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Correlation of Insulin-like Growth Factor-1 Level with Severity of Liver Disease in Patients with Cirrhosis

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ABSTRACT

Introduction: Serum Insulin-like Growth Factor-1 level decreases in cirrhosis due to reduced growth hormone receptors in hepatocytes and lowered hepatocyte synthesis ability. The purpose of this study was to investigate the correlation between Insulin-like Growth Factor-1 level and severity of liver disease in patients with cirrhosis. **Materials and methods:** The present descriptive cross-sectional study includes patients with cirrhosis who referred to the Department of Gastroenterology, Shahid Mohammadi Hospital, Bandarabbas, Iran. Liver disease and cirrhosis were diagnosed by a gastroenterologist on the basis of biopsy or clinical criteria. The International Normalized Ratio, Prothrombin Time, Alkaline Phosphatase, Alanine Aminotransferase, Aspartate Aminotransferase, Complete Blood Count, Albumin, Bilirubin, Creatinine, Blood Urea Nitrogen, Thyroid Stimulating Hormone and Insulin-like Growth Factor-1 tests were performed for all patients. A radiologist performed liver and spleen ultrasound and ascites examinations, and a gastroenterologist performed an endoscopy to examine esophageal varices. Data were analyzed by SPSS 21 software. **Results:** This study consisted of 101 patients with mean age of 52.11 ± 11.27 years. The most common etiology of cirrhosis was reported to be hepatitis C (36.1%). Splenomegaly and esophageal varices were reported in 97% and 86.1% of the patients, respectively. Moreover, 22.8% and 7.9% of the patients had moderate ascites and severe ascites, respectively. Mean duration of disease was 12.24±3.72 years. The mean Child, mean model for end-stage liver disease, and mean Insulin-like Growth Factor-1 scores were 6.64±1.76, 17.55±3.10, and 93.51±18.05, respectively. Spearman correlation coefficient was -0.472 between Child score and Insulin-like Growth Factor-1 (P<0.001) and -0.367 between model for end-stage liver disease score and Insulin-like Growth Factor-1 (P<0.001). The mean Insulin-like Growth Factor-1 level in the three classes of Child were compared with each other, and there was a significant difference between the three groups (P<0.001). **Conclusion:** Serum Insulin-like Growth Factor-1 level is an index to determine the severity of liver disease in patients with cirrhosis that is inversely correlated with disease severity criteria, namely Child and model for end-stage liver disease, suggesting that lower the serum Insulin-like Growth Factor-1 level, greater the severity of the involvement.

INTRODUCTION

Cirrhosis is a progressive liver fibrosis characterized by impaired hepatic structure. In advanced stages, cirrhosis is associated with high mortality, and liver transplantation may be the only treatment option. One consequence of liver disease is change in growth hormone axis and Insulin-like Growth Factor-1 (IGF-1) (1). IGF-1 is produced by various tissues to stimulate growth hormone, but the liver is a major source of IGF-1 production (2, 3). Patients with cirrhosis experience a wide range of metabolic problems, such as insulin resistance, malnutrition, osteopenia, and hypogonadism, which are associated with IGF-1 deficiency (4). This factor plays a very important role in growth, development, and metabolism, especially in the fetus, childhood, and adolescence wherein it stimulates the metabolism of amino acids andcarbohydrates, increases muscle mass, and improves bone mineral density (1). In cirrhosis, IGF-1 level decreases while growth hormone (GH) level increases. IGF-1 depletion in cirrhosis follows two mechanisms: decrease

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in growth hormone receptors and in production due to decrease in hepatocytes. Increased growth hormone is associated with decreased inhibitory effect of IGF-1 on the hypothalamus or pituitary gland. Failure of hepatocytes to respond to growth hormones in Child Class C represents an increased IGF-1 response of <10% compared with an increased response of >20% in normal population (5, 6) . A study investigated the antioxidant effect of IGF-1 in rat sample at advanced stage of cirrhosis and reported that a protective and antifibrotic effect of IGF-1 on the liver (7). Another study examined the correlation between IGF-1 and the severity of liver disease using the model for end-stage liver disease (MELD) and Child criteria and found that this factor is a predictor of the severity of liver cirrhosis when liver biopsy is impossible (6), whereas Castro reported a negative correlation between IGF-1 and MELD. Given that the severity of liver disease in cirrhotic patients is very important in controlling a patient's condition and therapeutic measures and that research has been conducted in this field, this study was performed to investigate the correlation between IGF-1 level and the severity of liver disease in patients with cirrhosis.

MATERIALS AND METHODS

Study design

The present descriptive cross-sectional study was conducted on 10–85-years-old 101 patients with cirrhosis who were referred to the Department of Gastroenterology, Shahid Mohammadi Hospital, Bandarabbas, Iran, in 2017 and diagnosed with liver disease and cirrhosis by biopsy or clinical criteria by a gastroenterologist. The patients with encephalopathy, hepatorenal syndrome, infection in previous week, diabetes, chronic kidney disease, hypothyroidism, gastrointestinal bleeding, and malignancy were excluded.

Initially, all patients were checked for International Normalized Ratio (INR), Prothrombin Time (PT), Alkaline Phosphatase (ALP), Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), Complete Blood Count (CBC), Albumin (Alb), Bilirubin (Bili), Creatinine (Cr), Blood Urea Nitrogen (BUN), Thyroid Stimulating Hormone (TSH), and IGF-1 tests. Blood samples were taken from all patients in fasting conditions (8–9 AM), and all tests were performed in the laboratory of Shahid Mohammadi Hospital. A radiologist performed liver and spleen ultrasound and ascites examinations, and a gastroenterologist performed an endoscopy to examine esophageal varices. Further, the patients were classified into A, B, and C groups according to Child–Pugh Classification criteria (Table 1). MELD score was also calculated for the patients using the following equation:

$$MELD = 0.975 \times \log [Cr(mg/dl)] + 0.378 \times \log [Billi\ (mg/dl)] + 1.12 \times \log (INR) + 0.634$$

IGF-1 level was measured by radioimmunoassay. There was no need to include controls for normal IGF-1 levels in the population by age, which was included in the relevant kit instructions. Based on total scores, 5 and 6 were scored by Class A; 7–8, by Class B; and higher, by Class C.

The MELD score was calculated by the free of charge software presented by myoclonic on the Internet (www.myoclinic.org). Written informed consent was obtained from all individuals.

Study design

The data were analyzed by SPSS version 21 software using descriptive statistics, such as frequency, percentage, percentile, mean, and standard deviation and also by Kruskal–Wallis test, post hoc test, and Spearman correlation coefficient. $P \leq 0.05$ was considered statistically significant.

RESULTS

Data obtained were evaluated and statistically analyzed. Total 61 patients were male (60.4%) and 40 were female (39.6%). The mean age of the patients was 52.11 ± 11.27 years, and the mean duration of disease was 12.24 ± 3.72 years.

The most common causes of cirrhosis were hepatitis C (36.1%), hepatitis B (23.7%), and nonalcoholic steatohepatitis (NASH) (15.5%) (Table 2).

Splenomegaly was reported in 97% (n= 98) and esophageal varices in 86.1% (n= 87) of the patients. Concerning ascites, 70 patients (69.3%) did not report ascites, 23 patients (22.8%) reported moderate ascites, and 8 patients (7.9%) had severe ascites.

Albumin, bilirubin, and PT Child scores were calculated; frequency of each score is reported in Table 3.

The mean Child score for the subjects was 6.64 ± 1.76. Moreover, the mean MELD score in patients was 17.5 ± 3.10. The mean IGF-1 level was 93.51 ± 18.05 ng/dl (Table 4).

Based on the Child score, the subjects were divided into three classes: A, B, and C. According to this score, 56 patients (58.9%) were in class A, 32 patients (23.7%) in class B, and 7 patients (7.4%) in class C.

Spearman correlation coefficient of -0.472 was calculated between Child score and IGF-1 level, which indicatedd that there was statistically significant inverse correlation between the two mentioned variables ($P< 0.001$). Spearman correlation coefficient of -0.367 was measured between MELD score and IGF-1, which showed statistically significant inverse correlation between the two variables ($P< 0.001$).

The mean IGF-1 levels were compared in the three Child classes, resulting in a statistically significant difference between the three groups ($P < 0.001$). The relevant information is reported in Table 5.

The correlation between mean IGF-1 level and gender was examined. Mean IGF-1 level was 93.49 ± 19.07 in males and 93.55 ± 16.66 in females; this difference was not statistically significant ($P= 0.873$). This mean did not correlate statistically with cirrhosis ($P= 0.333$).

This mean was correlated with ascites 87.16 ± 15.00 in severe ascites group, 102.30 ± 14.57 in moderate ascites group, and 123.87 ± 7.53 in no ascites group. There was a statistically significant difference between the three groups ($P< 0.001$). In pairwise comparison, there was no statistically significant difference between the groups with moderate ascites and no ascites ($P= 0.081$). The mean IGF-1 level in the group with esophageal varices was significantly lower ($P= 0.008$) than that in the group without esophageal varices. The mean IGF-1 level in the group with score 3 of bilirubin was significantly lower ($P< 0.001$) than that in the group with

score 1 of bilirubin. The mean IGF-1 level in the group with score 3 of PT was significantly lower ($P< 0.001$) than that in the group with score 1 of PT. There was no statistically significant difference between mean IGF-1 in albumin score groups ($P= 0.130$). The information is reported in Table 6.

DISCUSSION

In the present study, the male population was nearly 1.5 times larger than the female population, which was consistent with the studies of Khoshnood (6) and Assy (8). In the studies of Correa (1), Kaseb (9), Ronsoni (10), and Colombo (11), male population was nearly 70%–73% of female population, which is nearly 10% larger than the male population in the present study. In a study of Colakoglu, male population was nearly 1.6 times larger than female population (12) . According to the study, it can be stated that the majority of population (1.5–2 times more) of cirrhotic patients comprises males.

In this study, in terms of underlying etiology of liver disease, the three most common causes were hepatitis C (36.1%), hepatitis B (23.7%), and NASH (15.5%). In the study of Khoshnood (6), conducted between 2007 and 2008 at Imam Khomeini Hospital of Tehran, three common causes were hepatitis B (25%), autoimmune hepatitis (AIH) (25%), and hepatitis C (22%) . The percentage of hepatitis B was relatively similar between the two studies, but the reason for nearly 14% higher rate of hepatitis C in the present study can be attributed to nearly 10-year difference between the two studies, the lower mean age in the study of Khoshnood (6) (nearly 8 years), and different geographical conditions between Tehran and Bandarabbas. In the present study, the incidence rate of AIH was 2.8%, whereas that in the study of Khoshnood was 25%. In the studies of Correa (1), conducted nearly 3 years before the present study at the Federal University Hospital of Santa Catarina, one of the southern states of Brazil, hepatitis C and B were 36.2% and 4.3% in out-of-hospital group and 41.3% and 4.2% in hospitalized group, respectively. The reported percentage of hepatitis C in out-of-hospital patients in the study of Correa is similar to that in the present study, but the percentage of hepatitis B was much lower percentage in their study than in the present study. Nearly 9–17 years ago, Kaseb reported that 13.2% of patients had hepatitis B and 20.8% had hepatitis C (9) , which is in line with the present study. In the study of Castro, hepatitis C and B were found in 36% and 8% of patients with cirrhosis, respectively (13). In the study of Colombo, between 2011 and 2013, the underlying cause of the disease was hepatitis C in 40.8% and hepatitis B in 3.9% of patients (11).

In the present study, splenomegaly was reported in 98 patients (97%) and esophageal varices in 87 patients (86.1%). In terms of ascites, 70 patients (69.3%) did not report ascites, 23 patients (22.8%) had moderate ascites, and 8 patients (7.9%) reported severe ascites. In the study of Khoshnood, the prevalence of esophageal varices was 66%; moderate ascites, 66%; severe ascites, 16% (total of 82%); and splenomegaly, 87% (6). The prevalence of splenomegaly was higher than that of esophageal varices. In the study of Correa, the ascites was 20.3% in an out-of-hospital group and 48.7% in a hospitalized group (1) . In the study of Colombo, the ascites was present in 44.7% of patients (11). Ronsoni reported that the rate of ascites in patients was 45.9% (10). It seems that about 30%–50% ascites is present in outpatients with cirrhosis.

In the present study, the mean Child score in the study population was 6.64 ± 1.76. Moreover, the mean MELD score in patients was 17.55 ± 3.10, and the mean IGF-1 level was 93.51 ± 18.05 ng/dl. In the study of Khoshnood, the mean IGF-1 level was reported to be 92.95 ± 91.51 (6), which is similar to the mean value obtained in the present study. In the study of Correa, the mean MELD score was 9.84 ± 2.28 in an out-of-hospital group and 16.32 ± 6.53 in a hospitalized group (1). In the study of Castro, the mean MELD score was reported to be 18.1 ± 4.1 (13) , which is similar to the results of the present study. In the studies of Colombo (11) and Ronsoni (10), the MELD score was 15.7 ± 6.16 and 16.07 ± 6.98, respectively.

In the present study, 58.9% of patients were in class A based on Child score; the lowest value (7.4%) belonged to Class C. The results of the studies conducted by Correa (1) and Kaseb (9) were consistent with those of our study. However, most patients were in Class B in other studies (6, 8, 10, 11).

In the present study, the analysis of Spearman correlation coefficient between Child and MELD scores exhibited an inverse correlation with IGF-1, i.e., IGF-1 level decreased with increasing Child and MELD scores ($P< 0.001$). The correlation of Child score with IGF-1 level was relatively stronger than that of MELD and IGF-1 scores (-0.472 is stronger than -0.367). In the study of Khoshnood, the correlation of MELD and Child scores with IGF-1 level was reported to be -0.317 and -0.478 ($P= 0.001$), respectively (6). The correlation between the severity of disease and IGF-1 levels in the two studies, especially the correlation between the Child and IGF-1 scores, is similar. In the study conducted by Dehghani (14), the correlation between IGF-1 level was negative with Child score (r= -0.333, $P= 0.025$) and MELD score (r= -0.222, $P= 0.033$). The correlation pattern and higher correlation strength in the correlation between IGF-1 level and Child score are consistent with the present study; however, some correlations are weaker; the main difference with the present study is related to the mean age as Dehghani studied patients younger than 18 years. In the study of Ronsoni (10), the correlation between IGF-1 level was negative with Child score (I= -0.408, $P< 0.001$) and MELD score (I= -0.388, $P= 0.001$), which is similar to the pattern obtained in the present study. According to the study, IGF-1 levels are correlated with the severity of liver disease, and this correlation is stronger based on the rating of the Child–Pugh Classification System, and because the correlation is inverse, it can be said that lower the IGF-1 level, greater the severity of the disease and greater the duration of disease.

In the present study, the mean IGF-1 level decreased with increasing Child class, so that there was a statistically significant difference between each class and higher class ($P< 0.05$). In the study of khoshnood, the mean IGF-1 level was 167.43 ± 121 ng/ml in Class A, 64.65 ± 45.13 in Class B, and 57.61 ± 52.9 in Class C, which had statistically significant difference ($P< 0.001$) (6). In the study of Kaseb

(9), the mean IGF-1 level was 59.05 ± 38.62 in Class A, 42.49 ± 32.60 in Class B, and 35.77 ± 37.38 in Class C, with a statistically significant difference (*P*= 0.0021). In the study by Colaglu, IGF-1 level was 207 ± 97 in Class A, 180±84 in Class B, and 152 ± 63 in Class C. Comparison of Class A with C exhibited a statistically significant difference (*P*= 0.001), but there was no statistically significant difference between Classes A and B (*P*= 0.554) as well as between Classes B and C (*P*= 0.554) (12). Similarly, in the study of Dehghani, the serum IGF-1 levels were 5.90 ± 0.54 in Class A, 3.02 ± 0.25 in Class B, and 2.78 ± 0.16 in Class C. There was a statistically significant difference between Classes A and B (*P*= 0.047) as well as Classes A and C (P= 0.36), but Class B had no statistically significant difference with Class C (*P*= 0.986) (14). In the present study, the Child Class B with C had a statistically significant difference in IGF-1 levels. According to the evaluations, such as correlations, it was suggested that the level of IGF-1 decreases with increasing severity of involvement (i.e., with increasing Child class).

CONCLUSION

According to the findings from the present study, it can be concluded that the serum IGF-1 level is an index to determine the severity of liver disease in patients with cirrhosis and it is inversely correlated with disease severity criteria, namely, Child and MELD scores, suggesting that lower the serum IGF-1 level, greater the severity of disease.

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AUTHOR CONTRIBUTIONS

All authors contributed equally in this case and manuscript.

CONFLICT OF INTERESTS

None

ETHICAL STANDARDS

This study has been approved at Hormozgan University of Medical Sciences

Table 1. Child–Pugh Classification scores

Parameters	Scores		
	1	**2**	**3**
Albumin	>3–3.5 g/dl	3–3.5 g/dl	<3 g/dl
Bilirubin	<2 mg/dl	2-3 mg/dl	>3 mg/dl
Prothrombin Time	<15 seconds	15 to 17 seconds	>17 seconds
Ascites	No	Mild to moderate	Severe and resistance to treatment
Encephalopathy	No	Mild	Moderate to severe

Table 2. Report of qualitative characteristics for the studied patients

Variables	Subgroups	Frequency	Percentage
Etiology of Cirrhosis	Hepatitis C	35	36.1
	Hepatitis B	23	23.7
	NASH	15	15.5
	PSC	13	13.4
	AIH	8	8.2
	PBS	1	1
	Hemochromatosis	1	1

Abbreviations;
NASH: Non-alcoholic Steatohepatitis, PSC: Primary Sclerosing Cholangitis, AIH: Autoimmune hepatitis, PBS: Primary Biliary Cholangitis

Table 3. Frequency of scores for albumin, bilirubin and Prothrombin Time

Statistics	Albumin			Bilirubin			Prothrombin Time		
	>3.5	3-3.5	<3	<2	2-3	>3	<15	15-17	>17
Score	1	2	3	1	2	3	1	2	3
Frequency	40	51	10	79	13	6	68	22	5
Percentage	39.6	50.5	9.9	80.6	13.3	6.1	71.6	23.2	5.3

Table 4. Evaluation of Model for End-stage Liver Disease, Child and Insulin-like Growth Factor-1 scores

Variables	Mean	SD	MIN	MAX	Percentiles					
					5th	25th First Quarter	50th Mid	75th Third Quarter	95th	99th
Child score	6.64	1.76	5.00	13.00	5.00	5.00	6.00	7.00	10.00	13.00
MELD score	17.55	3.10	11.91	37.39	13.86	15.88	16.99	18.79	20.01	37.39
IGF-1	93.51	18.05	52	132	62.00	85	93	105	123	131

Abbreviations;
MELD: Model for End-stage Liver Disease, IGF-1: Insulin-like Growth Factor-1, SD: Standard Deviation, MIN: Minimum, MAX: Maximum

Table 5. Antibiogram obtained and their resistance or susceptibility to the samples observed in the serotype K2

Child classes	IGF-1 levels		Kruskal–Wallis test results	*P*	Pairwise comparison	*P*
	Mean	SD				
C	87.05	14.34	24.771	<0.001	C-B	0.005
B	97.91	19.33			A-C	<0.001
A	120.86	9.58			B-A	0.030

Abbreviations;
IGF-1: Insulin-like Growth Factor-1, SD: Standard Deviation

Table 6. Correlation of IGF-1 level with gender, etiology of cirrhosis, ascites, esophageal varices, and albumin, bilirubin, and PT scores

Variables	Subgroups	IGF-1 level		P	Pairwise comparison	P
		Mean	SD			
Gender	Male	93.49	19.07	0.873	-	-
	Female	93.55	16.60		-	-
etiology of cirrhosis	Hepatitis C	99.29	16.85	0.333	-	-
	Hepatitis B	91.09	17.73		-	-
	PSC	82.31	14.02		-	-
	PBC	91.00	-		-	-
	AIH	83.25	12.42		-	-
	NASH	95.27	22.73		-	-
	Hemochromatosis	102.00	-		-	-
Ascites	Severe	87.16	15.00	<0.001	Severe to moderate	<0.001
	Moderate	102.30	14.57		No with severe	<0.001
	No	123.87	7.53		Medium with no	0.081
esophageal varices	No	95.41	17.62	0.008	-	-
	Yes	81.71	16.67		-	-
Bilirubin score	3	90.10	16.89	<0.001	2-3	0.136
	2	100.00	17.74		3-1	0.001
	1	118.50	9.97		1-2	0.185
	3	89.43	16.20	<0.001	2-3	0.104

Prothrombin Time score	2	97.73	18.87		3-1	0.001
	1	124.60	7.44		1-2	0.040
Albumin score	3	89.35	16.77	0.130	-	-
	2	96.96	16.5		-	-
	1	92.60	27.10		-	-

Abbreviations;
IGF-1: Insulin-like Growth Factor-1, NASH: Non-alcoholic Steatohepatitis, PSC: Primary Sclerosing Cholangitis, AIH: Autoimmune hepatitis, PBS: Primary Biliary Cholangitis

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