

# Viusid, a nutritional supplement, in chronic hepatitis C and cirrhosis. A randomized and controlled study

Vilar E, PhD<sup>1</sup>. Arus E, PhD<sup>1</sup>. Sanchez Y, MD<sup>1</sup>. Gra B, MD<sup>2</sup>. National Institute of Gastroenterology, Havana, Cuba  
1. Department of Hepatology. 2. Department of Pathology

## Background

- ▶ The SVR rates in patients with CHC are 51-64%
- ▶ The SVR rates in cirrhotic patients are 30-40%
- ▶ In decompensated cirrhosis (Child >7 or MELD >18), antiviral therapy is deferred due to concerns over treatment-induced side effects with potential to further deteriorate hepatic function
- ▶ Antiviral therapy has demonstrated encouraging SVR (up to 33%) in decompensated cirrhotic patients
- ▶ No available pharmacological treatments are approved in the clinical practice
- ▶ As cirrhosis progresses, complications occur and the liver transplantation become the only option to improve patient survival
- ▶ After transplantation, HCV recurs and may rapidly progress to cirrhosis and graft loss
- ▶ The antioxidant therapy has not been tested in patients with hepatitis C and cirrhosis

## Ingredients of Viusid

Malic acid	0.666 g	Ascorbic acid	0.020 g
Glycyrrhizic acid	0.033 g	Folic acid	66 mcg
Glucosamine	0.666 g	Cyanocobalamin	0.3 mcg
Arginine	0.666 g	Zinc sulfate	0.005 g
Glycine	0.333 g	Pyridoxal	0.6 mg
Calcium pantothenate	0.002 g		

## Aim

To evaluate the efficacy and safety of Viusid, a nutritional supplement, in patients with chronic hepatitis C and cirrhosis

## Methods

### Study design

**Study type:** Interventional  
**Allocation:** Randomized Controlled Trial  
**Masking:** Double blind  
**Experimental group:** Viusid (a nutritional supplement)  
**Control group:** Placebo  
**Assignment:** Parallel  
**Endpoint:** Safety/efficacy  
**Primary outcomes measures:**

- The mortality secondary to liver failure at 96 weeks

### Secondary outcomes measures:

- Time to disease progression at 96 weeks defined as:
  - Clinical hepatic decompensation (bleeding esophageal varices, ascites, encephalopathy and spontaneous bacterial peritonitis)
  - MELD score impairments of at least 4 points as compared with baseline score
  - Cumulative risk of hepatocellular carcinoma

### Subjects

#### Eligibility criteria

#### Inclusion criteria:

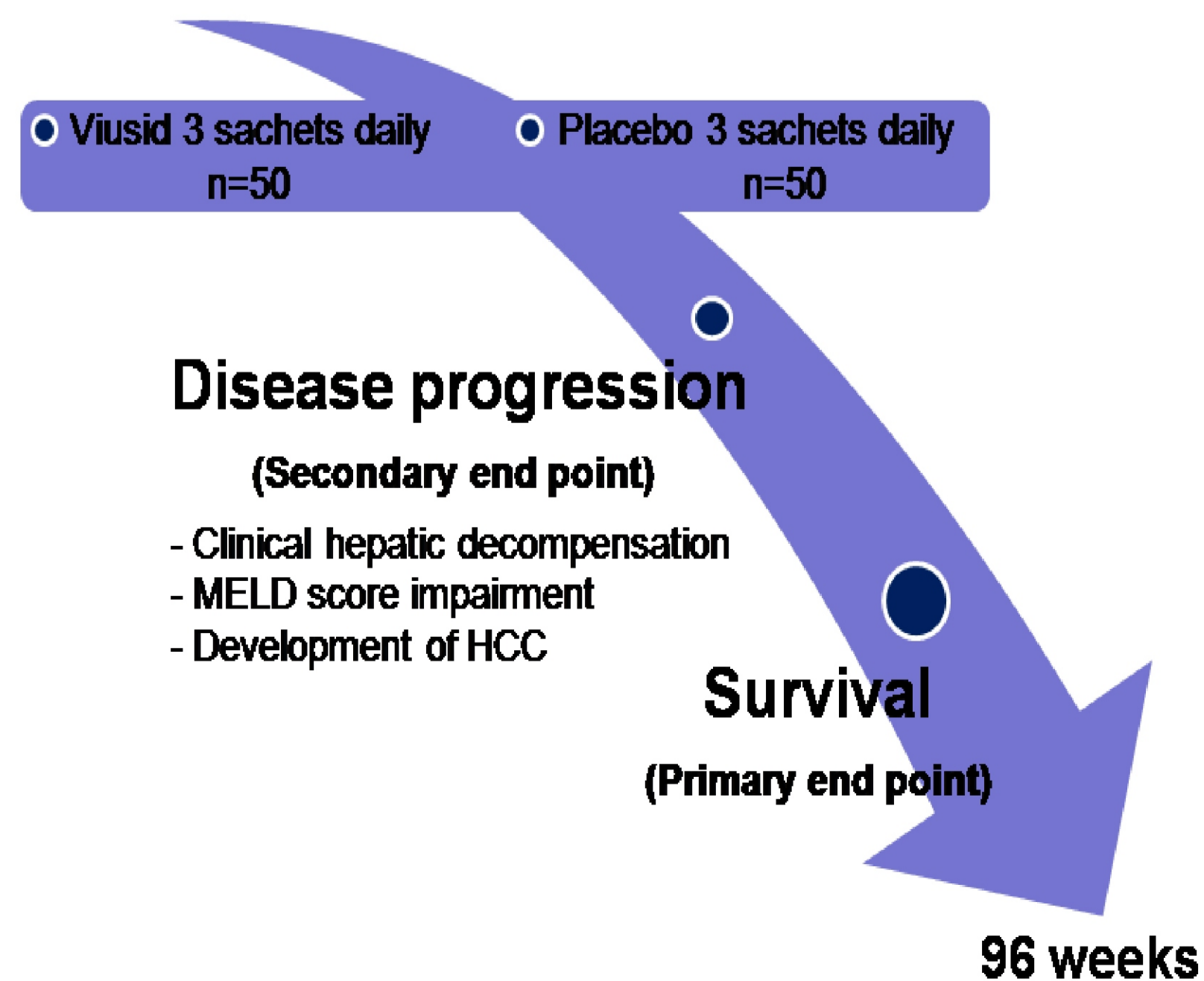
- Histological or clinical diagnosis of cirrhosis
  - HCV infection confirmed on a positive test for anti-HCV antibody and HCV RNA detectable in serum by PCR
  - Patients who were non-responders to previous treatment with pegylated interferon and ribavirin or naïve patients with decompensated cirrhosis (Child-Pugh score > 7) who had contraindicated the antiviral treatment.
  - Absence of clinical and ultrasonographic evidence of liver cancer, with  $\alpha$ -fetoprotein levels < 200 ng/ml.
- Exclusion criteria:**
- Age less than 18 or greater than 70 years.
  - Presence of uncontrollable clinical or biochemical complications related to severe liver failure (hepatic encephalopathy, hepatorenal syndrome, gastrointestinal bleeding, serum bilirubin level greater than 5 mg/dL, international normalized ratio greater than 2.5).
  - Active alcoholism.
  - Serum creatinine greater than 2 mg/dL.
  - Refusal to participate in the study.
  - Concomitant disease with reduced life expectancy.
  - Severe psychiatric conditions.
  - Co-infection with hepatitis A or B or HIV.
  - Drug dependence.
  - Pregnancy.

• Treatment and assessment are summarized in figure 1

### Statistical analysis

- Intention to treat analysis included all patients who were randomly assigned to receive either Viusid or placebo
- Treatment were compared with the use of a Cox proportional-hazards model
- The data from patients without end points were censored at the last date of available follow-up after treatment
- A two-sample t test was used to compare differences between the groups for continuous variables

Figure 1. Treatment and assessment



## Results

- ▶ One hundred patients with chronic hepatitis C who had clinically suspected or histologically confirmed cirrhosis were randomly assigned in a 1:1 ratio to receive 3 sachets of Viusid or placebo daily for a maximum of 96 weeks. Figure 1
- ▶ Demographic and baseline characteristic were comparable between the two groups. Table 1
- ▶ The survival (primary end point) was reached by 92 percent (46 of 50) of patients receiving Viusid and 72 percent (36 of 50) of those receiving placebo (hazard ratio, 3 [95% CI. 1.09-9.2]; P=0.035). Figure 2
- ▶ The clinical hepatic decompensation was observed in 50 percent (25 of 50) of patients receiving placebo in comparison with 25 percent (9 of 50) of those receiving Viusid (hazard ratio for time to disease progression, 2.9 [95% CI. 1.2-6.9]; P=0.010). Figure 3
- ▶ There was a significant reduction in the MELD score in the course of the follow-up period in those patients who received Viusid as compared with placebo. Figure 4
- ▶ The hepatocellular carcinoma occurred in 5 patients assigned to placebo as compared with 1 patient assigned to Viusid (hazard ratio, 4.3 [95% CI. 0.5-36.9]; P=0.126). Figure 5
- ▶ The disease progression was observed in 50 percent (25 of 50) of patients receiving placebo in comparison with 25 percent (9 of 50) of those receiving Viusid (hazard ratio for time to disease progression, 3 [95% CI. 1.4-6.6]; P=0.004). Figure 6
- ▶ Nauseas and diarrhea was reported in three subjects who received Viusid. No laboratory adverse event was associated with the use of Viusid.

Table 1. Baseline characteristics of the patients

Characteristics	Viusid (n=50)	Placebo (n=50)
Age – years, Mean $\pm$ SD*	59 $\pm$ 10	57.2 $\pm$ 8.7
Sex – no. (%)		
Male	16 (46%)	13 (37%)
Female	19 (54%)	22 (63%)
Child Score – no. (%)†		
= 7	39 (78%)	38 (76%)
> 8	11 (22%)	12 (24%)
Child-Pugh score		
Mean $\pm$ SD	6.1 $\pm$ 1.2	6.2 $\pm$ 1.2
MELD Score – no. (%)		
= 18	42 (84%)	42 (84%)
> 18	8 (16%)	8 (16%)
Alpha-fetoprotein $\mu$ g/liter		
Mean $\pm$ SD	8.6 $\pm$ 1.1	7.9 $\pm$ 1.3
Alanine aminotransferase U/L		
Mean $\pm$ SD	78.6 $\pm$ 48.3	78.9 $\pm$ 40.9
Aspartate aminotransferase U/L		
Mean $\pm$ SD	89.8 $\pm$ 80.7	101.2 $\pm$ 88.5
Albumin – g/L		
Mean $\pm$ SD	38.4 $\pm$ 3.5	38.1 $\pm$ 3.4
Bilirubin – $\mu$ mol/L		
Mean $\pm$ SD	21.3 $\pm$ 15.6	21.1 $\pm$ 13.3
Creatinine – mg/dL		
Mean $\pm$ SD	1.1 $\pm$ 0.3	1.02 $\pm$ 0.2
Hemoglobin – g/L		
Mean $\pm$ SD	125 $\pm$ 12.7	126 $\pm$ 16
Platelet count per mm <sup>3</sup>		
Mean $\pm$ SD	205 $\pm$ 43.2	199 $\pm$ 43.2
Prothrombin time - sec ‡		
Mean $\pm$ SD	4.9 $\pm$ 3	5 $\pm$ 3.7
White-cell count per mm <sup>3</sup>		
Mean $\pm$ SD	6000 $\pm$ 1900	6670 $\pm$ 1800
Encephalopathy		
Absent	48 (96%)	48 (96%)
Medically controlled	2 (4%)	2 (4%)
Ascites		
Absent	46 (92%)	46 (92%)
Medically controlled	4 (8%)	4 (8%)

\* All values expressed with a plus/minus sign are means  $\pm$  SD.

† The Child-Pugh score (range = 7, indicates good liver function and >8 indicates poor liver function) is a measure of the severity of liver disease.

‡ The prothrombin time was evaluated as seconds upper the control value.

Figure 2. Survival rates during the 96-week treatment period

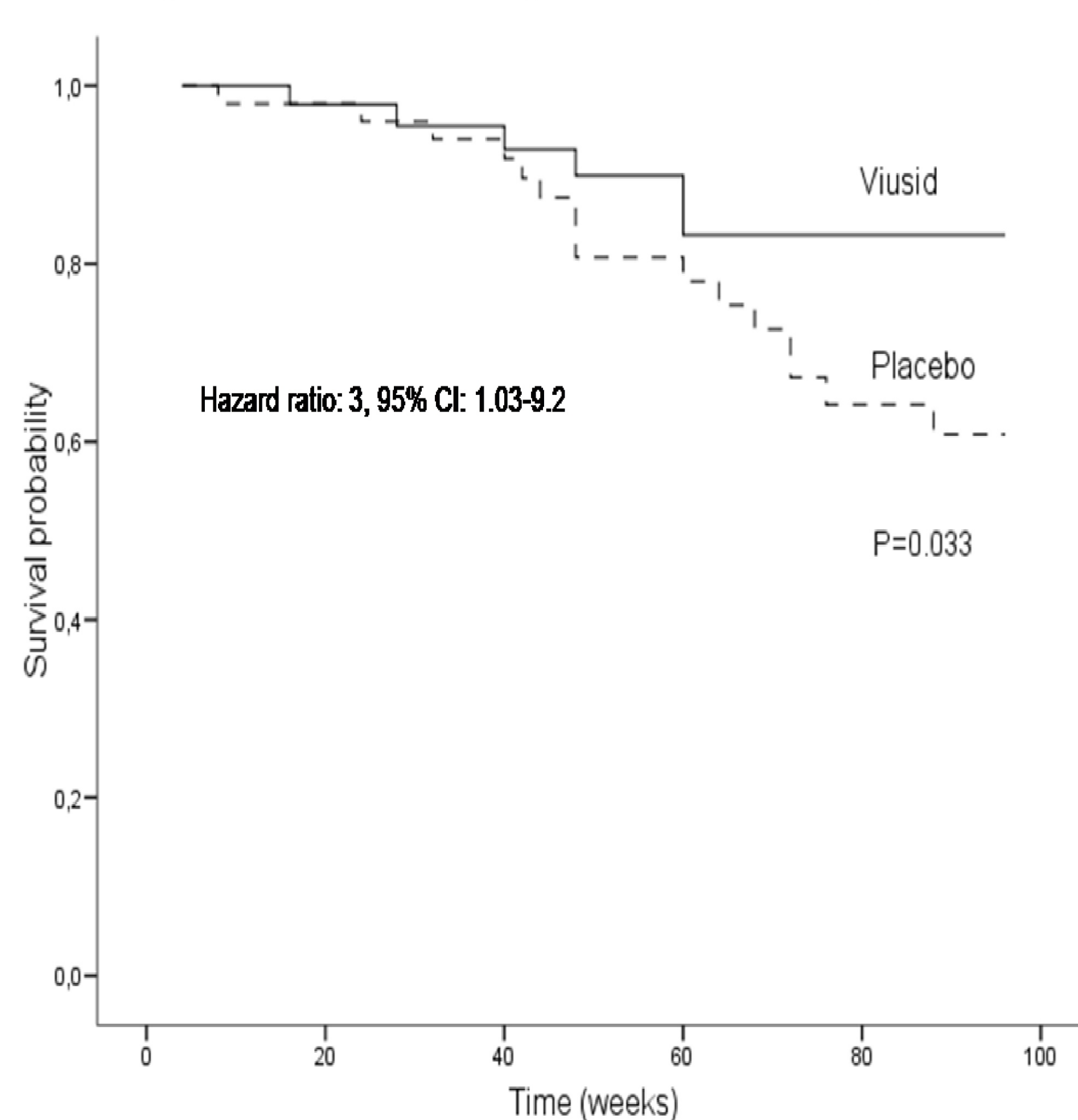
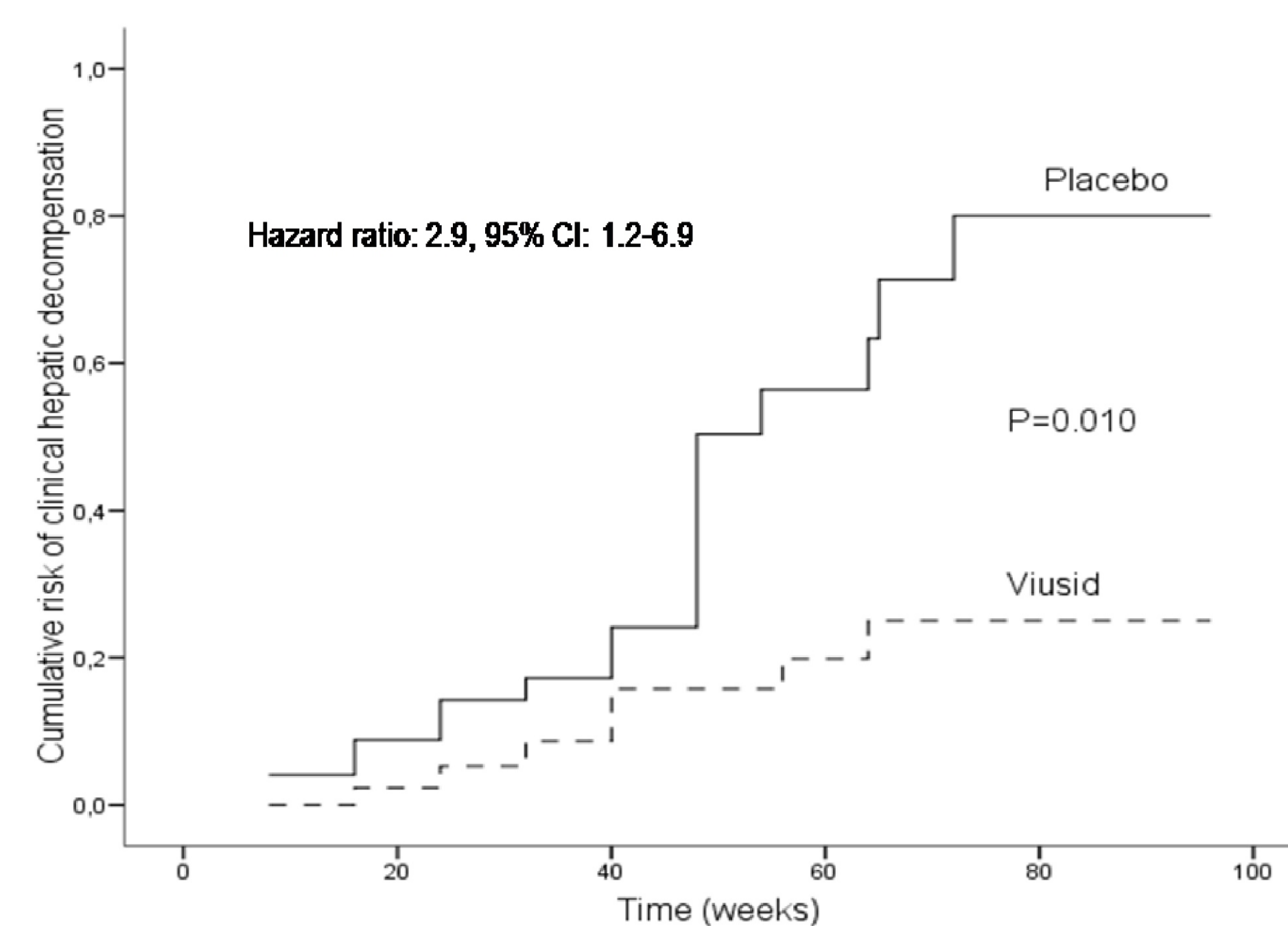


Figure 3. Cumulative risk of clinical hepatic decompensation\*



\*Clinical hepatic decompensation was defined as first occurrence or relapse of ascites, variceal bleeding, encephalopathy and spontaneous bacterial peritonitis

Figure 4. Change in MELD score

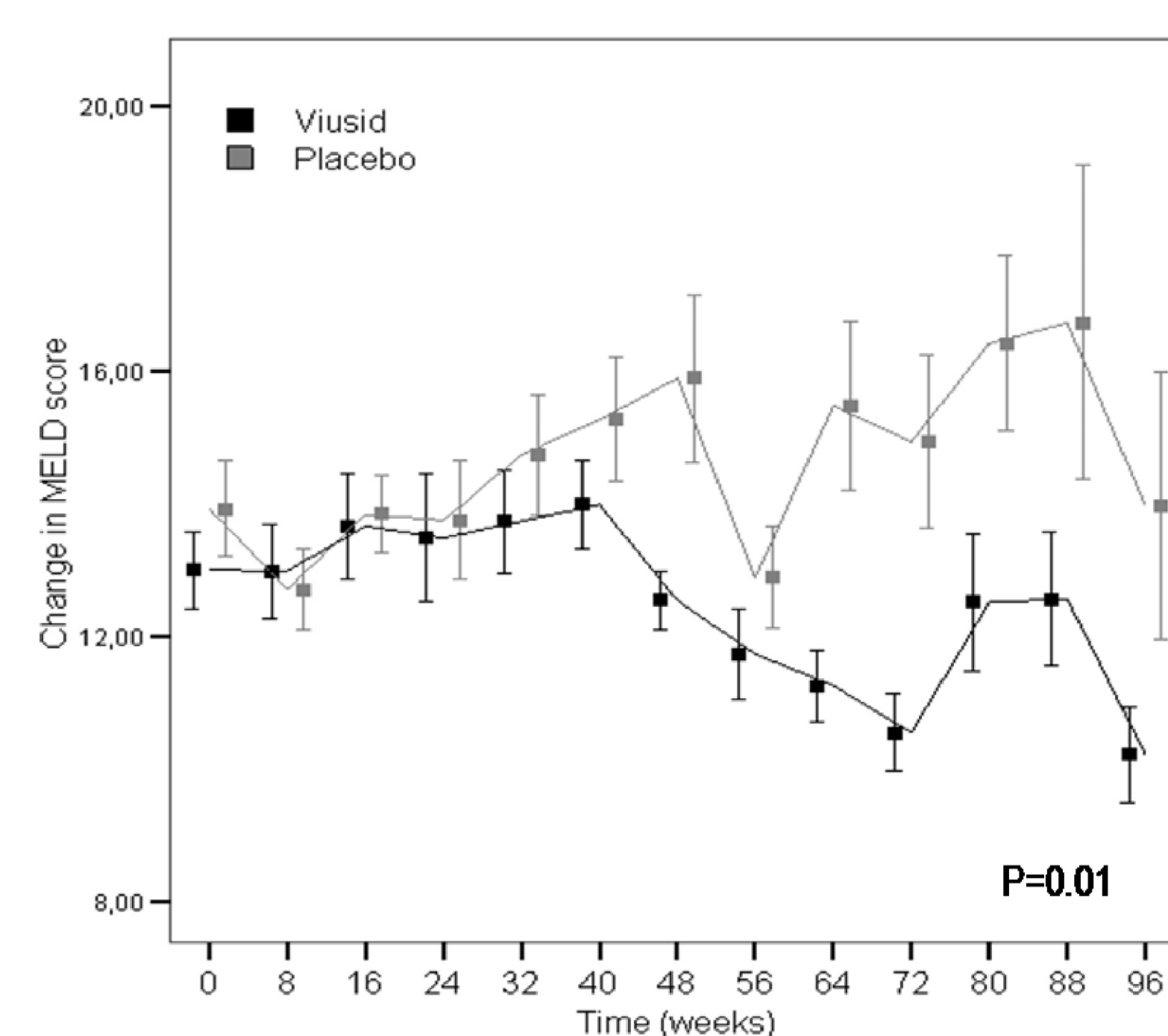


Figure 5. Cumulative risk of hepatocellular carcinoma

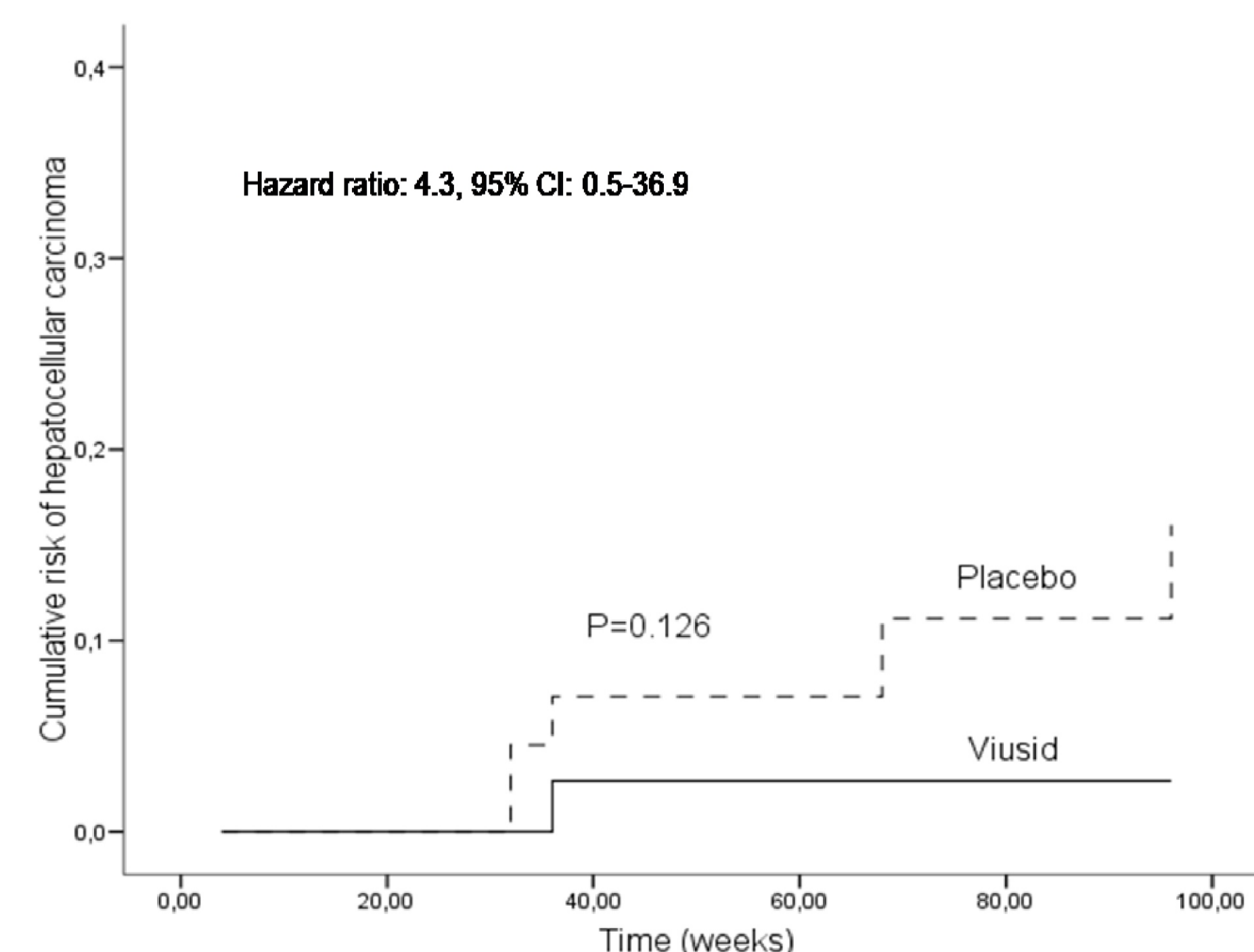
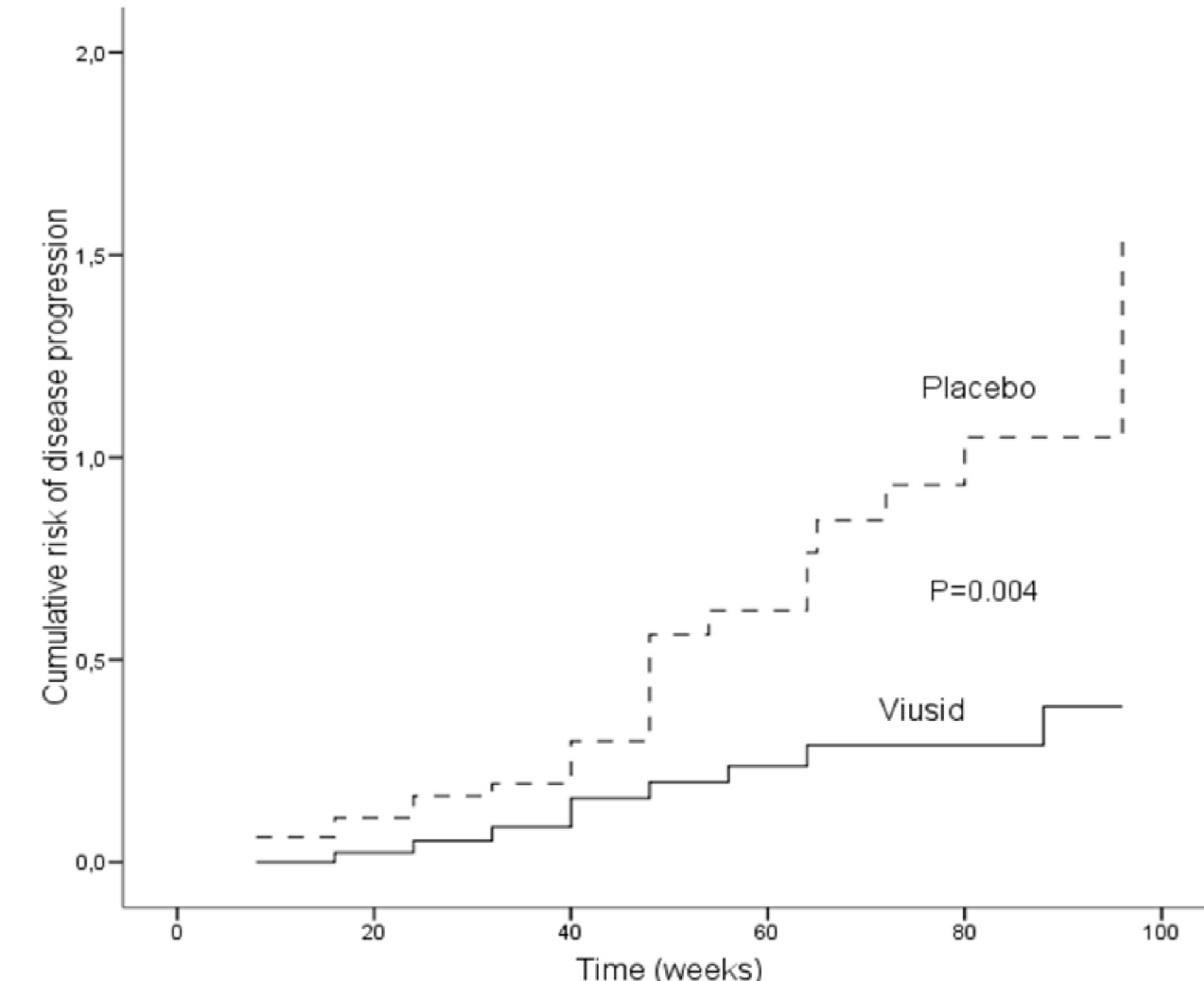


Figure 6. Cumulative risk of disease progression\*



\*Disease progression was defined as first occurrence of any of the following: presence or relapse of ascites, variceal bleeding, encephalopathy and spontaneous bacterial peritonitis, an increase of at least 4 points in the MELD score and the development of hepatocellular carcinoma

## Conclusions

- ▶ Our results indicate that continuous treatment with Viusid can leads to notable reduction in the mortality of patients with chronic hepatitis C and cirrhosis
- ▶ The administration of Viusid decrease the risk of disease progression by significantly reducing the clinical decompensation, MELD score and hepatocellular carcinoma
- ▶ Viusid tolerability was excellent and none severe adverse event was reported

tended to be higher in INF-HRS. (3) Survival was associated to the type of response and was higher in INF-HRS. (4) These results justify TLP+ALB in INF-HRS, where the results can be even better than classic-HRS.

### 312 DEFINING THE IMPACT OF ORGAN DYSFUNCTION IN CIRRHOSIS: SURVIVAL AT A COST?

D.L. Shawcross, M.J. Austin, R.D. Abeles, M. McPhail, A. Yeoman, A.J. Portal, W. Bernal, G. Auzinger, E. Sizer, J.A. Wendon. *Liver Intensive Care, Institute of Liver Studies, King's College Hospital, London, UK*  
E-mail: debbie.shawcross@kcl.ac.uk

**Introduction:** The incidence of cirrhosis is increasing exponentially and it is projected that there will be a 5 fold increase in demand for liver transplantation in the next 6–10 years. Historically, the perception of cirrhosis with organ dysfunction as having a poor prognosis has fuelled a self-fulfilling prophecy with iniquitous access to intensive care (ICU). However, recent data to support this view is lacking. We report the 7 year experience of the outcome, physiological disturbance and resource utilisation of 658 emergency admissions with cirrhosis and organ dysfunction to a specialist liver ICU.

**Aims and Methods:** We prospectively collected and analysed physiological and biochemical variables on day 1/3 of admission. Outcome variables, organ scores [Child Pugh, MELD, SOFA and APACHE II] and number of days requiring vasopressors, ventilation and renal replacement therapy (RRT) were recorded. The Therapeutic Intervention Scoring System (TISS) score, validated as a tool for estimating cost in ICU, was calculated.

**Results:** Alcohol was the most common aetiology (47%) and variceal bleeding the most common reason for admission (35%). 51% required inotropes, 72% invasive ventilatory support and 49% RRT. Despite this, ICU admission for many of these patients was not futile, with 55% surviving their ICU stay and 41% surviving to discharge. Variceal bleeders had a 30 day survival of 53% versus 33% with a non-variceal indication for admission ( $p < 0.0001$ ). 19% of survivors subsequently underwent transplantation. Survival was at a significant cost [median cost/patient: £12,403 (4,636–27,283) for a median 7 day admission (3–15)]. Admissions with multi-organ failure (MOF) cost significantly more (MOF  $p < 0.001$ ; RRT  $p < 0.0001$ ) and had more prolonged lengths of stay ( $p < 0.0001$ ). RRT was well tolerated and facilitated recovery in 23/59 (39%) patients who were subsequently transplanted.

**Conclusion:** More than 50% of patients admitted as emergencies will survive their ICU stay with the majority surviving to hospital discharge. These data challenge the widely held prejudice that patients with cirrhosis requiring emergency admission to ICU inevitably die. This endorses the establishment of managed clinical care networks and demands the engagement of all levels of critical care and ward-based care models in the treatment of organ dysfunction in cirrhosis.

### 313 HYDROXIZYNE IMPROVED INSOMNIA IN CIRRHOTIC INPATIENTS WITH GRADE I ENCEPHALOPATY

S. Soto, E. Castro, J.L. Ulla, S. Vazquez, R. Baltar, V. Alvarez, J. Vazquez-Sanluis, L. Ledo, E. Vazquez-Astray. *Gastroenterology Unit, Complejo Hospitalario De Pontevedra, Pontevedra, Spain*  
E-mail: iagosoto@hotmail.com

**Introduction:** Sleeplessness frequently occurs in cirrhotic patients with mild hepatic encephalopathy. The central histaminergic system is implicated in the control of arousal and circadian rhythmicity. In these patients histamine neurotransmission is altered and it modifies circadian rhythmicity. A selective up-regulation of brain H1 could contribute to the neuropsychiatric symptoms characteristic of human HE, and may be amenable to treatment with selective histamine H1 receptor antagonists.

**Aims and Methods:** We have studied the effects of hydroxycyane (histamine H1 blocker) in sleep alterations in cirrhotic inpatients with mild

encephalopathy. We were also interested to evaluate this drug security and its adverse effects.

This is a prospective, randomized study.

24 consecutive inpatients with hepatic cirrhosis with portal hypertension with hepatic encephalopathy were included during 12 months. The mean age was 67 years (27–78) and mean Child–Pugh score was 9 (7–15).

Patients with TIPS or surgical shunts were excluded. Benzodiazepines consumers and patients with alcoholic deprivation were also ruled out.

The 24 patients were randomized to have hydroxyzine 25 mg at 23:00 p.m. (n=12) or placebo (n=12) during a week.

**Results:** Subjective sleep improvement evaluated by the “Epworth Sleepiness Scale” was observed in 66.6% of hydroxyzine-treated patients but in none receiving placebo ( $p < 0.05$ ).

Hepatic encephalopathy deterioration happened in two of hydroxycyane-treated patients and in one of placebo-treated group (non statistical significance) All these patients improved after conventional treatment and cessation of hydroxycyane (in those patients who were having it).

**Conclusions:** Hydroxycyane 25 mg at 23:00 p.m. improved sleeplessness in patients with cirrhosis and mild encephalopathy.

Risk of encephalopathy deterioration was not higher in the hydroxycyane group.

### 314 VIUSID, A NUTRITIONAL SUPPLEMENT, IN PATIENTS WITH CHRONIC HEPATITIS C AND CIRRHOSIS. A RANDOMIZED AND CONTROLLED STUDY

E. Vilar Gomez<sup>1</sup>, Y. Sanchez Rodriguez<sup>1</sup>, E. Arus Soler<sup>1</sup>, B. Gra Oramas<sup>2</sup>. <sup>1</sup>Department of Hepatology, <sup>2</sup>Department of Anatomy Pathology, National Institute of Gastroenterology, Vedado, Cuba  
E-mail: eduardovilar2000@yahoo.com

**Introduction:** Recent studies have validated the feasibilities of IFN-based therapies for decompensated cirrhotic patients but have provided no data on benefit of therapy in disease progression and survival rates.

**Aims:** The efficacy and safety of antioxidant therapy in preventing disease progression in patients with chronic hepatitis C with compensated and decompensated cirrhosis is unknown.

**Methods:** One hundred patients with chronic hepatitis C who had clinically suspected or histologically confirmed cirrhosis were randomly assigned in a 1:1 ratio to receive 3 sachets of Viusid or placebo daily for a maximum of 96 weeks. The primary end point was the survival rate and the secondary end points were time to disease progression, defined as clinical hepatic decompensation (ascites, encephalopathy, bleeding gastroesophageal varices and spontaneous bacterial peritonitis) or MELD score impairments of at least 4 points as compared with the pretreatment score, and hepatocellular carcinoma. An independent data and safety monitoring board monitored the progress of the study and performed interim analyses of the data. The study was terminated after a median duration of treatment of 64 weeks (ranges, 24–96) owing to a significant difference between each group of treatment and number of end points reached.

**Results:** Primary end point was reached by 92 percent (46 of 50) of patients receiving Viusid and 72 percent (36 of 50) of those receiving placebo (hazard ratio, 3 [95% CI. 1.09–9.2];  $P = 0.035$ ). The secondary end point was reached by 50 percent (25 of 50) of patients receiving placebo in comparison with 25 percent (9 of 50) of those receiving Viusid (hazard ratio for time to disease progression, 3 [95% CI. 1.4–6.6];  $P = 0.002$ ). Hepatocellular carcinoma occurred in 5 patients assigned to placebo as compared with 1 patient assigned to Viusid (hazard ratio, 3.9 [95% CI. 0.5–33];  $P = 0.17$ ). Viusid tolerability was excellent and none severe adverse event was reported.

**Conclusions:** Continuous treatment with Viusid delays clinical progression in patients with chronic hepatitis C and cirrhosis by significantly reducing the time to disease progression and increasing the survival rates.