Association between Insulin-Like Growth Factor- 1 and Severity of Liver Disease in Patients with Liver Cirrhosis

Naglaa El-Toukhy[1],Mohamed Abd El-Hamed Khidr[2], Mona Youssef[3]

[1] *Departments of Hepatology, Gastroenterology and Infectious Diseases, Faculty of Medicine, Benha University, Egypt .*

[2] *Department of Diagnostic Clinical and Chemical Pathology, Faculty of Medicine, El Azhar University, Egypt.*

[3] *Department of Hepatology, Gastroenterology and Infectious Diseases, Benha Teaching Hospital, Egypt.*

Corresponding Author
Mona Youssef

Mobile:
+01225529030

E mail:
mona.yussef@yahoo.com.

Key words:

Liver cirrhosis, Severity, Insulin-like growth factor-1

Background and study aim: Liver cirrhosis is the end result of chronic liver disease and it is a dynamic process that needs close monitoring to prevent its progression and complications. Insulin-like growth factor-1 (IGF-1) is an anabolic hormone secreted mainly by the liver. The aim of this study was to evaluate the serum IGF-1 level and its association with the severity of liver disease in patients with liver cirrhosis.

Method: This study was conducted on 85 patients with liver cirrhosis. Child's classification, MELD, uMELD and IGF-1 were assessed in all patients.

Results: The studied patients were 45 males and 40 females. Their mean age was 45.25±5.88 ranging from 34-60 years. As regard the severity of liver disease 70.59% of patients were Child C, 16.47% were Child B and 12.94% were Child A. The mean value of IGF-1 was significantly lower in Child C (35.09± 7.74 ng/ml) cirrhotic patients than Child B (123.5±41.35 ng/ml) and Child A (249.82±49.11 ng/ml) patients. Also, IGF-1 was significantly lower in patients with MELD score > 17 and uMELD > 4.18. Applying the ROC curves to assess IGF-1 as a marker of liver disease severity according to Child's, MELD and uMELD scores at IGF-1 cutoff value of 69.5 µg/ml, 196 µg/ml,196 µg/ml and AUCs were 0.9840, 0.7046, 0.8991 respectively. IGF-1 is negatively correlated with the severity of liver disease.

Conclusion: IGF-1 could be used to assess the severity of liver disease in patients with liver cirrhosis.

INTRODUCTION

Cirrhosis is the final stage of chronic liver disease, characterized by necroinflammation, fibrosis and regeneration nodules leading to alteration of the hepatic vascular liver architecture and reduction of its functional mass **[1,2]**. Cirrhosis is a dynamic process that needs to be monitored regularly to prevent progression and\or reverse fibrosis **[3]**.

Insulin-like growth factor 1(IGF-1) is a 70-aminoacidic anabolic hormone, which has many endocrine, autocrine and paracrine functions **[4]**. IGF-1 is mainly produced by the liver (accounting for 75% of circulating IGF-1), but almost any tissue can secrete IGF-1 for autocrine/paracrine function **[5]**. IGF-1 can be assessed in the blood in 10-1000 ng/ml amount. Normal range values have been reported by percentiles for specific age groups **[6]**. Pituitary GH and liver derived IGF-1 have a negative feedback mechanism **[7]**.

Liver cirrhosis is accompanied by a low level of IGF-1 and more decrease of IGF-1 level with disease progression. In cirrhotic patients, IGF-1 level would be decreased as there is a decrease in growth hormone receptors and a decrease in hepatocytes leading to reduced IGF-1 production while growth hormone would be increased **[8]**. This study aimed to evaluate serum Insulin-Like Growth Factor-1 (IGF-1) levels and its association with the severity of liver disease in patients with liver cirrhosis.

PATIENTS AND METHODS

The study was approved by the Ethics and Research Committee of the Benha Faculty of Medicine, Benha University, Egypt. Serum samples were collected from 85 patients with liver cirrhosis admitted to the Department of Hepatology, Gastroenterology and Infectious Diseases, Benha University Hospital and Department of Hepatology, Gastroenterology and Infectious Diseases, Kafr Elshikh Hospital from October 2017 to May 2018. An informed written consent was taken from all cases before their involvement in the study. Cirrhosis was diagnosed by clinical, laboratory and abdominal ultrasonography, which may reveal (surface nodularity, coarse echopattern of the liver, rarefied hepatic central vein, enlarged caudate lobe, ascites, splenomegaly and collateralls) according to Obrador et al., **[9]**. Patients with advanced encephalopathy, chronic renal diseases, hepatorenal syndrome, gastrointestinal bleeding, recent infection, history of malignancy and diabetes mellitus were excluded. Patients' clinical data, including age, sex, viral markers (HCV-Ab and HBsAg), biochemical liver profile were recorded. Liver disease severity was evaluated by the modified Child-Pugh score **[10]**, MELD (model for end-stage liver disease) score **[11]** and the updated MELD (uMELD) score **[12]**. Upper gastrointestinal endoscopy was done using upper gastrointestinal video scope (OLYMPUS Evis EXERAΠ CLV-180, Tokyo, Japan) after good preparation of the patient.

Blood sampling and biochemical assays:

Fasting venous blood samples (10 ml) were collected. A portion of blood was allowed to clot and centrifuged with 3500 grams for 5 min in order to isolate the serum used for the measurement of aspartate aminotransferase (AST), alanine-aminotransferase (ALT), alkaline phosphatase, total bilirubin, direct bilirubin, albumin, creatinine and glucose levels. HCV- Ab and HBsAg were assessed. Measurement of IGF-l 600 ELISA using Mybiosource kits (MyBioSource, Inc., San Diego, CA 92195-3308, USA). All measurements were performed according to the instructions of the manufacturer.

Statistical Analysis:

The sample size was calculated based on past review of literatures estimated the mean difference of serum Insulin-like growth factor-1 (IGF-1) to achieve the power 80% and confidence interval 95%. The required sample was calculated using Open Epi, version 3, open source calculator-SSMean print.The statistical analysis was conducted using STATA/SE version 11.2 for Windows (STATA corporation, College Station, Texas).The collected data were summarized in terms of mean± standard deviation (SD) and range for quantitative data and frequency and percentage for qualitative data. Comparisons between the different study groups were done using Student t-test (t) was, to detect the difference in the mean between two parametric data, while use one- way analysis of variance (ANOVA; F) for comparison of more than two groups. For determining the correlation between IGF-1 and estimated parameters as appropriate Pearson correlation coefficient (r) and Spearman correlation coefficient (rho; ρ) were done . Analysis of receiver operating characteristics (ROC) was conducted to evaluate the diagnostic performance of IGF-1 levels for liver disease severity in patients with cirrhosis.

Estimation of the best cutoff point and the corresponding sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and area under the curve (AUC) was carried out. Statistical significance was set at P value <0.05 and P value <0.001 was considered highly significant.

RESULTS

Table (1) showed the characteristics of the study patients whose mean age was 45.25±5.88 Ys (ranging from 34-60 Ys). Regarding the severity of liver disease, 70.59% of patients were Child C, 16.47% were Child B and 12.94% were Child A. Most of the patients showed advanced values of both MELD and uMELD scores. The mean value of IGF-1 in cirrhotic patients was 201.22 ng/dl.

The level of IGF-1 was significantly decreased in Child C cirrhotic patients than patients with Child B and Child A. Also, The level of IGF-1 was significantly lower in cirrhotic patients with MELD score > 17 and uMELD > 4.18. Moreover, IGF-1 was decreased in ascitic patients and patients with oesophageal varices, gastric varices and portal hypertensive gastropathy with a statistically highly significant difference as shown in table (2).

Table (3) showed that there was a statistically significant correlation between IGF-1 and Child's score, MELD, uMELD, portal vein diameter and esophageal varices.

Table (1): Characteristics of the studied patients:

Variable	Group	No.	%
Gender	Males	45	52.94
	Females	40	47.06
Age (years)	Mean ±SD; (range) 45.25±5.88; (34-60)		
Occupation	Farmers	43	50.59
Residence	Rural	43	50.59
	Urban	42	49.41
HCV Ab	Positive	80	94.1
HBs Ag	Positive	5	5.9
Child's classification	Child A	11	12.94
	Child B	14	16.47
	Child C	60	70.59
MELD score	Mean ±SD 19.60±6.32		
uMELD	Mean ±SD 4.02±0.76		
IGF-1 (ng/dl)	Mean ±SD 201.22±90.96		
Upper endoscopic findings	Esophageal varices	58	68.24
	Gastric varices	28	32.94
	portal hypertensive gastropathy	58	68.24

HCV: Hepatitis C virus antibodies, HBsAg: Hepatitis B surface antigen, MELD:Model for end- stage liver disease, uMELD: Updated MELD, IGF-1: insulin growth factor-1, SD: standard deviation.

Table (2): Variation of IGF-1 and some parameters:

Variable		IGF-1					T	P
		No.	Mean	±SD	Min.	Max.		
Child's classification	Child A	11	249.82	49.11	125	349		
	Child B	14	123.5	41.35	72	195		
	Child C	60	35.09	7.74	29	52		
MELD	<17	42	241.24	55.66	76	349	4.43	<0.001
	>17	43	162.14	101.77	29	325		
uMELD	< 4.18	55	248.89	48.58	125	345	9.28	<0.01
	> 4.18	30	113.83	85.79	29	349		
Ascites	Ascites	59	95.15	65.98	29	270	11.31	<0.001
	No ascites	26	247.97	53.29	76	349		
Esophageal varices	E.V	58	101.81	73.38	29	275	10.33	<0.001
	No E.V	27	247.5	53.63	76	349		
Gastric varices	Yes	28	117.38	79.67	29	272	8.16	<0.001
	No	57	244.64	61.47	32	349		
portal hypertensive gastropathy	Yes	58	101.81	73.38	29	275	10.33	<0.001
	No	27	247.5	53.63	76	349		

MELD:Model for end- stage liver disease, uMELD: Updated MELD, IGF-1: insulin growth factor-1, E.V:Esophageal varices.

Table (3): Correlation between IGF-1 and some parameters:

Variable (No.=85)	Correlation coefficient	P
Child score	r= -0.82	<0.001
MELD score	r= -0.76	<0.001
uMELD	r= -0.83	<0.001
Portal vein diameter (mm)	r= -0.65	<0.001
Esophageal varices	r= -0.70	<0.001

Table (4): ROC analysis for IGF-1 as a marker for severe liver disease in patients with cirrhosis according to Child's score:

	cutoff point	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Area under the curve (AUC)
IGF-1 (ng/dl)	69.5	88%	99%	88%	95%	0.9840

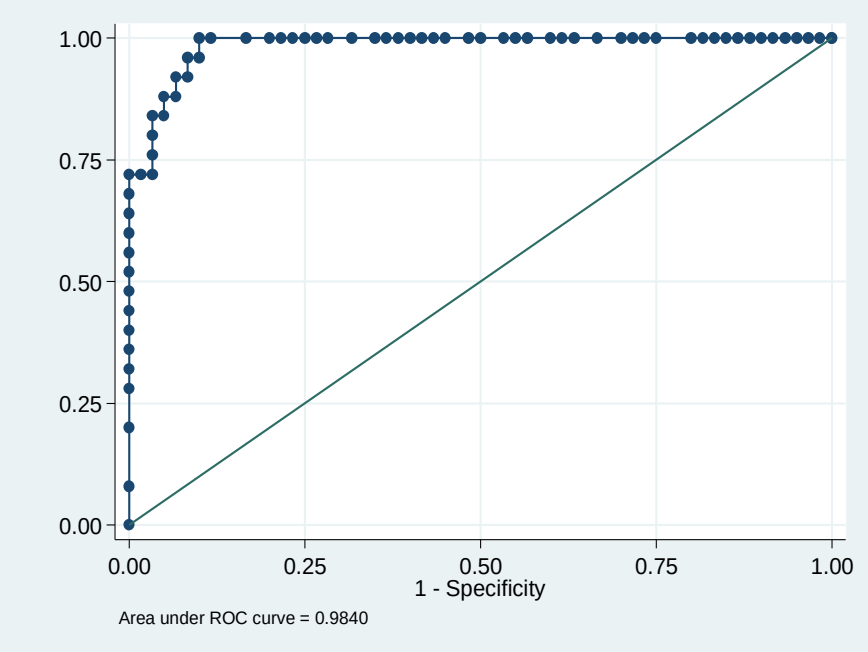

Fig. (1): ROC analysis for IGF-1 as a marker for severe liver disease in patients with cirrhosis according to Child score (Child C & B versus Child A).

Table (5): ROC analysis for IGF-1 as a marker for severe liver disease in patients with cirrhosis according to (MELD score > median;17):

	cutoff point	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Area under the curve (AUC)
IGF-1 (ng/dl)	196	60.47%	88.10%	68.5%	83.9%	0.7046

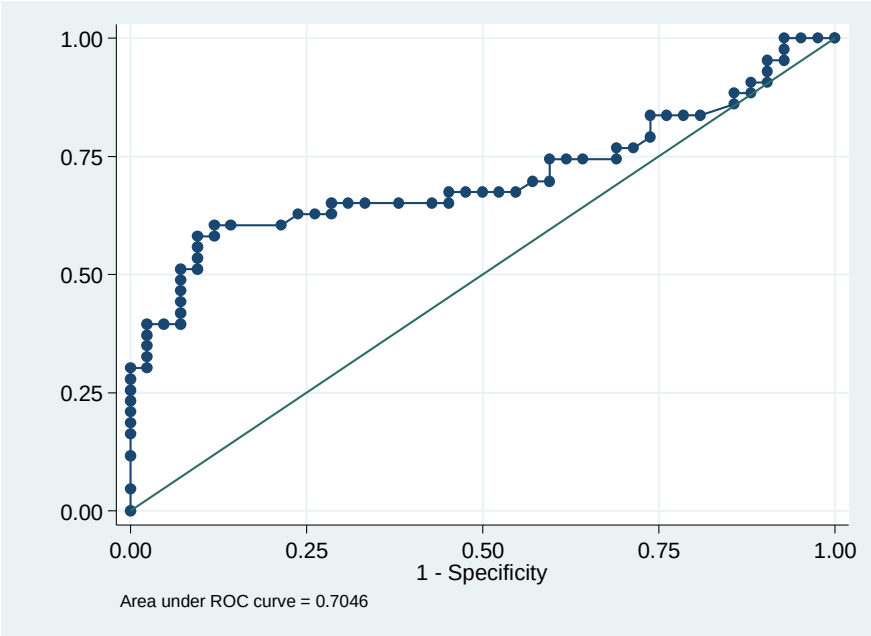

Fig. (2): ROC analysis for IGF-1 as a marker for severe, moderate liver disease in patients with cirrhosis according to (MELD score > median;17).

Table (6): ROC analysis for IGF-1 as a marker for severe liver disease in patients with cirrhosis according to (uMELD score > median;4.18):

	cutoff point	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Area under the curve (AUC)
IGF-1 (ng/dl)	196	83.33%	89.09%	90.74%	80.6%	0.8991

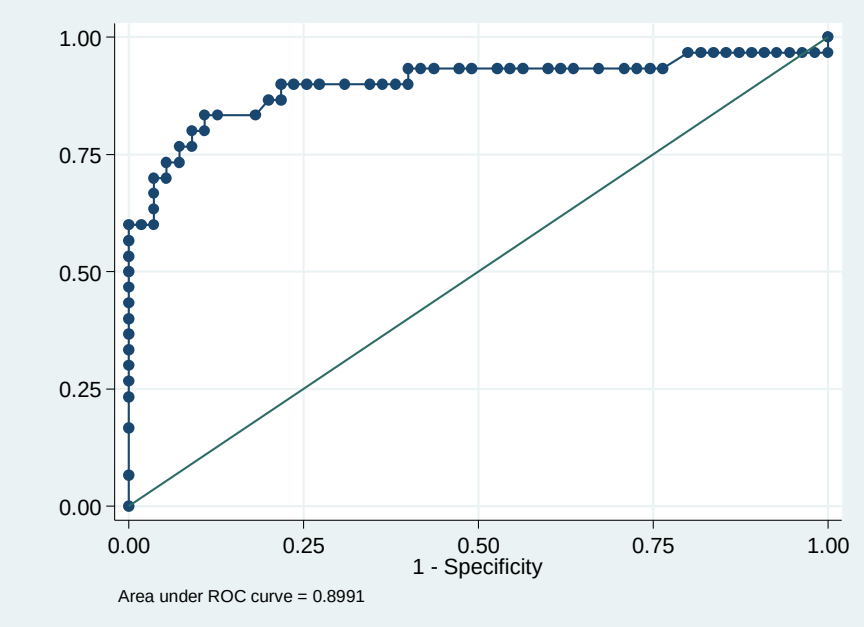

Fig. (3): ROC analysis for IGF-1 as a marker for severe liver disease in patients with cirrhosis according to uMELD score (uMELD score > median;4.18).

DISCUSSION

Liver cirrhosis (LC) is the end stage of chronic liver disease and it is associated with multiple complications as gastrointestinal bleeding, ascites, hepatic encephalopathy, spontaneous bacterial peritonitis, hepatorenal syndrome, hepatopulmonary syndrome, hepatocellular carcinoma and increase mortality **[13]**.

Insulin-like growth factor-1 (IGF-1) is a polypeptide, which has some structural similarities with the insulin molecule and has autocrine, endocrine, paracrine effects **[14]**. IGF-1 is secreted by many tissues. Most of IGF-1 is secreted by the liver and is transported to other tissues **[5]** .

In this study, the mean value of Insulin-like Growth Factor 1 (IGF-1) in studied patients was 201.22 ng/dl, these results were in agreement with Khoshnood et al. **[15]** who reported that IGF-1 was 190 ng/dl in cirrhotic patients, as liver cirrhosis is associated with a decrease in IGF-1 level and progression of the disease, while growth hormone would be elevated. In cirrhosis the growth hormone receptors decreased and also, there is a decrease in hepatocytes which leads to a progressive reduction in IGF-1 production.

IGF-1 level was significantly decreased in cirrhotic patients with ascites, rather than those without ascites. These results were in agreement with Correa et al. **[16]** who found that the level of IGF-1 had an inverse relation to the degree of ascites.

In this study, IGF-1 level was significantly decreased in cirrhotic patients with esophageal varices in comparison to patients without esophageal varices results may be due to the fact that with the progression of cirrhosis, IGF-1 significantly decreased as stated by Friedrich et al.**[17]** .

IGF-1 level was significantly lower in patients with Child C and Child B than Child A, this came in agreement with Helaly et al.**[18]** who found that Child B and C patients showed a significant reduction of insulin-like growth factor-1 levels in comparison to Child A patients

IGF-1 level was significantly decreased in cirrhotic patients, with mean MELD score 17, these findings were in agreement with Wu et al. **[19]** who stated that IGF-1 significantly decreased with the high MELD score in cirrhotic patients, this may be explained by the fact that most of the included patients in this study presented in late stage.

IGF-1 level was significantly lower in cirrhotic patients, with mean uMELD score 4.18, these results were in agreement with Wu et al. **[19]** who reported that IGF-1 significantly decreased with high uMELD score in patients with liver cirrhosis, this may be explained by the fact that most of the included cases in this study presented in late stage.

There was a significant negative correlation between IGF-1 and the Child, MELD and uMELD scores in this study which came in agreement with Ronsoni et al. **[20]** who found that there was an inverse relationship between IGF-1 and the MELD and uMELD and Child-Pugh score.

The ROC analysis IGF-1 as marker of severe liver disease in patients with cirrhosis according to Child's classification, a cutoff value of 69.5 µg/ml gives optimum balance between sensitivity, specificity, the sensitivity was 88%, specificity 99%, positive predictive value (PPV) was 88%, negative predictive value (NPV) was 95%, area under the curve was 0.9840 denoting good prediction of IGF-1 in prediction of severe liver cirrhosis.

This came in agreement with Weber et al.**[21]** who stated that at a cutoff value of 66.7 ng/ml, the sensitivity and specificity of IGF-1 in patients with decompensated cirrhosis were 86% and 95%, respectively.

The ROC analysis for IGF-1 as marker of severe liver disease in patients with cirrhosis according to MELD score, (MELD score > median;17) cutoff value of 196 µg/ml gives optimum balance between sensitivity, specificity, the sensitivity was 60.47%, specificity 88.10%, PPV was 68.5%, NPV was 83.9%, AUC was 0.7046 denoting good prediction of IGF1 in prediction of severe liver cirrhosis.

This came in agreement with Rincon et al. **[22]** who found that at a cutoff value of 190 ng/ml, the sensitivity and specificity of IGF-1 in decompensated cirrhotic patients were 58% and 86% respectively.

The ROC analysis for IGF-1 as marker of sever liver disease in patients with cirrhosis according to uMELD score, (uMELD score > median;4.18) a cutoff value of 196 µg/ml gives optimum balance between sensitivity, specificity, the

sensitivity was 83.33%, specificity 89.09%, PPV was 90.47%, NPV was 80.6%, AUC was 0.8991 denoting good prediction of IGF-1 in prediction of severe liver cirrhosis.

In conclusion, IGF-1 is negatively correlated with the severity of liver disease in patients with cirrhosis assessed by Child, MELD and uMELD scores and it could be used to assess the severity of the disease. Moreover, IGF-1 could differentiate early from advanced disease in patients with cirrhosis.

Acknowledgment: We would thank all colleagues who helped us in conducting this work.

Funding: None

Conflict of interest: None

Author contribution: All authors shared in conception of the idea, searching the literature, drafting the manuscript and all approved the final manuscript.

Ethical Approval: A written informed consent was taken from all included patients, and the study was approved by the Ethical Committee of our institution.

REFERENCES

1. Anthony PP, Ishak KG, Nayak NC, Poulsen HE, Scheuer PJ, Sobin LH. The morphology of cirrhosis: definition, nomenclature, and classification. *Bull World Health Organ* 1977; 55(4):521-540.
2. Schuppan D, Afdhal NH. Liver cirrhosis. *Lancet* 2008; 371(9615): 838-851.
3. Hytiroglou P, Snover DC, Alves V, Balabaud C, Bhathal PS, Bioulac-Sage P, et al. Beyond 'cirrhosis': a proposal from the International Liver Pathology Study Group. *Am J Clin Pathol* 2012 Jan; 137(1):5-9.
4. Le Roith D. Insulin-Like Growth Factors. *N Engl J Med* 1997; 336: 633-640.
5. Lapierre LR, Hansen M. Lessons from C. elegans: signaling pathways for longevity. *Trends Endocrinol Metab*. 2012; 23 (12): 637–44.
6. Friedrich N, Alte D, Volzke H, Spilcke-Liss E, Ludemann J, Lerch MM, et al. Reference ranges of serum IGF-1 and IGFBP-3 levels in a general adult population: results of the Study of Health in Pomerania (SHIP). *Growth Horm IGF Res* 2008; 18(3): 228-37.
7. de la Garza RG, Morales-Garza LA, Martin-Estal I, Castilla-Cortazar I. Insulin-Like Growth Factor-1 Deficiency and Cirrhosis Establishment. *J Clin Med Res* 2017 Apr; 9(4):233-247.
8. Girnita L, Worrall C.; Takahashi S, Seregard S, Girnita A. Something old, something new and something borrowed: emerging paradigm of insulin-like growth factor type 1 receptor (IGF-1R) signaling regulation. *Cellular and Molecular Life Sciences* 2013; 71 (13): 2403–27.
9. Obrador BD, Prades MG, Gómez MV, Domingo JP, Cueto RB, Rué M, Real J, Guiteras PM. A predictive index for the diagnosis of cirrhosis in hepatitis C based on clinical, laboratory, and ultrasound findings. *Eur J Gastroenterol Hepatol* 2006 Jan;18(1):57-62.
10. Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. *Br J Surg* 1973; 60 (8): 646-9.
11. Kamath PS, Wiesner RH, Malinchoc M, Kremers W, Therneau TM, Kosberg CL, et al. A model to predict survival in patients with end-stage liver disease. *Hepatology* 2001; 33(2):464–70.
12. Sharma P, Schaubel DE, Sima CS, Merion RM, Lok AS. Re-weighting the model for end-stage liver disease score components. *Gastroenterology* 2008; 135(5): 1575-1581.
13. Jensen, DM. Endoscopic screening for varices in cirrhosis: findings, implications, and outcomes. *Gastroenterology* 2002; 122(6):1620- 1630.
14. Giustina, A, Chanson P, Kleinberg, D, Bronstein MD, Clemmons DR, Klibanski, A, et al. Expert consensus document: A consensus on the medical treatment of acromegaly. *Nat Rev Endocrinol* 2014; 10 (4): 243–8.
15. Khoshnood A, Nasiri Toosi M, Faravash MJ, Esteghamati A, Froutan H, Ghofrani H, et al. A survey of correlation between insulin-like growth factor-I (IGF-1) levels and severity of liver cirrhosis. *Hepatitis monthly* 2013; 13(2): e6181.
16. Correa CG, Colombo Bda S, Ronsoni MF, Soares E Silva PE, Fayad L, Silva TE, et al. Circulating insulin-like growth factor binding protein 3 as prognostic biomarker in liver cirrhosis. *World J Hepatol* 2016 Jun 18; 8(17): 739–748.
17. Friedrich N, Alte L, Volzke H, Spilcke-Liss E, Ludemann J, Lerch MM, et al. Reference ranges of serum IGF-1 and IGFBP-3 levels in a general adult population: results of the Study of Health

in Pomerania. (SHIP). *Growth Horm IGF Res* 2008; 18(3): 228-37.

18. Helaly GF, Hussein NG, Refai W, Ibrahim M. Relation of serum insulin-like growth factor-1 (IGF-1) levels with hepatitis C virus infection and insulin resistance. *Transl Res* 2011; 8(3): 155-62.
19. Wu YL, Ye J, Zhang S, Zhong J, Xi RP. Clinical significance of serum IGF-I, IGF-II and IGFBP-3 in liver cirrhosis. *World J Gastroenterol* 2004;10(18):2740-2743.
20. Ronsoni MF, Lazzarotto C, Fayad L, Silva MC, Nogueira CL, Bazzo ML, et al. IGF-I and IGFBP-3 serum levels in patients hospitalized for complications of liver cirrhosis. *Ann Hepatol* 2013; May-Jun;12(3):456-63.
21. Weber MM, Auernhammer CJ, Lee DK, Zachoval R. Insulin-like growth factors and insulin-like growth factor binding protein in adult patients with sever liver disease before and after orthotopic liver transplantation. *Hormon Research*. 2002;(3-4):105-112.
22. Rincon M, Rudin E, Barazilia N. Insulin-like growth factor I signaling in mammals and its relevance to human longevity. *Experimental Gerontology* 2005; 40(11):873-877.