patients died and 22 underwent liver transplant. In long term follow up, a clinically meaningful decrease in MELD of ≥3 occurred in 29% and a final MELD score of <10 was achieved in 25%.

Conclusion: In a large real-world experience of patients with advanced/decompensated HCV cirrhosis treated with DAA, there were only marginal improvements in MELD, total bilirubin, or albumin in long-term follow up (median of 4 years after treatment) after achieving SVR; a clinically meaningful decrease in MELD of ≥3 occurred in 29% and a final MELD score of <10 was achieved in 25%. These

patients may remain at high risk of decompensation and must continue to be closely followed.

Lay Summary:

Hepatitis C virus infection can now be cured with medications, even in patients who have advanced scaring of the liver (cirrhosis). In this study, we evaluated whether liver function improves or deteriorates in the long-term following successful treatment of hepatitis C. We found that overall liver function was relatively stable with only 29% achieving a clinically meaningful improvement in liver function, and we therefore believe that patients require ongoing monitoring of liver function and complication of liver disease despite being cured of the virus.

Introduction:

The high rates of sustained virologic response (SVR) in patients with HCV-compensated cirrhosis, in both clinical trials and real-world settings, has led to widespread recommendations for treatment in this setting[1] and concurrently there has been a decline in new listings for liver transplantation due to HCV-related liver disease.[2] However, some controversy exists in the treatment of patients with decompensated cirrhosis due to suboptimal SVR rates, and concerns regarding the impact of SVR on long-term outcomes among liver transplant candidates.[3,4]

While most studies have reported improvements in MELD score and/or CTP class in a significant proportion of patients[3], the impact on the long-term trajectory of liver function, including resolution of portal hypertension, and transplant-free survival remains uncertain. Predictors of short-term resolution in liver dysfunction may include normal body mass index, lack of encephalopathy or ascites at treatment initiation, and normal serum levels of alanine aminotransferase and albumin.[5] However, those with severe portal hypertension complications and MELD >20 may be less likely to achieve clinical improvement.[6-8] Concern remains that many patients with life-threatening complications of liver disease may be inadvertently disadvantaged in terms of transplant access by a moderate treatment-related decrease in MELD score and without resolution of cirrhosis complications.[3,6,7] Thus, we aimed to determine effectiveness of DAA therapy in a large real-world cohort of patients with advanced/decompensated cirrhosis. In particular, we evaluated the impact of SVR on hepatic function in long-term follow up, at a median of 4 years after completion of treatment.

Methods:

Patients and Study Design:

HCV-TARGET is an international consortium of academic (n=46) and community (n=16) medical centers in the U.S., Germany, Israel and Canada conducting a longitudinal, prospective observational cohort study of real-world administration of DAA therapy (NIH Clinical Trial NCT01474811). All patients were adults ≥18 years, who underwent HCV treatment administered according to local standard of care. Data from enrolled patients undergoing HCV therapy were captured from medical records within a common database utilizing centralized data abstraction.

Patients included in this analysis were those with advanced/decompensated cirrhosis who started HCV treatment between March, 2014 and September, 2018 with an all oral DAA regimen. Patients with prior liver transplantation were excluded.

The independent ethics committee at each participating study center or a central institutional review board approved the protocol. All patients provided written informed consent. All authors had complete access to the study data and reviewed and approved the final manuscript. Study data were collected and managed using REDCap electronic data capture tools[9] hosted at the University of North Carolina Chapel Hill. REDCap (Research Electronic Data Capture) is a secure, web-based application.

Advanced/Decompensated Cirrhosis Assessment

Cirrhosis was defined at the time of enrollment by biopsy (METAVIR stage 4 fibrosis) or FibroScan (liver stiffness of ≥12.5 kPa) and/or a combination of clinical, laboratory, histologic, and imaging criteria. Patients with METAVIR stage 3 fibrosis by

liver biopsy/Fibroscan were considered to have cirrhosis if they had any of the following: platelet count <140,000/mL; presence of esophageal varices on esophagogastroduodenoscopy; nodular liver, portal hypertension, or ascites by radiologic imaging; or non-invasive serum panels such as FibroSURE (Laboratory Corporation of America, Burlington, NC) consistent with stage 4 fibrosis. In the absence of cirrhosis being confirmed by liver biopsy and/or Fibroscan, cirrhosis was defined as meeting any two of the earlier described non-histologic criteria. Advanced/decompensated cirrhosis was defined as having both cirrhosis and a MELD score ≥10. While there is no MELD cutoff that is known to define decompensated liver disease, this cutoff was chosen as it is associated with at least 6% 3-month mortality and also is low enough to capture patients with complications of portal hypertension that are out of proportion to MELD score elevation[10,11].

History of hepatic decompensation was defined as evidence of prior or current diagnosis of ascites, hepatic encephalopathy, spontaneous bacterial peritonitis, variceal hemorrhage, or baseline concomitant medications with a specific indication for ascites, hepatic encephalopathy, spontaneous bacterial peritonitis, or variceal hemorrhage. Baseline Child-Turcotte-Pugh (CTP) score was estimated based on a validated algorithm[12], including laboratory values within 90 days of HCV treatment initiation. Clinical records were reviewed up to 6 months prior to HCV treatment initiation for evidence of ascites and encephalopathy, and quantified for severity according to the operational definitions of the algorithm of Kaplan et al. in order to calculate CTP score[12].

OUTCOMES:

Efficacy:

Treatment efficacy was measured as sustained virologic response (SVR 12), defined as HCV RNA level below the limit of quantitation or undetected at least 9 weeks after treatment was discontinued (n=577, Figure 1 Efficacy population). Those who were lost to follow up, died or had data missing at the time of this analysis were excluded.

Safety:

All patients who started therapy during the study period and completed or discontinued therapy due to lack of efficacy, adverse event (AE), or death were included in the safety population (n=642, Figure 1). Safety events are reported for up to 30 days following treatment completion. Death, liver transplantation, and development of HCC, were captured for all patients throughout the entire study period and were not restricted to 30 days post-treatment.

Adverse events (AEs) included any new, untoward events or exacerbated baseline conditions noted in the medical record. Abnormal lab values were captured as AEs if the abnormality was treated with a prescription therapy or required adjustment/discontinuation of HCV therapy. Serious adverse events (SAEs) were any AEs that required hospitalization or met criteria for expedited reporting per Food and Drug Administration form MEDWATCH 35000.

Hepatic decompensation during therapy was defined as experiencing one or more of the following: hepatic decompensation listed as an AE by a healthcare professional, new onset or exacerbation of hepatic encephalopathy, spontaneous bacterial peritonitis, variceal hemorrhage, ascites or hepatic hydrothorax, hepatorenal

syndrome, hepatopulmonary syndrome as well as liver failure or if the patient received a new prescription for a medication to treat one of the aforementioned indications.

Impact of Treatment on Hepatic Function:

Changes in measures of hepatic function from baseline to either the short-term or the long-term follow-up time-point were calculated for all patients in the efficacy population who had sufficient follow-up time as well as availability of the laboratory data needed for MELD score calculation. Short-term follow-up was defined as the last available value recorded between 9-26 weeks after the end of treatment. Long-term follow-up was defined as the last available value recorded at least 36 weeks after the end of treatment. Hepatic function measures examined include total bilirubin, albumin, as well as the calculated MELD score. If a patient underwent liver transplant, all measures recorded at or after transplant were dismissed.

Statistical Analysis:

To assess treatment efficacy, unadjusted SVR12 rates with exact binomial confidence intervals were calculated for the overall efficacy population as well as by baseline MELD category (10–15, 16-20 and ≥21). To assess treatment effectiveness, SVR rates were also calculated for a subpopulation, which included the efficacy population and patients with no virologic outcomes because of death at or within one year after the end of treatment, with the latter considered ‘failures’. Associations between SVR12 and each of the most well-established baseline characteristics were estimated with univariable logistic regression. In an attempt to better understand the

relationship among risk factors and odds of achieving SVR, we also performed multivariable analysis.

MELD score, total bilirubin and albumin were compared between baseline, the short-term follow-up time-point, and the long-term follow up time-point. Associations between short-term improvements in MELD of ≥3 points as well as achievement of final MELD <10, and baseline characteristics were also estimated. We selected at least a 3 MELD point improvement as clinically meaningful as it has been observed that intra-laboratory variability can have a significant impact on measured/calculated MELD, and most of this variability leads to a change in mean MELD of 3 points or less[13]. MELD analyses were performed excluding patients on dialysis at baseline to ensure that chronic kidney disease requiring dialysis did not have a significant impact on the trajectory of calculated MELD.

Time-to-event analysis was performed using the SAS PROC LIFETEST, for the events of death and liver transplant. Kaplan-Meier estimates of survivor functions were used for comparison of survival curves between groups of participants using a log-rank test. Analyses were performed using SAS software, version 9.4 (SAS Institute Inc., Cary, NC).

Results:

Patients:

A total of 667 patients with advanced/decompensated cirrhosis in HCV-TARGET were treated with DAA therapy in the study period. Patients who discontinued treatment early due to non-compliance (n=3), or administrative reasons (n=4), were lost to follow up/withdrew from study (n=15), underwent liver transplantation (n=2) or had records unavailable at the time of analysis (n=1) were not included in the cohort (Figure 1). The remaining 642 patients comprised the safety population. The overall median age was 60 years, 68% of patients were men and 68% Caucasian (Table 1). The majority of patients had HCV genotype 1 (70%), and 45% were treatment experienced.

The median MELD at the time of treatment initiation was 12 (range 10-39), with 521 (81%) with MELD 10-15, 78 (12%) MELD 16-20 and 43 (7%) MELD ≥ 21. Overall 309 patients (48.1%) had Child class B, 64% had experienced prior clinical decompensation events, and 4% of patients were on dialysis at treatment initiation.

The efficacy population (n=577) was restricted further by excluding patients who did not have a virologic outcome reported due to death (7 died during treatment and 26 died after treatment concluded but prior to evaluation of SVR, 21 of them within a year after treatment), and 32 who were lost to post-treatment follow-up.

Antiviral Treatment Regimen:

The most common DAA regimen was sofosbuvir/ledipasvir (56%), followed by sofosbuvir/velpatasvir (19%), sofosbuvir/daclatasvir (14%), elbasvir/grazoprevir (6%), glecaprevir/pibrentasvir (4%), and sofosbuvir/velpatasvir/voxilaprevir (2%). The most

common regimen in patients with MELD ≥ 21 was elbasvir/grazoprevir, all of whom had a baseline GFR < 30 ml/min. Ribavirin was used in 31% (197/642) of patients in the safety population with 32% (169/521) in the MELD 10-15 group, 31% (24/78) in the MELD 16-20 group, and 1% (4/43) in the MELD ≥ 21 group. Median (interquartile range) treatment duration for the entire cohort was 90 days (85-169), and 91.0 days (85-169) among patients who completed treatment.

Treatment Response:

Of the 577 patients in the efficacy population, 522 (90.5%) achieved SVR12 and rates by MELD categories were: 427/475 (89.9%, 95%CI: 86.8-92.5) in MELD 10-15, 62/68 (91.2%, 95%CI: 81.8-96.7) in MELD 16-20, and 33/34 (97.1%, 95%CI: 84.7-99.9) in MELD ≥21 (Figure 2).

However, the efficacy population (defined as those with available virologic SVR status) does not include patients with no virologic outcome due to death (7 on and 21 within 1 year after the DAA treatment; 16 of these patients had MELD 10-15, 4 with MELD 16-20 and 8 with MELD ≥21.) To assess treatment effectiveness, we assigned virologic outcomes for these patients as 'failures' and calculated SVR rates by adding these 28 patients to the efficacy population defined above. SVR12 rates including these cases were statistically similar throughout all MELD categories: 427/491 (87.0%, 95%CI: 83.7-89.8) in MELD 10-15, 62/72 (86.1%, 95%CI: 75.9-93.1) in MELD 16-20 and 33/42 (78.6%, 95%CI: 63.2-89.7) in MELD ≥21 (Supplemental Figure 1).

In univariable analysis, negative predictors of SVR included the presence of ascites (OR 0.33, 95%CI 0.17-0.59, p<0.001), hepatocellular carcinoma (HCC)(OR

0.33, 95%CI 0.17-0.69, p=0.002), albumin level <3.5 mg/dl (OR 0.31, 95%CI 0.14-0.61, p=0.001) and proton pump inhibitor (PPI) use (OR 0.47, 95% CI 0.26-0.83, P=0.010), while treatment experience, baseline MELD and ribavirin use did not show association with treatment response. Positive predictors of SVR were total bilirubin <=1.2.mg/dl (OR 1.94, 95% CI 1.05-3.80, P=0.042) and Child-Pugh A (OR 4.33, 95% CI 1.90-12.04, P=0.002)(not shown).

The multivariable model with LASSO-selected covariates for association with SVR included the presence of ascites (OR 0.58, 95% CI 0.26-1.21, p=0.157), albumin level <3.5 mg/dl (OR 0.41, 95%CI 0.14-1.04, p=0.070), history of HCC (OR 0.40, 95% CI 0.18-0.91, p=0.024), PPI use (OR 0.59, 95% CI 0.31-1.08, p-value =0.099), age<60 (OR 0.58, 95% CI 0.30-1.09, p=0.085), male sex (OR 0.49, 95% CI 0.23-0.98, p=0.049), MELD<16 (OR 0.36, 95% CI 0.11-0.93, p=0.053), and Child-Pugh A (OR 1.84, 95% CI 0.53-7.28, p=0.342)(Supplemental Figure 2).

Short-Term Changes in Hepatic Function:

During short-term follow-up, MELD score decreased in 187 (56%), did not change in 54 (16%) and increased in 92 (28%) patients (Figure 3A). A decline of at least 3 MELD points occurred in 80 (24%) patients and was more common among patients with a baseline MELD ≥16 (41%)(Figure 3A). Short-term MELD change among patients who achieved SVR and who failed DAA treatment were similar (Figure 3B).

In multivariable model with LASSO-selected covariates, male sex (OR 0.51, 95% CI 0.27-0.93, p=0.029), baseline ALT<60 u/l (OR 0.41, 95% CI 0.22-0.75, p=0.004), Child-Pugh score A (OR 0.48, 95% CI 0.21-0.99, p=0.058) and MELD<16 (OR 0.33, 95% CI

0.16-0.69, p=0.003) were negatively associated with MELD improvement of at least 3 points, and age<60 (OR 2.15, 95% CI 1.20-3.93, p=0.012) was predictive of this improvement (Figure 4).

Long-Term Changes in Hepatic Function:

A total of 218 patients in the efficacy population who achieved SVR who were not on dialysis at baseline were evaluable for long-term outcomes. Of these, 158 had MELD scores available at least 36 weeks after the end of treatment. The median (interquartile range) follow-up after the end of treatment was 213 (174-224) weeks. Baseline demographics were similar between patients with and without long-term follow-up, including age (mean 58.5 vs. 59.8, p=0.168), HCC (8.2% vs 11.9%, p=0.290), baseline MELD (mean 13.2 vs. 12.9, p=0.417), and baseline albumin (mean 3.2 vs. 3.3, p=0.257) (Table 2). However, patients with long-term follow up were more likely to have ascites at baseline (55.7% vs. 44.1%, p=0.044) and prior hepatic decompensation events (71.5 % vs. 60.8 %, p=0.050).

The overall mean decrease in MELD score from the start of treatment until the end of long-term follow up was 0.30 (95% CI -1.10, 0.50) points. Patients with a baseline MELD ≥16 had a mean of 1.90 (95% CI -3.66, -0.15) points improvement in MELD, while those with a baseline MELD <16 had a mean increase of 0.09 (95% CI -0.80, 0.99)(Figure 5). A decline of at least 3 MELD points in long-term follow up occurred in 45 (29%) patients and was more common among those with a baseline MELD ≥16 (45 %). During long term follow up, 40 (25%) patients achieved a reduction

in MELD score to <10, 38 of them with a baseline MELD 10-15 and 2 with a baseline MELD 16-20.

In univariable analysis, baseline MELD <16 (OR 5.08, 95% CI 1.57-25.81, p=0.020) and baseline INR <1.5 (OR 2.67, 95% CI 1.00-8.82 p=0.074) were predictive of achieving a final MELD score of <10 in long term follow up. The presence of ascites (OR 0.49, 95% CI 0.24-1.01, p=0,057) and ALT<60 u/l (OR 0.40, 95% CI 0.19-0.83, p=0.016) were negatively associated with this improvement, while age, gender, history of HCC and other baseline laboratory values did not show associations. We further evaluated CPT score and impact on long-term MELD outcome of <10 and noted that Child-Pugh A did not show an association with long-term MELD<10 (OR 1.55, 95% CI 0.64-3.59; p-value =0.324) while Child-Pugh C was negatively associated with long-term MELD<10 (OR 0.15, 95% CI 0.02-0.60; p-value =0.029). In multivariable analysis, LASSO regression identified baseline ALT<60 u/l (OR 0.39, 95% CI 0.17-0.86, p=0.022) and Child-Pugh C (OR 0.25, 95% CI 0.03-1.14, p=0.127) as negative predictors and MELD <16 (OR 2.75, 95% 0.76-14.7, p=0.165) as positive predictor for this improvement.

In long-term follow up, there was an overall increase in mean total bilirubin of 0.23 (95% CI -0.44, 0.89) mg/dl (Supplemental Figure 3). Patients with a baseline MELD of ≥16 had a mean decrease of 0.67 (95% CI -1.31, -0.03) mg/dl in total bilirubin, while those with a baseline MELD <16 experienced a mean increase in total bilirubin of 0.41 (95% CI -0.38, 1.20) mg/dl. In long-term follow-up there was also an increase in mean albumin of 0.36 (95% CI 0.28, 0.45) g/dl (Supplemental Figure 4). Patients with a baseline MELD of ≥16 had a mean improvement of 0.36 (0.14, 0.58) g/dl in albumin,

and those with a baseline MELD <16 experienced a mean improvement of 0.36 (0.27, 0.46) g/dl.

Safety:

Overall, 468 (73%) patients of the safety population experienced an AE, leading to treatment discontinuation in 3.6%. SAEs occurred in 20% of the entire safety population, including 17% in MELD 10-15, 39% in MELD 16-20 and 28% in MELD ≥21 patients (Table 3).

The most common liver-related SAEs of interest were the development of hepatic encephalopathy (4.4%), ascites (0.9%), and bacterial peritonitis (0.8%). Overall, 83 patients (12.9%) had new decompensating events either on treatment or up to 30 days after the end of treatment and 41 patients (6.4%) had decompensating events that were classified as SAEs. Of the 83 patients, only 7 patients (8%) had not had any history of decompensating events reported prior to DAA regimen. 94 (69%) of the 137 AEs experienced by 61 (73%) of these 83 patients were exacerbations of previously recorded condition. 15 remaining patients (18%) with prior history of decompensating events had developed a different decompensating event than what was recorded prior to start of DAA treatment.

There was a total of 16 patients with baseline MELD ≥21 treated with elbasvir/grazoprevir. All of these patients had eGFR of <30 mg/dl and 15 of them were on dialysis at baseline. There were no decompensating events characterized as SAEs recorded in this subpopulation.

Survival:

Seven patients died on treatment (coronary artery disease, hepatic encephalopathy, hepatic failure, multi-organ failure, septic shock, and unknown cause in two patients), four of whom had a baseline MELD 10-15, one MELD 16-20 and two MELD ≥ 21. In addition, at least 44 patients died after the end of DAA treatment. Death was attributable to advanced liver disease in 12 patients, while the cause of death in the others was liver unrelated or unknown. Median duration (range) of time for survival follow-up was 15.5 (0–50.8) months. Baseline MELD <16 was predictive of overall survival (log rank, p<0.0001). One-, two-, and three- year survival rates in participants with baseline MELD 10-15 and baseline MELD ≥16 were 96.0%-93.6%-89.7% and 85.9%-82.4%-71.7%, respectively.

Five patients underwent liver transplantation while on treatment. Three achieved SVR, one failed treatment, and virologic data was unavailable in one patient. In addition, 17 patients underwent liver transplant after the end of treatment. Median (range) follow up time for liver transplant events was 14.1 (0–50.8) months. The proportion of patients with baseline MELD 10-15, and baseline MELD ≥16, who underwent liver transplant 1-, 2-, and 3 years after treatment initiation was 2.6%- 5.4%- 9.0% and 1.2%- 2.9%-2.9%, respectively. Median duration (range) of time for HCC diagnosis follow-up was 14.1 (0–50.8) months. Total of 13 patients with baseline MELD 10-15 and 3 patients with baseline MELD > 16 developed HCC.

Discussion:

Chronic Hepatitis C therapy in those with advanced stage of liver disease may achieve improvement in hepatic function, as measured by MELD or CTP scores, although who will achieve this improvement and whether long-term transplant-free survival is a realistic goal of treatment remain uncertain[5,6,14-19]. This is a large real-life cohort of patients with HCV treatment in advanced/decompensated liver disease with the longest post-treatment follow up available to date.

The overall SVR12 rate in the efficacy population (90.5%) is similar to those reported in clinical trials and previous real-world experiences.[3,4] Remarkably, 97% of the 34 patients with MELD over 21 who had available virologic outcome achieved viral eradication, though this SVR rate decreased to 78.6%, when patient deaths on or after treatment but prior to SVR 12 timepoint were classified as failures. Elbasvir/grazoprevir, which is contraindicated in patients with advanced liver disease, was more commonly used in patients with MELD score of ≥21 because most patients in this high MELD group had advanced kidney disease. Despite high SVR rates, changes in MELD score and hepatic function tests in short- and long-term follow-up in this cohort were marginal. While 56% of patients experienced some improvement in MELD at the time of SVR12, the overall mean short-term change in MELD was less than a point and a clinically meaningful improvement of ≥3 MELD points occurred in only 24% of patients. Predictors of this improvement included female sex, age<60, high baseline ALT (≥60 IU/ml), and baseline MELD ≥16. Our data are in line with clinical trials with a variety of regimens where median MELD improvement, over the short term, was by 2 points in

60% of patients; and MELD score remained unchanged or worsened by a median MELD of 1 in the remaining 40%.[3]

Unique to this cohort is the long-term follow-up - median >4 years post-treatment. Patients with long-term follow up were not dissimilar from those without, except that ascites and prior decompensating events were more common among patients included in the long-term follow up, thus indicating that those in follow up were as sick if not sicker than those lost to follow up. At a median of 213 weeks of follow-up, there were only minimal overall mean changes in MELD score (decrease 0.30 points), total bilirubin (increase by 0.23 mg/dl) and albumin (increased by 0.36 g/dl). In addition, only 29% of patients experienced a clinically meaningful improvement in MELD by 3 or more points and 25% achieved a MELD score of <10; a threshold we used as a surrogate for reasonably good synthetic function and functional status.

Previous reports had noted improvements in hepatic function, to the degree of de-listing patients on a liver transplant list. Improvements in CPT scores have been noted and predictors of improvement have been described.[5-8] A prior study has evaluated changes in MELD in CPT B and C patients and noted that at 36 months after HCV treatment, a substantial number of patients with MELD ≥15 still remained in that category.[20] A few reports have suggested that some patients achieving SVR after DAA had an improvement in portal hypertension below the clinically significant portal hypertension threshold of 10 mm of Hg while MELD score may not reflect such benefit[21,22]. Unfortunately given the lack of widespread use and availability of hepatic venous pressure measurements in real life scenario, we were limited in generating such data.

While there has been a decrease in listings for liver transplantation with HCV as an etiology in national database, it is unclear if this is because of preventing progression of liver disease and development of HCC in those with compensated cirrhosis or if it is due to improvements in hepatic function in those with decompensated cirrhosis.[2,23] Further, listing or de-listing criteria are arbitrary, and center specific and thus difficult to compare across studies and across liver centers. Our data would suggest that there is improvement in hepatic function in some patients but not necessarily to the degree where the risk of death and functional incapacity are mitigated if MELD changes were to be used as a surrogate for these events.

There are limitations to this study inherent to the real-world study design. In particular, the lack of data available to determine change in CTP class over time limits our ability to understand the impact of treatment on non-MELD based indications for liver transplant. We do not have quality of life and liver specific symptom data, particularly pertaining to ascites and hepatic encephalopathy resolution to verify ongoing symptoms of portal hypertension. It is possible that there are patients with elevated MELD scores due to factors other than decompensated liver disease, such as advanced chronic kidney disease. To mitigate this potential misclassification, patients on dialysis were excluded from MELD trajectory analysis.

In summary, in this real-world cohort of HCV treatment among patients with advanced/decompensated cirrhosis, while SVR rates were high, the improvement in MELD score, bilirubin or albumin after a median follow-up of 4 years were minimal. Thus, while an optimistic position would be that there was no worsening in the severity of liver disease in the majority of patients and few required liver transplant during follow-

up, a state of MELD “purgatory” may evolve in some patients and most patients require ongoing close monitoring.

References:

1. AASLD/IDSA/IAS-USA. HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C. http://hcvguidelines.org.
2. **Goldberg D, Ditah IC,** Saeian K, Lalehzari M, Aronsohn A, Gorospe EC, et al. Changes in the Prevalence of Hepatitis C Virus Infection, Nonalcoholic Steatohepatitis, and Alcoholic Liver Disease Among Patients With Cirrhosis or Liver Failure on the Waitlist for Liver Transplantation. *Gastroenterology.* 2017;152(5):1090-1099 e1091. doi: 10.1053/j.gastro.2017.01.003
3. Bunchorntavakul C, Reddy KR. Treat chronic hepatitis C virus infection in decompensated cirrhosis - pre- or post-liver transplantation? the ironic conundrum in the era of effective and well-tolerated therapy. *J Viral Hepat.* 2016;23(6):408-418. doi: 10.1111/jvh.12534
4. Verna EC. The Dynamic Landscape of Liver Transplant in the Era of Effective HCV Therapy. *Hepatology.* 2017;65(3):763-766. doi: 10.1002/hep.29054
5. **El-Sherif O, Jiang ZG,** Tapper EB, Huang KC, Zhong A, Osinusi A, et al. Baseline Factors Associated With Improvements in Decompensated Cirrhosis After Direct-Acting Antiviral Therapy for Hepatitis C Virus Infection. *Gastroenterology.* 2018;154(8):2111-2121 e2118. doi: 10.1053/j.gastro.2018.03.022
6. Belli LS, Berenguer M, Cortesi PA, Strazzabosco M, Rockenschaub SR, Martini S, et al. Delisting of liver transplant candidates with chronic hepatitis C after viral eradication: A European study. *Journal of hepatology.* 2016;65(3):524-531. doi: 10.1016/j.jhep.2016.05.010
7. Fernandez Carrillo C, Lens S, Llop E, Pascasio JM, Crespo J, Arenas J, et al. Treatment of hepatitis C virus infection in patients with cirrhosis and predictive value of model for end-stage liver disease: Analysis of data from the Hepa-C registry. *Hepatology.* 2017;65(6):1810-1822. doi: 10.1002/hep.29097
8. Terrault NA, McCaughan GW, Curry MP, Gane E, Fagiuoli S, Fung JYY, et al. International Liver Transplantation Society Consensus Statement on Hepatitis C Management in Liver Transplant Candidates. *Transplantation.* 2017;101(5):945-955. doi: 10.1097/TP.0000000000001708
9. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform.* 2009;42(2):377-381. doi: 10.1016/j.jbi.2008.08.010
10. Wiesner R, Edwards E, Freeman R, Harper A, Kim R, Kamath P, et al. Model for end-stage liver disease (MELD) and allocation of donor livers. *Gastroenterology.* 2003;124(1):91-96. doi: 10.1053/gast.2003.50016
11. Reddy KR, Lim JK, Kuo A, Di Bisceglie AM, Galati JS, Morelli G, et al. All-oral direct-acting antiviral therapy in HCV-advanced liver disease is effective in real-world practice: observations through HCV-TARGET database. *Alimentary pharmacology & therapeutics.* 2017;45(1):115-126. doi: 10.1111/apt.13823
12. Kaplan DE, Dai F, Aytaman A, Baytarian M, Fox R, Hunt K, et al. Development and Performance of an Algorithm to Estimate the Child-Turcotte-Pugh Score From a National

Electronic Healthcare Database. *Clin Gastroenterol H.* 2015;13(13):2333-+. doi: 10.1016/j.cgh.2015.07.010
13. Verna EC, Connelly C, Dove LM, Adem P, Babic N, Corsetti J, et al. Center-Related Bias in MELD Scores Within a Liver Transplant UNOS Region: A Call for Standardization. *Transplantation.* 2019. doi: 10.1097/tp.0000000000003031
14. Afdhal N, Everson GT, Calleja JL, McCaughan GW, Bosch J, Brainard DM, et al. Effect of viral suppression on hepatic venous pressure gradient in hepatitis C with cirrhosis and portal hypertension. *J Viral Hepat.* 2017;24(10):823-831. doi: 10.1111/jvh.12706
15. Crespo G, Trota N, Londono MC, Mauro E, Baliellas C, Castells L, et al. The efficacy of direct anti-HCV drugs improves early post-liver transplant survival and induces significant changes in waiting list composition. *Journal of hepatology.* 2018;69(1):11-17. doi: 10.1016/j.jhep.2018.02.012
16. Di Marco V, Calvaruso V, Ferraro D, Bavetta MG, Cabibbo G, Conte E, et al. Effects of Eradicating Hepatitis C Virus Infection in Patients With Cirrhosis Differ With Stage of Portal Hypertension. *Gastroenterology.* 2016;151(1):130-139 e132. doi: 10.1053/j.gastro.2016.03.036
17. **Saez-Gonzalez E, Vinaixa C,** San Juan F, Hontangas V, Benlloch S, Aguilera V, et al. Impact of hepatitis C virus (HCV) antiviral treatment on the need for liver transplantation (LT). *Liver Int.* 2018;38(6):1022-1027. doi: 10.1111/liv.13618
18. Simmons B, Saleem J, Heath K, Cooke GS, Hill A. Long-Term Treatment Outcomes of Patients Infected With Hepatitis C Virus: A Systematic Review and Meta-analysis of the Survival Benefit of Achieving a Sustained Virological Response. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.* 2015;61(5):730-740. doi: 10.1093/cid/civ396
19. Vinaixa C, Strasser SI, Berenguer M. Disease Reversibility in Patients With Post-Hepatitis C Cirrhosis: Is the Point of No Return the Same Before and After Liver Transplantation? A Review. *Transplantation.* 2017;101(5):916-923. doi: 10.1097/TP.0000000000001633
20. Mangia A, Lawitz E, Gane E, Conway B, Ruane P, Abergel A, et al. Long-term Follow-up of Patients With Chronic HCV Infection and Compensated
or Decompensated Cirrhosis Following Treatment With Sofosbuvir-Based Regimens. *Journal of hepatology.* 2018;68:S67. doi:
21. **Mandorfer M, Kozbial K,** Schwabl P, Freissmuth C, Schwarzer R, Stern R, et al. Sustained virologic response to interferon-free therapies ameliorates HCV-induced portal hypertension. *Journal of hepatology.* 2016;65(4):692-699. doi:
22. Lens S, Alvarado-Tapias E, Mariño Z, Londoño M-C, LLop E, Martinez J, et al. Effects of all-oral anti-viral therapy on HVPG and systemic hemodynamics in patients with hepatitis C virus-associated cirrhosis. *Gastroenterology.* 2017;153(5):1273-1283. e1271. doi:
23. Flemming JA, Kim WR, Brosgart CL, Terrault NA. Reduction in Liver Transplant Wait-Listing in the Era of Direct-Acting Antiviral Therapy. *Hepatology.* 2017;65(3):804-812. doi: 10.1002/hep.28923

Tables:

Table 1: Baseline characteristics of the Safety population patients by MELD score

	MELD 10-15 (n=521)	MELD 16-20 (n=78)	MELD ≥21 (n=43)	Total (n=642)
Male (%)	352 (67.6%)	52 (66.7%)	30 (69.8%)	434 (67.6%)
Age (years), median (range)	60 (25-89)	60 (37-83)	60 (31-80)	60 (25-89)
Race (%)				
White	357 (68.5%)	53 (67.9%)	27 (62.8%)	437 (68.1%)
Black	79 (15.2%)	14 (17.9%)	13 (30.2%)	106 (16.5%)
Other	85 (16.3%)	11 (14.1%)	3 (7.0%)	99 (15.4%)
Hispanic Ethnicity (%)	67 (12.9%)	10 (12.8%)	5 (11.6%)	82 (12.8%)
Treatment Experienced (%)	250 (48.0%)	23 (29.5%)	15 (34.9%)	288 (44.9%)
Prior 2nd Gen DAA	114 (21.9%)	11 (14.1%)	5 (11.6%)	130 (20.2%)
HCV Genotype				
1	359 (68.9%)	60 (76.9%)	32 (74.4%)	451 (70.2%)
1a	255 (49.1%)	44 (56.4%)	23 (53.5%)	322 (50.3%)
1b	82 (15.8%)	14 (17.9%)	9 (20.9%)	105 (16.4%)
2	40 (7.7%)	5 (6.4%)	4 (9.3%)	49 (7.6%)
3	101 (19.4%)	11 (14.1%)	6 (14.0%)	118 (18.4%)
4	15 (2.9%)	2 (2.6%)	0 (0.0%)	17 (2.6%)
other/not reported	6 (1.2 %)	0 (0.0%)	1 (2.3 %)	7 (1.2 %)
HCV RNA, median (range), (IU/mL, log10)	5.8 (2-8)	5.9 (2-7)	5.6 (0-7)	5.8 (0-8)
HCC (%)	57 (10.9%)	9 (11.5%)	4 (9.3%)	70 (11.9%)
PPI use	238 (45.7%)	41 (52.6%)	30 (69.8%)	309 (48.1%)
Prior Clinical Decompensation (%)	325 (62.4%)	59 (75.6%)	28 (65.1%)	412 (64.2%)
Lab values, median (range)				
Albumin (n/dl)	3.2 (1.8-4.7)	2.9 (2.0-4.6)	3.6 (1.9-4.9)	3.2 (1.8-4.9)
Total bilirubin (mg/dl)	1.6 (0.0-9.3)	2.8 (0.2-11.3)	0.7 (0.3-16.1)	1.6 (0.0-16.1)
ALT	55.5 (9-398)	52.5 (9-166)	32.5 (9-163)	53 (9-398)
AST	79.5 (10-639)	77.5 (20-393)	41.5 (15-356)	76.5 (10-639)
Platelet count ($x10^3$/ul)	82 (15-647)	75 (28-545)	118 (23-258)	83 (15-647)
INR	1.3 (0.9-2.0)	1.5 (0.9-3.1)	1.2 (0.9-4.5)	1.3 (0.9-4.5)
Creatinine (mg/dl)	0.8 (0.4-2.4)	1.1 (0.4-10.3)	4.9 (0.6-12.8)	0.9 (0.4-12.8)
MELD	12 (10-15)	17 (16-20)	23 (21-39)	12 (10-39)
On dialysis (%)	0 (0.0%)	4 (5.1%)	22 (51.2%)	26 (4.0%)
Treatment Regimen (%)				
LDV/SOF	299 (57.4)	49 (62.8)	11 (25.6)	359 (55.9)
DAC/SOF	75 (14.4)	9 (11.5)	4 (9.3)	88 (13.7)
VEL/SOF	107 (20.5)	11 (14.1)	6 (14.0)	124 (19.3)
EBR/GRZ	14 (2.7)	6 (7.7)	16 (37.2)	36 (5.6)

G/P VSV	15 (2.9) 11 (2.1)	2 (2.6) 1 (1.3)	6 (14.0) 0 (0.0)	23 (3.6) 12 (1.9)
Ribavirin used (%)	169 (26.3)	24 (3.7)	4 (0.6)	197 (30.7)
Child-Pugh score				
A	145 (27.8)	10 (12.8)	23 (53.5)	178 (27.7)
B	276 (53.1)	26 (33.3)	7 (16.3)	309 (48.1)
C	39 (7.5)	35 (44.9)	10 (23.3)	84 (13.1)
Not available	61 (11.7)	7 (9.0)	3 (7.0)	71 (11.1)

Table 2. Comparison of patients with available long-term MELD change vs. patients with no available long-term MELD change (efficacy population who achieved SVR, were not on dialysis at baseline and with available short-time (9-23 weeks after treatment) change in MELD). P-values represent Chi-square or two sample t-test.

	With long-term MELD (n=158)	Without long-term MELD (n=143)	p-value
Male (%)	97 (61.4%)	100 (69.9%)	0.120
Age (years), mean (range)	58.5 (31-83)	59.8 (37-86)	0.168
Race (%)			
White	107 (71.3%)	98 (69.5%)	0.732
Non-white	43 (28.7%)	43 (30.5%)	
Hispanic Ethnicity (%)			0.019
Hispanic	29 (18.6%)	13 (9.2%)	
Non-Hispanic	127 (81.4%)	129 (90.8%)	
HCV Genotype			
1	123 (78.3%)	93 (65.5%)	0.013
2-6	34 (21.7%)	49 (34.5%)	
HCC (%)	13 (8.2%)	17 (11.9%)	0.290
Ascites (%)	88 (55.7%)	63 (44.1%)	0.044
Child-Pugh assessment			
A	32 (22.7%)	40 (31.2%)	0.103
B	84 (59.6%)	75 (58.6%)	
C	25 (17.7%)	13 (10.2%)	
PPI use	76 (48.1%)	60 (42.0%)	0.285
Prior Clinical Decompensation (%)	113 (71.5%)	87 (60.8%)	0.050
Lab values, mean (range)			
Albumin (n/dl)	3.2 (2.0-4.5)	3.3 (2.0-4.9)	0.257
Total bilirubin (mg/dl)	1.9 (0.0-10.3)	1.7 (0.2-8.7)	0.065
ALT	64.4 (9-283)	69.4 (9-326)	0.321
AST	91.4.0 (20-316)	95.3 (10-639)	0.596
Platelet count ($x10^3$/ul)	87.8 (26-237)	99.8 (20-329)	0.037
INR	1.35 (0.9-3.0)	1.34 (0.9-4.5)	0.799
Creatinine (mg/dl)	1.09 (0.4-7.6)	1.12 (0.5-6.7)	0.756
MELD	13.2 (10-28)	12.9 (10-27)	0.417

Table 3: Adverse events and Serious Adverse events by MELD score (Safety population patients)

	MELD 10-15 (n=521)	MELD 16-20 (n=78)	MELD≥21 (n=43)	Total (n=642)
Total number with AE*, n (%)	369 (70.8)	72 (92.3)	27 (62.8)	468 (72.9)
Total number with SAE*, n (%)	86 (16.5)	30 (38.5)	12 (27.9)	128 (19.9)
Hepatic decompensation, n (%)	61(11.7)	17 (21.8)	5 (11.6)	83 (12.9)
SAEs, n (%)	31 (6.0)	8 (10.3)	2 (4.7)	41(6.4)
SAEs of interest, n (%)				
Ascites	5 (1.0)	0 (0.0)	1 (2.3)	6 (0.9)
Esophageal variceal hemorrhage	2 (0.4)	0 (0.0)	0 (0.0)	2 (0.3)
Acute Hepatic failure	0 (0.0)	1 (1.3)	0 (0.0)	1 (0.2)
Hepatorenal syndrome	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Bacterial peritonitis	5 (1.0)	0 (0.0)	0 (0.0)	5 (0.8)
Hepatic encephalopathy	18 (3.5)	8 (10.3)	2 (4.7)	28 (4.4)
Hepatic hydrothorax	2 (0.4)	0 (0.0)	0 (0.0)	2 (0.3)
Death, n (%) During treatment	4 (0.8)	1 (1.3)	2 (4.7)	7 (1.1)
Liver Transplantation, n (%) During treatment	4 (0.9)	1(1.5)	0 (0.0)	5 (1.0)

Figure Legends:

Figure 1: Cohort Description

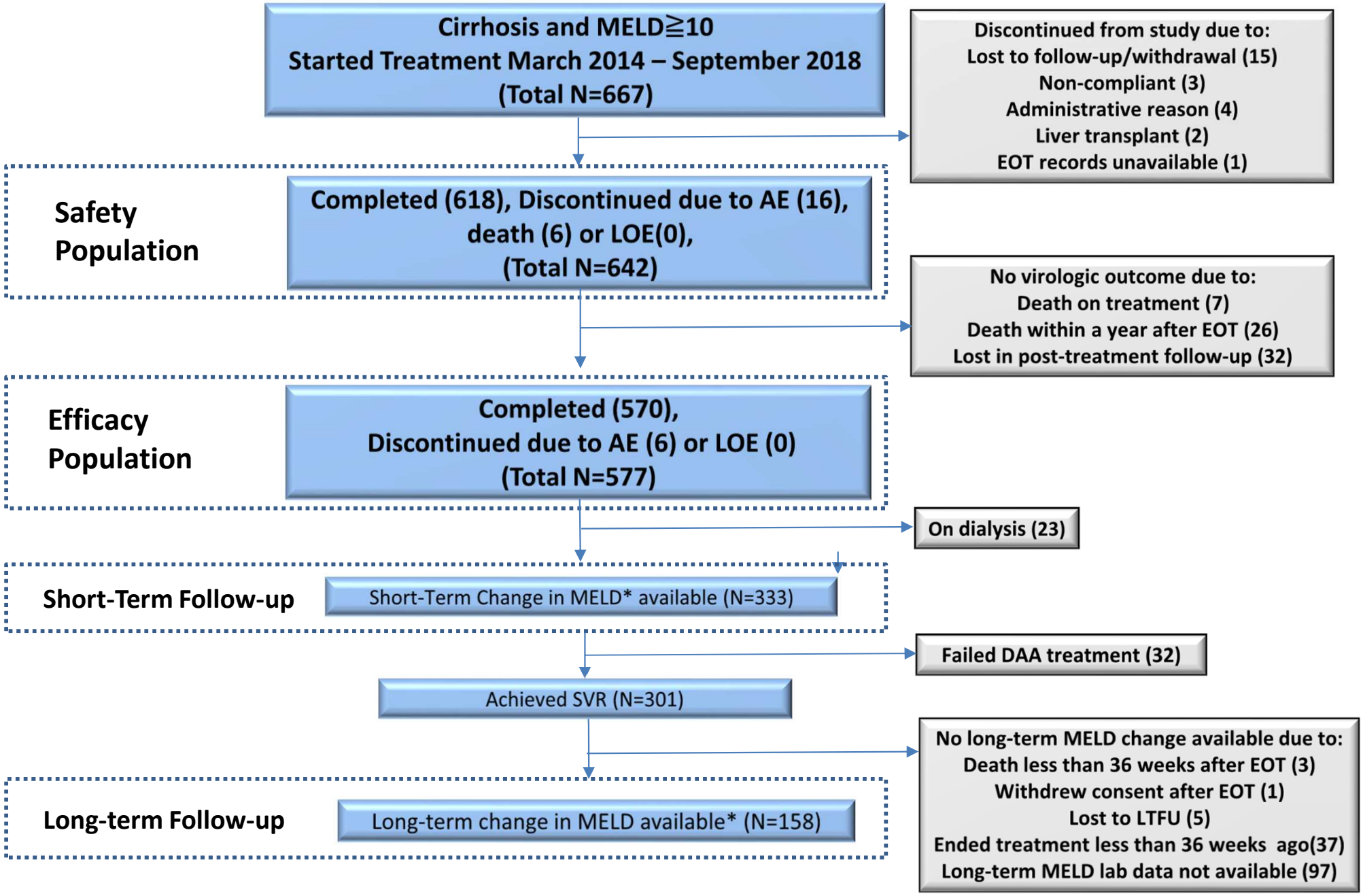
Figure 2: SVR12 by MELD Category and Ribavirin Use (Efficacy population patients)

Figure 3: Short-Term Change in MELD Score from Baseline to 9-26 Weeks Post-End of treatment. (Efficacy population patients who were not on dialysis at baseline) A. Pre-treatment to post-treatment value change among individual patients. B. Change from pre-treatment to post-treatment value by treatment outcome.

Figure 4: Multivariable Analysis to Predict improvement in MELD (decrease by ≥ 3 points) from Baseline to 9-26 Weeks Post-End of treatment. LASSO (least absolute shrinkage and selection operator) regression was used to select variables that contributed to the outcome.

Figure 5: Long-Term Change in MELD score from Baseline to the End of Long-Term Follow-Up. At a median of 213 weeks post-treatment, the mean change in MELD was -0.30 points

Figure 1



** Similar analyses were performed on TBIL and ALB.*

Figure 2

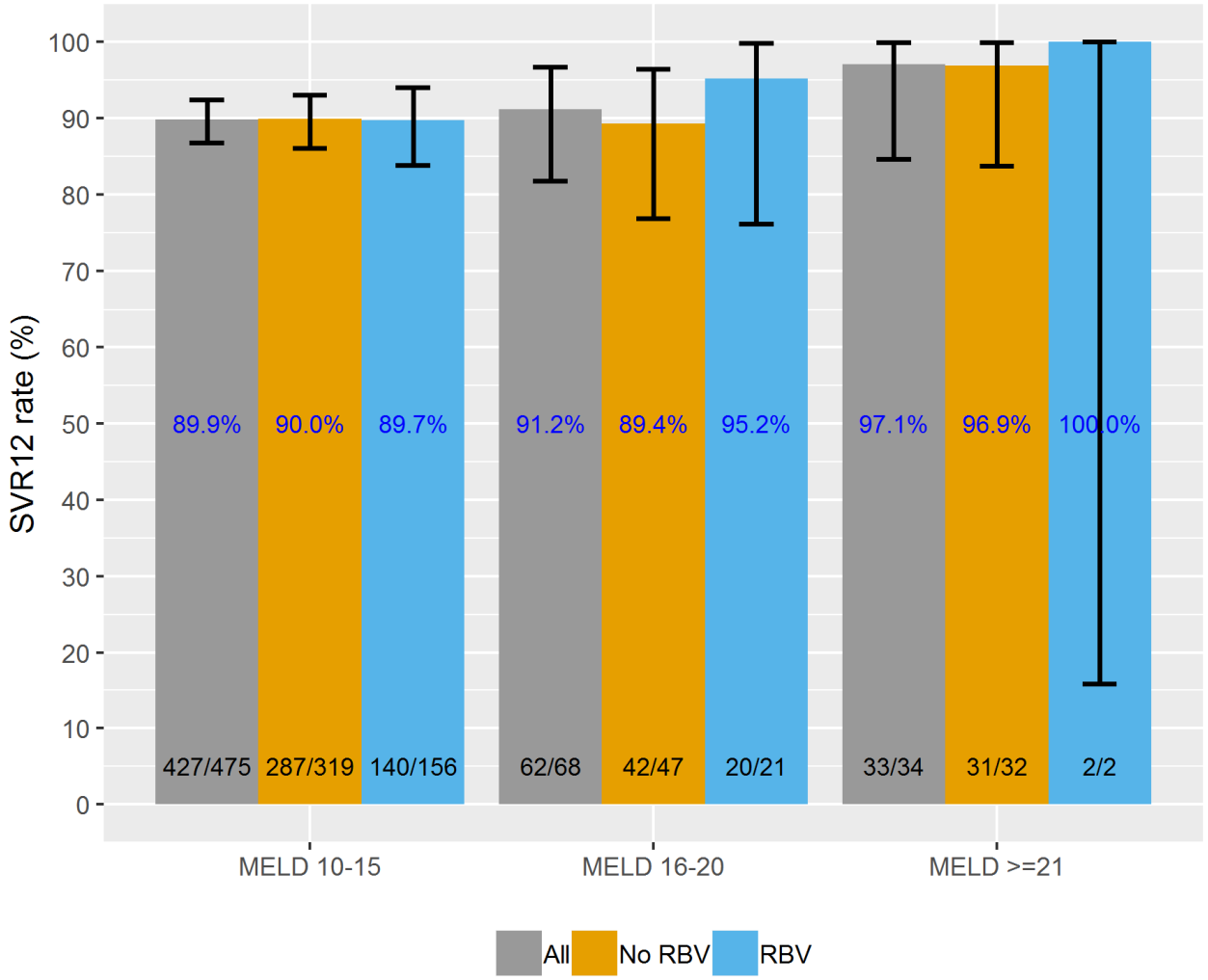
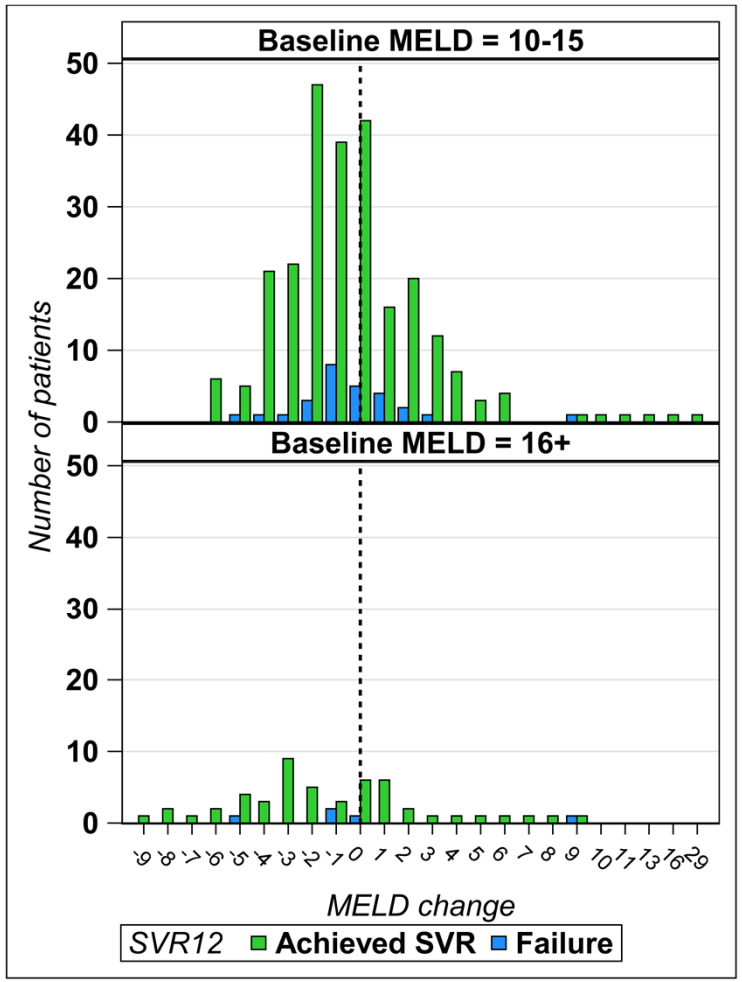

SVR12 rate (%)
100
90
80
70
60
50
40
30
20
10
0
89.9%
90.0%
89.7%
91.2%
89.4%
95.2%
97.1%
96.9%
100.0%
427/475
287/319
140/156
62/68
42/47
20/21
33/34
31/32
2/2
MELD 10-15
MELD 16-20
MELD >=21
All
No RBV
RBV

Figure 3

A


Baseline MELD = 10-15
Baseline MELD = 16+
Number of patients
MELD change
SVR12
Achieved SVR
Failure

B

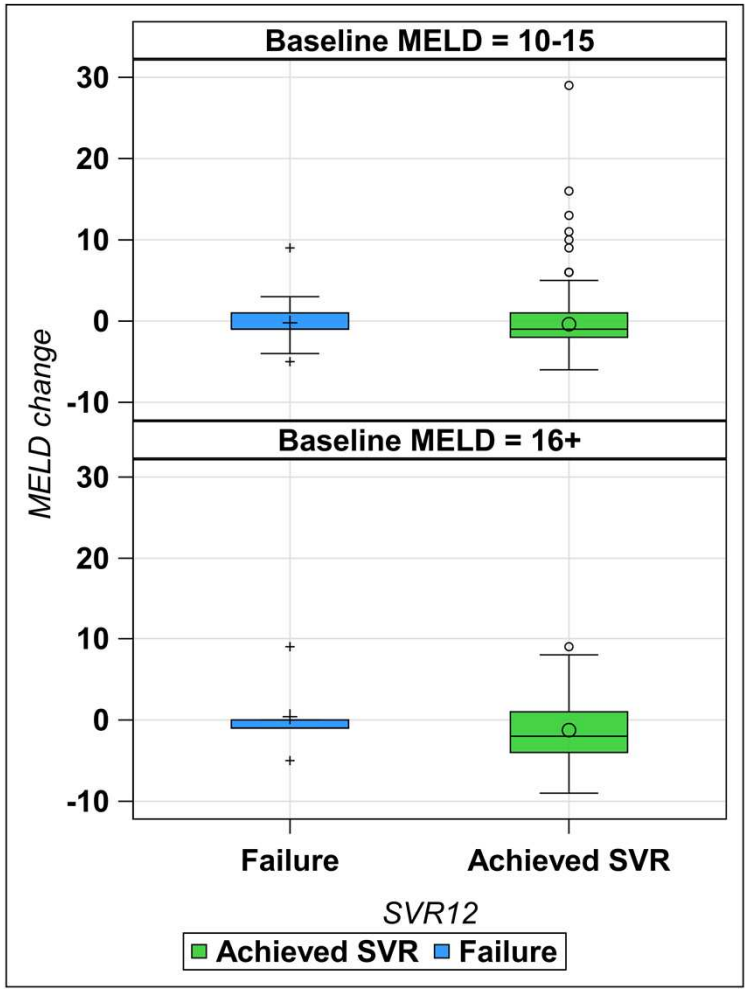

Baseline MELD = 10-15
Baseline MELD = 16+
MELD change
Failure
Achieved SVR
SVR12
Achieved SVR
Failure

Figure 4

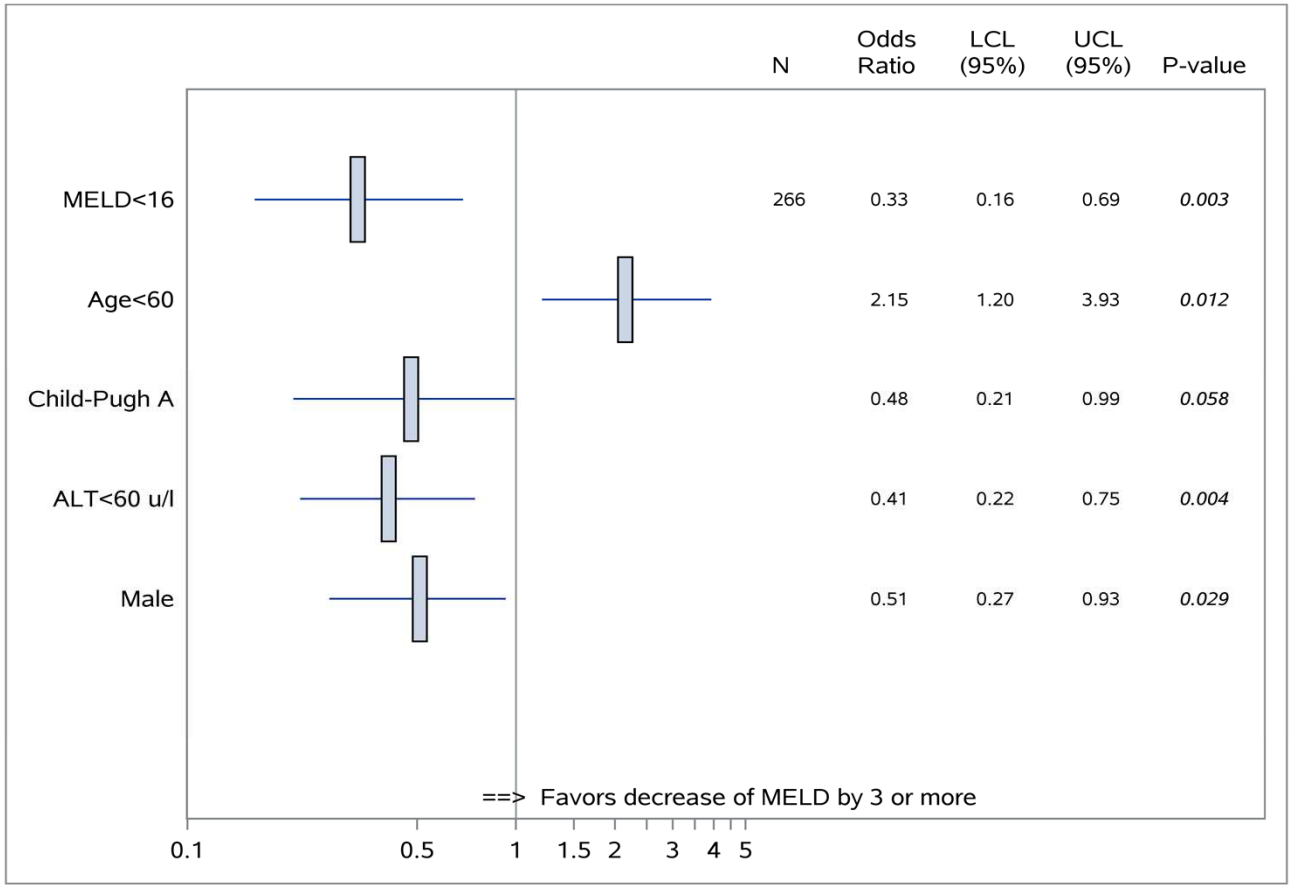
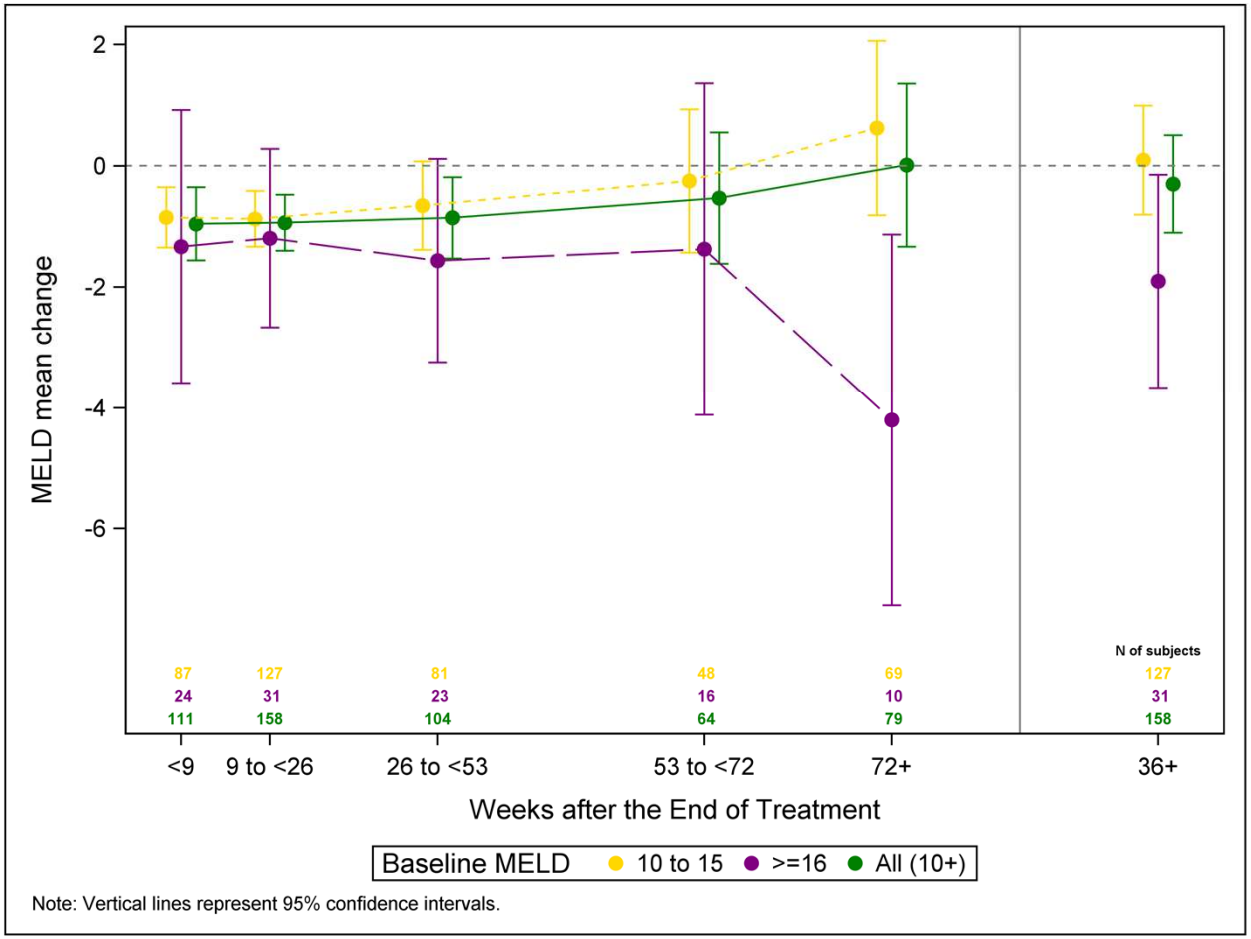

N
Odds Ratio
LCL (95%)
UCL (95%)
P-value
MELD<16
266
0.33
0.16
0.69
0.003
Age<60
2.15
1.20
3.93
0.012
Child-Pugh A
0.48
0.21
0.99
0.058
ALT<60 u/l
0.41
0.22
0.75
0.004
Male
0.51
0.27
0.93
0.029
==> Favors decrease of MELD by 3 or more
0.1
0.5
1
1.5
2
3
4
5

Figure 5


MELD mean change
2
0
-2
-4
-6
N of subjects
87
24
111
127
31
158
81
23
104
48
16
64
69
10
79
127
31
158
<9
9 to <26
26 to <53
53 to <72
72+
36+
Weeks after the End of Treatment
Baseline MELD
10 to 15
>=16
All (10+)
Note: Vertical lines represent 95% confidence intervals.

Highlights:

- Sustained virologic response was achieved in 90.5% of patients with advanced/decompensated cirrhosis treated with directly acting antiviral therapy
- In long-term follow up (median of 4 years after treatment), overall mean changes in MELD, total bilirubin and albumin were marginal
- A clinically meaningful decrease in MELD of ≥ 3 occurred in 29% and a final MELD score of < 10 was achieved in 25%
- Patients with advanced/decompensated liver disease should continue to be monitored following SVR