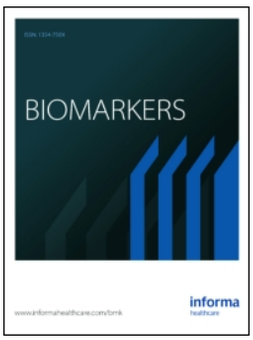

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Prognostic significance of insulin-like growth factor-I serum levels in acute decompensation of cirrhosis

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List of abbreviations:

GH-IGF: growth hormone-insulin-like growth factor

IGF-I: insulin-like growth factor I

IGFBP-3: insulin-like growth factor binding protein-3

AD: acute decompensation

PPI: Proton pump inhibitors

INR: international normalized ratio

CPR: C-reactive protein

SBP: Spontaneous bacterial peritonitis

MELD: Model for End-Stage Liver Disease

ACLF: Acute-on-chronic liver failure

ROC: receiver operating characteristics

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ABSTRACT

Context: IGF-I serum levels are suppressed in cirrhosis but its prognostic significance is unknown.

Objectives: To investigate the prognostic value of IGF-I in patients admitted for acute decompensation of cirrhosis.

Materials and methods: Cohort study that included 103 patients. IGF-I was measured by ELISA.

Results: Ninety-day mortality was 26.2% and it was independently associated with MELD, age and IGF-I. The Kaplan-Meier survival probability at 90 days was 94.3% in patients with IGF-I ≥ 13 ng/mL and 63.2% for patients with IGF-I < 13 ng/mL (P=0.001).

Discussion and conclusion: IGF-I levels are independently associated with mortality in acute decompensation of cirrhosis.

Introduction

Liver cirrhosis is a pathologically defined entity characterized by the development of regenerative nodules surrounded by fibrous bands in response to chronic liver injury, which leads to portal hypertension and end-stage liver disease (Schuppan & Afdhal, 2008). The course of cirrhosis is typically variable, and depends on several factors, including the etiology of cirrhosis and the hepatic synthetic function (Durand & Valla, 2008). In general, the natural course of cirrhosis is characterized by a longstanding asymptomatic phase, also known as the compensated phase, followed by a rapidly progressive phase characterized by specific complications (Durand & Valla, 2008). This transition from compensated to decompensated cirrhosis occurs at a rate 5–7% per year and is associated with a marked decrease in life expectancy (D'Amico et al., 2013).

Changes in the growth hormone-insulin-like growth factor (GH-IGF) axis observed as a result of liver disease has been reported in cirrhosis and may be responsible, at least in part, for several metabolic disorders characteristically observed in the course of the disease, including malnutrition, insulin resistance, osteopenia and hypogonadism (Huisman et al., 2011, Berzigotti & Abraldes, 2013, Luxon, 2011). GH is a peptide hormone released from the anterior pituitary that stimulates growth, cell reproduction and regeneration, exerting metabolic effects on bone, cartilage, fat, muscles, the heart, the immune system and other organs (Perrini et al., 2010, Colakoglu et al., 2007). In the liver, GH activation of GH receptors induces IGF-I gene transcription, and subsequently the synthesis and release of IGF-I to the plasma (Juul, 2003). Even though various tissues secrete IGF-I, in the post-natal period the liver is the main

source of circulating IGF-I (Juul, 2003). IGF-I exerts anabolic effects on amino acid and carbohydrate metabolism, increases muscle mass and improves bone mineral content and intestinal barrier function (Juul, 2003). The majority of circulating IGF-I is bound to IGF binding protein-3 (IGFBP-3), which, therefore, lowers the bioavailability of IGF-I and limits its access to IGF-I receptor. The IGFBPs strongly regulate the biological activity of IGF-I, which is additionally adjusted via individual levels of the IGFBP subtypes and by affinity-modulating proteases (Ferry et al., 1999, Hwa et al., 1999).

Changes in the GH/IGF/IGFBP axis are well documented in cirrhosis, and the peptides involved have been proposed as markers of hepatocellular dysfunction, malnutrition and survival (Perrini et al., 2010, Colakoglu et al., 2007). Lower IGF-I serum levels have been reported in patients with cirrhosis compared with healthy controls, likely reflecting decreased hepatic synthetic function (Colakoglu et al., 2007, Wu et al., 2004). In addition, circulating IGF-I appears to correlate with the degree of hepatic dysfunction as decreased levels were reported in more advanced stages of cirrhosis (Colakoglu et al., 2007, Wu et al., 2004, Ronsoni et al., 2013). Although these results indicate that determining IGF-I serum levels may be of clinical relevance in patients with cirrhosis, there are very few data on the prognostic significance of this biomarker in this context. Therefore, we sought to investigate the relationship between serum levels of IGF-I and short-term prognosis in patients hospitalized for acute decompensation (AD) of cirrhosis.

Materials and Methods

Patients

This is a cohort study that included consecutive subjects admitted to the emergency room of a Brazilian tertiary hospital due to AD of liver cirrhosis between December 2011 and November 2013. The following exclusion criteria were adopted: hospitalization for elective procedures, admissions not related to complications of liver cirrhosis, hepatocellular carcinoma outside Milan criteria and a doubtful diagnosis of liver cirrhosis. All patients were initially admitted in the emergency room. The decision to transfer the patient to the ward or the intensive care unit was made at the discretion of the attending physician according to the severity of the AD.

The diagnosis of cirrhosis was established either histologically (when available) or by the combination of clinical, imaging and laboratory findings in patients with evidence of portal hypertension.

The study protocol complies with the ethical principles of the Declaration of Helsinki and was approved by the Ethics Committee on Human Research of the Federal University of Santa Catarina.

Methods

All patients admitted for AD, as defined by the acute development of hepatic encephalopathy, large ascites, gastrointestinal bleeding, bacterial infection or any combination of these, were screened. Patients were evaluated within 24 hours of admission by one of the researchers involved in the study, and the following clinical variables were collected: age, gender, race, etiology of

cirrhosis, history of previous decompensation, current complications of cirrhosis, active alcoholism and regular propranolol and and proton pump inhibitors (PPI) use. All subjects underwent laboratory evaluation at admission, and the following tests were performed for this study: total leukocytes, platelet count, serum sodium, creatinine, international normalized ratio (INR), albumin, C-reactive protein (CRP) and total bilirubin.

Active alcoholism was defined as an average overall consumption of 21 or more drinks per week for men and 14 or more drinks per week for women during the 4 weeks before enrollment (one standard drink is equal to 12 g absolute alcohol) (Addolorato et al., 2007). Patients were followed during their hospital stay and 30- and 90-day mortality was evaluated by phone call, in case of hospital discharge. Ninety-day mortality rates were estimated as transplant-free mortality (patients who received a liver transplant were considered lost to follow-up).

Individuals with a suspected infection at hospital admission received a clinical examination to confirm this diagnosis and to establish the primary source of infection. The diagnosis of infection was made according to the criteria of the Center for Disease Control (Garner et al., 1988). A diagnostic paracentesis was performed in all patients with ascites at admission. Spontaneous bacterial peritonitis (SBP) was diagnosed when the neutrophil count of the ascitic fluid was ≥ 250 neutrophils/mm^3 in the absence of intra-abdominal source of infection, regardless of negative culture (Runyon, 2009). All patients with SBP received ceftriaxone plus weight-based intravenous albumin in the first and third day after the diagnosis. Hepatic encephalopathy was graded according to the West-Haven criteria (Bajaj, 2010) and, if it was

present, a precipitant event was actively investigated and lactulose was initiated and the dose was adjusted as needed. All subjects with acute variceal bleeding received intravenous octreotide, an antibiotic (either oral quinolone or intravenous ceftriaxone), and underwent urgent therapeutic endoscopy after stabilization. Acute kidney injury (AKI) was defined as a serum creatinine elevation $\geqslant$ 0.3 mg/dL within the first 48 hours of admission or a raise $\geqslant$ 50% from baseline presumably occurred over the last seven days (Angeli et al., 2015). The severity of liver disease was estimated by the Child-Pugh classification system (Angermayr et al., 2003) and Model for End-Stage Liver Disease (MELD) (Kamath et al., 2001) calculated based on laboratory tests performed at admission. Acute-on-chronic liver failure (ACLF) was defined as proposed by the EASL-CLIF Consortium (Moreau et al., 2013).

IGF-I serum levels

IGF-I levels were measured in serum samples collected within 24 hours of admission and stored at -80°C until use. IGF-I levels were measured in duplicate by an enzyme-linked immunosorbent assay (Quantikine® ELISA – Human IGF-I, R&D Systems, Minneapolis, MN, USA). The reported analytic sensitivity of this assay was 0.026 ng/mL.

Statistical analysis

The normality of the variable distribution was determined using the Kolmogorov-Smirnov test. The correlation between the numerical variables was evaluated using Spearman's correlation coefficient. Continuous variables were

compared using the Student's *t*-test in the case of a normal distribution or the Mann-Whitney test in remaining cases. Categorical variables were evaluated by chi-square test or Fisher's exact test, as appropriate. After checking for multicollinearity among potential independent predictors, multiple logistic regression analysis (forward stepwise regression) was used to investigate the factors independently associated with 90-day mortality. Based on the receiver operating characteristics (ROC) curve, the best cutoff point for IGF-I to predict 90-day mortality was chosen. The survival curve was calculated using the Kaplan-Meier method and survival differences between groups were compared using the log-rank test. Paired samples t-test or Wilcoxon signed rank-test were used for comparing variables at two times (hospitalization and outpatient assessment). All tests were performed using SPSS software, version 17.0 (SPSS, Chicago, IL, USA). A P value of less than 0.05 was considered statistically significant.

Results

Characteristics of the sample

One hundred and three patients were included between December 2011 and November 2013. Table 1 lists the characteristics of the included patients. The mean age was 54.2 ± 11.3 years, 62.7% were caucasians, and a male predominance was observed (69.9%).

When evaluated according to the Child-Pugh classification, 14.6% of patients were classified as stage A, 48.5% were classified as stage B and 36.9% were classified as stage C. At admission, 19 patients (18.4%) fulfilled the criteria for ACLF. ACLF was classified as grade 1 in 15 patients (14.6%), grade

2 in 3 patients (2.9%) and grade 3 in 1 patient (1.0%).

Relationship between IGF-I levels and the studied variables

Mean IGF-I levels were 11.99 ± 13.56 ng/mL (median: 9.00 ng/mL). IGF-I levels positively correlated with albumin (r = 0.298, P = 0.003). A negative correlation was observed between IGF-I levels and INR (r = -0.202, P = 0.042), total bilirubin (r = -0.195, P = 0.049), MELD (r = -0.272, P = 0.005) and Child-Pugh score (r = -0.269, P = 0.006). No significant correlations were observed between IGF-I levels and age, leukocyte count, platelet count, CRP, sodium or creatinine.

When IGF-I levels were evaluated according to specific complications of cirrhosis observed at admission, no associations with the presence of ascites, hepatic encephalopathy, bacterial infection or SBP were noted (P > 0.05). Those individuals with upper gastrointestinal bleeding at admission had lower IGF-I levels compared to the other patients (6.30 ng/mL vs. 11.60 ng/mL, P = 0.038). Child-Pugh C patients also exhibited lower IGF-I levels than Child-Pugh A or B patients (5.80 ng/mL vs. 11.60 ng/mL, P < 0.001). No significant differences in IGF-I levels were observed between subjects with or without ACLF at admission (7.10 ng/mL vs. 10.80 ng/mL, P = 0.222), as well as with or without AKI (6.10 ng/mL vs. 10.80 ng/mL, P = 0.135).

Prognostic significance of IGF-I in hospitalized patients with cirrhosis

The overall 90-day mortality was 26.2% and it was associated in the bivariate analysis (Table 2) with older age, ascites, hepatic encephalopathy, bacterial infection, Child-Pugh C, higher MELD scores and ACLF at admission.

Ninety-day mortality was also related to higher median creatinine, INR, CRP, total bilirubin and lower mean albumin, lower median, and IGF-I levels.

A stepwise forward logistic regression analysis (Table 3) including IGF-I, age and the most important prognostic models in liver cirrhosis (MELD, Child-Pugh C, ACLF) was performed. Thys analysis showed that MELD score (OR 1.334, 95% CI 1.181–1.506, P < 0.001), age (OR 1.121, 95% CI 1.045–1.202, P = 0.001) and IGF-I levels (OR 0.926, 95% CI 0.860–0.998, P = 0.043) were independently associated with 90-day mortality. The AUROC for prediction of 90-day mortality was 0.691 (CI 0.588 – 0.794). Based on the ROC curve, the best IGF-I cutoff (13 ng/mL) was chosen to predict 90-day mortality. Figure 1 shows the Kaplan-Meier curves for mortality during the follow-up period, according to the IGF-I categories. The Kaplan-Meier survival probability at 90 days was 94.3% for patients with IGF-I ≥ 13 ng/mL and 63.2% for those with IGF-I < 13 ng/mL (P = 0.001). For the prediction of 90-day mortality, IGF-I at a cutoff of 13 ng/mL showed a sensitivity of 93% and a specificity of 43%, and a negative predictive value of 94% but a positive predictive value of only 37%. The positive likelihood ratio was 1.637 and the negative likelihood ratio was 0.171.

IGF-I levels after hospital discharge

Twenty-one patients that had been included in the above analysis underwent laboratory evaluation within a median 105 days after discharge and were compared at two time points to investigate the impact of AD on IGF-I levels. At outpatient evaluation, 9 patients were classified as Child-Pugh A and 12 subjects as Child-Pugh B, with a median MELD score of 10.19. As compared to

inpatient assessment, significantly higher IGF-I levels were observed at outpatient evaluation (21.9 ± 23.3 ng/mL vs. 49.3 ± 33.3 ng/mL, P < 0.001) (Figure 2). Likewise, an increase in IGF-I levels at outpatient evaluation were observed in 17 out of 21 patients included in this analysis (81%). As expected, outpatient assessment was also associated with lower MELD (10.59 ± 2.26 vs. 13.58 ± 2.99, P < 0.001), INR (1.27 ± 0.14 vs.1.44 ± 0.19, P < 0.001), total bilirubin (1.28 ± 0.74 mg/dL vs.1.75 ± 1.29 mg/dL, P = 0.058), CRP median (3.50 mg/L vs. 6.31 mg/L, P =0.016) and higher albumin levels (3.27 ± 0.49 g/dL vs. 2.62 ± 0.56 g/dL, P < 0.001).

Discussion

Acute complications of cirrhosis are common causes of hospital admission and are associated with significant morbidity and mortality. Although major advances in the knowledge of natural history of cirrhosis were achieved over the last few years, there is still a need for new markers of prognosis in cirrhotics with AD. It was previously shown that IGF-I levels in cirrhosis are related to the severity of liver dysfunction and that this marker undergoes little influence from other factors not related to liver synthesis capacity. As a result, IGF-I levels represent a promising tool as a prognostic marker in liver cirrhosis (Colakoglu et al., 2007, Wu et al., 2004, Ronsoni et al., 2013).

In the present study, IGF-I levels were correlated with other variables directly or indirectly associated with the intensity of liver dysfunction, including albumin, INR, bilirubin and MELD score. . The correlations were weak, although statistically significant. In addition, Child-Pugh C patients exhibited lower IGF-I than Child-Pugh A or B ones. These findings are in agreement with previous

studies that demonstrated an association between lower IGF-I levels and the severity of liver disease (Colakoglu et al., 2007, Wu et al., 2004, Ronsoni et al., 2013, Donaghy et al., 1995, Assy et al., 2008). In a recent study, also including patients admitted for AD of cirrhosis, we found lower IGF-I in Child-Pugh B or C patients and a correlation of IGF-I with several variables related to severity of cirrhosis, with no interference of other parameters such as gender, etiology of cirrhosis and comorbidities (Ronsoni et al., 2013). In addition, previous data indicate that the low levels of IGF-I observed in patients with advanced cirrhosis are promptly corrected by successful orthotopic liver transplantation, supporting the investigation of IGF-I as a potential biomarker for the assessment of liver function (Castro et al., 2013, Weber et al., 2002, Bassanell et al., 2004).

In this study, 90-day mortality was 26.2% and was associated in the logistic regression analysis with higher MELD scores, older age and lower IGF-I levels. On the one hand, the MELD score and older age are traditional prognostic factor in cirrhosis (Fayad et al., 2015, Kamath & Kim, 2007); on the other hand, there are very few data about the significance of circulating IGF-I in patients with chronic liver diseases. A small study of 36 patients with alcoholic cirrhosis reported significantly lower survival among subjects with IGF-I below 3 nmol/L (equivalent to 22.9 ng/mL) (Moller et al., 1993). A subsequent study from the same group evaluated IGF-I levels in 354 patients with alcohol-induced liver disease from a large multicenter trial of the effect of malotilate on survival (Moller et al., 1996). The mean follow-up period was 569 days and low IGF-I levels were associated with poor prognosis, especially at a cutoff of 56 ng/mL (Moller et al., 1996). It is important to note that this study included both patients with and without cirrhosis and no detailed analysis of those with only cirrhosis

was provided (Moller et al., 1996). Nevertheless, the authors found a significant relationship between IGF-I and the intensity of liver dysfunction and also indicated the potential of its levels as a prognostic marker on liver diseases.

The Kaplan-Meier survival probability at 90 days was 94.3% in patients with IGF-I ≥ 13 ng/mL and 63.2% in those with IGF-I < 13 ng/mL. Although the proposed cutoff showed a good sensitivity (93%) and negative predictive value (94%), less impressive results were observed regarding specificity and positive predictive values. This fact indicates that IGF-I may be a good biomarker to identify those cirrhotics with low risk of death, but it is likely less useful for predicting mortality. This hypothesis is reinforced by the significantly low negative likelihood ratio observed (0.171) in relation to a modest positive likelihood ratio (1.637). The cutoff of 13 ng/mL suggested here is significantly lower than the values reported in the two other studies discussed above (Moller et al., 1993, Moller et al., 1996). In fact, mean IGF-I levels in patients with cirrhosis vary significantly across studies, ranging from 25 ng/mL to 152 ng/mL (Colakoglu et al., 2007, Wu et al., 2004, Ronsoni et al., 2013, Donaghy et al., 1995, Assy et al., 2008). This discrepancy may be explained by methodological differences in IGF-I measurement or by the distinct clinical contexts and inclusion criteria across the studies. Since we included only patients hospitalized for complications of cirrhosis, it is possible that factors related the acute insult or, more importantly, a rapid decrease in hepatic function might justify the lower IGF-I levels observed.

When patients with AD were evaluated after discharge, a significant increase was observed in IGF-I levels in 17 out of 21 patients. The mean IGF-I levels in this subgroup of subjects were 21.9 ± 23.3 ng/mL during hospitalization

and 49.3 ± 33.3 ng/mL at outpatient evaluation. This increase of IGF-I after stabilization was accompanied by an improvement in various other parameters related to the severity of liver disease, such as MELD, INR, total bilirubin and albumin. Although data regarding dynamic changes in IGF-I are scarce, a previously discussed small Danish study evaluated IGF-I just before discharge in 18 out of 36 patients included (Moller et al., 1993). In agreement with our results, the authors reported a significant increase in IGF-I levels, from 23.7 ng/mL to 48.8 ng/mL (Moller et al., 1993). These findings suggest that the initially low circulating IGF-I levels in cirrhosis can become even more suppressed during acute complications, likely reflecting a worsening in liver function. However, once the acute insult is removed and liver dysfunction improves, IGF-I levels tend to return to their basal values. This hypothesis is corroborated by the rapid recovery of IGF-I levels observed after liver transplantation, as discussed above (Castro et al., 2013, Weber et al., 2002, Bassanello et al., 2004).

We acknowledge some limitations to our analysis. First, the relatively small number of patients evaluated could limit our ability to generalize these findings to other populations. In fact, there is still a need for validation of our results in larger cohorts before this biomarker is incorporated into clinical practice. However, we believe that our study may represent an important starting point for research aimed at evaluating IGF-I in different clinical scenarios, such as acute liver failure and outpatient cirrhotics on waiting list for liver transplant. Secondly, patients were admitted to the emergency department of a general hospital and, although we followed protocols for specific complications of cirrhosis, these guidelines were not specifically created for the

purpose of this study and some variation in the approach of specific cases is to be expected. Nevertheless, this issue is common to almost all studies investigating biomarkers in clinical settings, especially in acutely ill patients. The heterogeneity of the included subjects was anticipated and likely reflects the characteristics of patients with cirrhosis that seek medical care in emergency situations.

In conclusion, in patients admitted for AD of cirrhosis, circulating IGF-I is related to the severity of liver disease and is independently associated with short-term prognosis. IGF-I increases after stabilization of liver disease, suggesting an impact of transient worsening in liver function on its levels. These findings reinforce the potential role of IGF-I in assessing the severity of liver dysfunction and indicate that this marker can be used as a prognostic tool for patients with cirrhosis admitted for acute complications of the disease.

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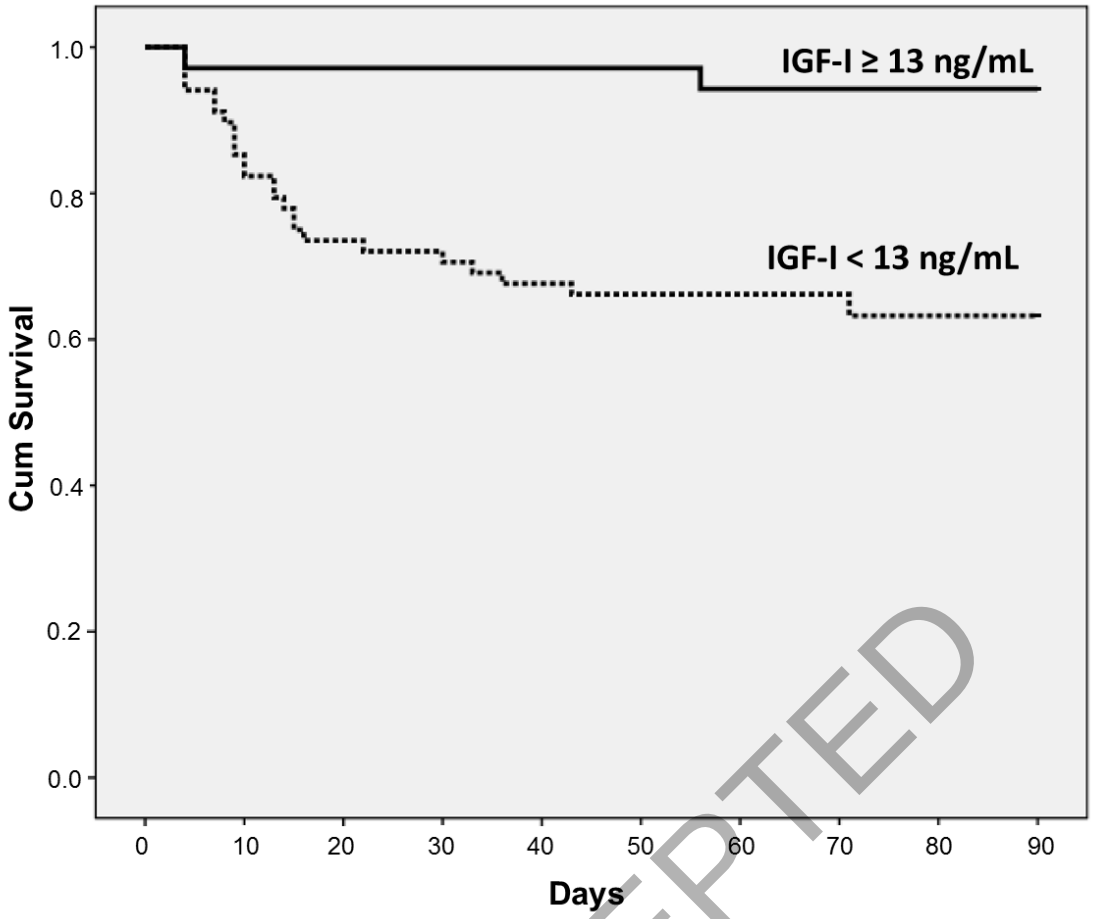
Figure legends

Fig. 1. Cumulative 90-day survival of patients with cirrhosis according to the IGF-I categories. Survival was significantly lower in patients with IGF-I < 13 ng/mL as compared to those with values ≥ 13 ng/mL (P = 0.001, long-rank test).

Fig. 2. Box plot of IGF-I according to the moment of evaluation (inpatient or outpatient). The line across the box indicates the median value; the box contains the 25% to 75% interquartile range; and the whiskers represent the highest and the lower values. IGF-I levels were significantly higher at outpatient assessment (P < 0.001).



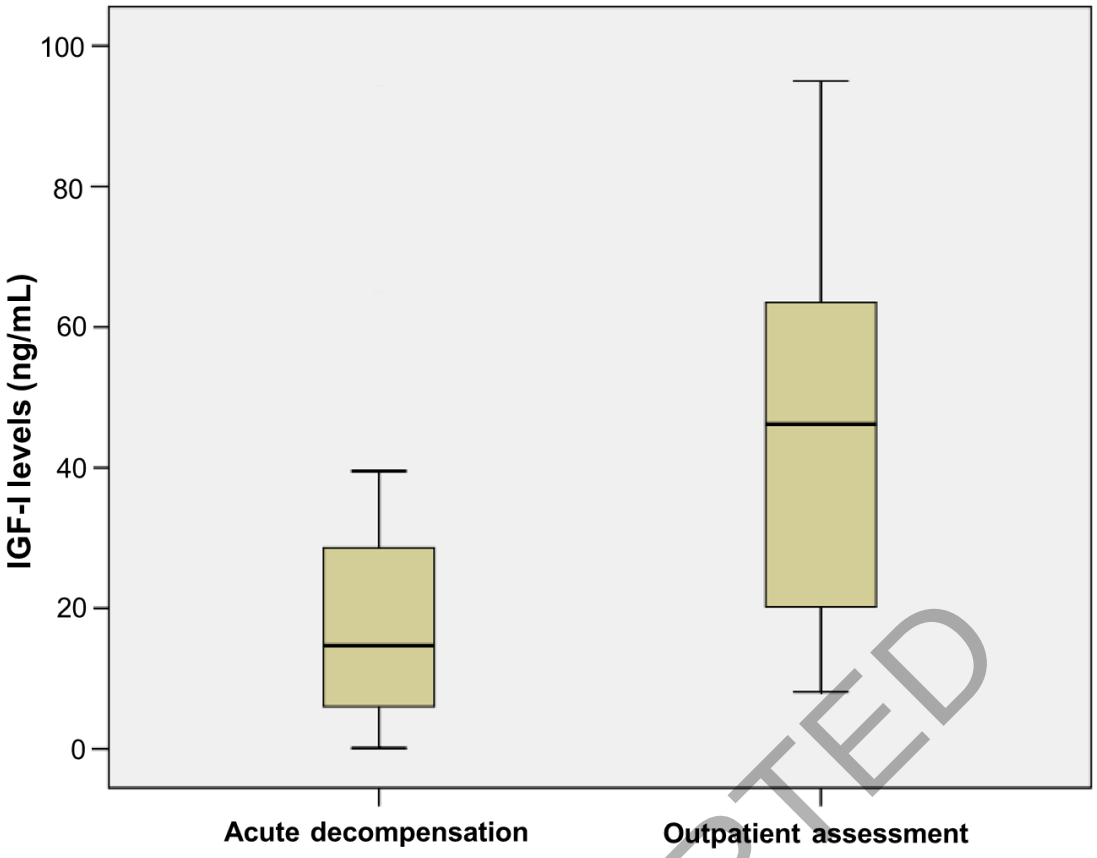


Table 1. Demographic, clinical and biochemical features of included patients

	All patients (n = 103)
Age; years, mean ± SD	54.2 ± 11.3
Male gender, n (%)	72 (69.9)
Ethnicity (Caucasians), n (%)	65 (62.7)
Etiology of cirrhosis, n (%)	
Alcohol	18 (17.5)
Hepatitis C	42 (40.8)
Hepatitis B	4 (3.9)
Cryptogenic	9 (8.7)
Other	30 (29.1)
Previous decompensation, n (%)	63 (61.2)
Active alcoholism, n (%)	35 (34.0)
Propranolol*, n (%)	43 (41.7)
PPI*, n (%)	25 (24.3)
Complication at admission, n (%)	
Ascites	46 (44.7)
Hepatic encephalopathy	58 (56.3)
Gastrointestinal bleeding	53 (51.5)
Bacterial infection	21 (20.4)
SBP	10 (9.7)
Laboratory data	
Leucocyte count (x 10^9), median	6.97
Platelet count (x 10^9), median	84.00
Sodium (meq/L), median	137.00
Creatinine (mg/dl), median	1.10
INR, median	1.37
Albumin (g/dL), mean ± SD	2.41 ± 0.66
CRP (mg/L), median	9.32
Total bilirubin (mg/dl), median	2.10
IFG-I (ng/mL), median	9.00
Child-Pugh Classification, n (%)	
A	15 (14.6)
B	50 (48.5)
C	38 (36.9)
ACLF at admission, n (%)	19 (18.4)
MELD score, mean ± SD	15.7 ± 6.14

SD = Standard deviation; PPI = Proton pump inhibitors; INR = international normalised ratio; CRP = C-reactive protein; IGF-I = Insulin-like growth factor-I; MELD = Model for End-stage Liver Disease

* Prior hospitalization

Table 2. Factors associated with 90-day mortality among patients hospitalized for acute decompensation of cirrhosis

	Survivors (n = 76)	Deaths (n = 27)	P
Age (years), mean ± SD	52.57 ± 10.82	58.74 ± 11.44	0.014
Male gender, n (%)	53 (69.7)	19 (70,4)	0.951
Etiology of cirrhosis, n (%)			
Alcohol	11 (14.5)	7 (25.9)	0.237
Hepatitis C	33 (43.4)	9 (33.3)	0.360
Hepatitis B	3 (3.9)	1 (3.7)	1.000
Cryptogenic	7 (9.2)	2 (7.4)	1.000
Previous decompensation, n (%)	46 (60.5)	17 (63.0)	0.823
Active alcoholism, n (%)	11 (14.5)	7 (25.9)	0.237
Propranolol*, n (%)	36 (47.4)	7 (25.9)	0.052
PPI*, n (%)	19 (25.0)	6 (22.2)	0.772
Complication at admission, n (%)			
Ascites	23 (30.3)	23 (85.2)	< 0.001
Hepatic encephalopathy	38 (50.0)	20 (74.1)	0.030
Gastrointestinal bleeding	47 (61.8)	6 (22.2)	< 0.001
Bacterial infection	11 (14.5)	10 (37.0)	0.012
SBP	5 (6.6)	5 (18.5)	0.123
Laboratory data			
Leucocyte count (x 10^9), median	6.63	7.25	0.680
Platelet count (x 10^9), median	84.00	94.00	0.406
Sodium (meq/L), median	137.00	133.00	0.002
Creatinine (mg/dl), median	1,00)	1.50	< 0.001
INR, median	1.35	1.56	0.003
Albumin (g/dL), mean ± SD	2.56 ± 0.65	1.99 ± 0.51	< 0.001
CRP (mg/L), median	7.80	23.40	0.004
Total bilirubin (mg/dL), median	1.40	3.60	< 0.001
IFG-I (ng/mL), median	11.60	5.50	0.003
Child-Pugh C, n (%)	17 (22.4)	21 (77.8)	< 0.001
MELD score, mean ± SD	13.66 ± 4,63	21.44 ± 6.31	< 0.001
ACLF, n (%)	5 (6.6)	14 (51.0)	< 0.001

SD = Standard deviation; PPI = Proton pump inhibitors; MAP = Mean arterial pressure; INR = international normalised ratio; CRP = C-reactive protein; IGF-I = Insulin-like Growth Factor I; MELD = Model for End-stage Liver Disease; ACFL = Acute-on-chronic liver failure

* Prior hospitalization

Table 3. Stepwise forward logistic regression analysis of factors associated with 90-day mortality (Variables included: IGF-1, age, MELD, Child-Pugh C, ACLF).

Factors	Odds Ratio	95% CI	P
MELD score	1.334	1.181 – 1.506	<0.001
Age	1.121	1.045 – 1.202	0.001
IGF-I levels	0.926	0.860 – 0.998	0.043

CI = Confidence interval.