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Combined CTP-IGF-1 Score: A New Score for Assessment of Disease Severity in Patients With HCV- Related Liver Cirrhosis

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ABSTRACT

Background: Liver is the largest endocrine organ in the body. It is the key organ in insulin mediated metabolism, growth hormone and insulin like growth factors (IGF) pathway. Liver cirrhosis is the end result of many chronic diseases including hepatitis C virus infection. Child-Turcotte-Pugh (CTP) score is the standard used in assessment of hepatic reserve but it has its drawbacks in the form of subjective variables, hepatic encephalopathy and ascites.

Objective: The work aimed to assess IGF-1 in patients with liver cirrhosis and its correlation with CTP score and to assess the value of modified combined CTP-IGF-1 score.

Patients and methods: This was a case-control study that enrolled 170 patients with chronic liver disease (CLD) and 72 healthy controls. CLD (liver cirrhosis) in the study group was caused by chronic hepatitis C virus (HCV) infection. Liver cirrhosis was identified by clinical assessment, abdominal ultrasonography (US), and laboratory assessment.

Results: IGF1 showed highly significant low values in the study group compared to controls (42.15 ± 27.976 and 66.31 ± 33.084 ng/ml respectively, p <0.001). The combined CTP-IGF-1 score in comparison with the classic CTP score showed improved area under curve (0.848 and 0.854), sensitivity (71.2% and 88%), negative predictive value (41.7% and 53.7%), false negative results (49 and 19) and accuracy (75.73% and 83.98%) but decreased specificity (97.22% and 61.1%), positive predictive value (99.2% and 91.5%) and higher false positive results (1 and 14) respectively.

Conclusion: IGF-1 showed progressive decrements with progression of liver cirrhosis and is negatively correlated with CTP score. Addition of IGF-1 to CTP score to formulate combined score improves the AUC, negative predictive value, sensitivity, and the accuracy of CTP score and decreases the false negative results.

Keywords: IGF-1, Child, Turcotte-Pugh, Liver cirrhosis.

INTRODUCTION

Liver is the main metabolic organ in the body, involved in glucose, lipid and hormone metabolism. Liver is the largest endocrine organ in the body and it is a key organ in insulin-mediated metabolism and insulin like growth factors (IGFs) pathway including insulin like growth factors-1, 2 (IGF-1, 2), and their binding proteins (IGFBPs) [1, 2].

In mammals, IGF-1 is related to post-natal growth mediated by growth hormone and IGF-2 is related to stimulation of foetal and placental growths that are less dependent on growth hormone [3]. Growth factors produced in the liver, including IGF-1 and IGF-2, affect hepatocytes proliferation, differentiation and apoptosis [4].

Liver cirrhosis is the end result of many chronic liver diseases (CLD) including alcoholic liver diseases, chronic viral hepatitis, and non-alcoholic fatty liver disease. Liver cirrhosis is characterized by replacement of liver tissue by fibrotic tissue, necrosis and regenerating nodules [5, 6].

Liver cirrhosis is associated with IGF pathway changes that result in progressive hepatocellular function deterioration [5]. Patients with chronic liver disease show reductions in hepatic response to growth hormone resulting in elevated growth hormone levels and decreased IGFs levels. This leads to clinical features of IGF1 deficiency [6, 7].

Negative correlations between IGF1 and International Normalization Ratio (INR) [8], Model for End stage Liver Disease (MELD) score [8] and splenic size [9] was reported, and correlation was positive with serum albumin levels [8, 9].

Reduced IGF1 levels were reported in cases with hepatocellular carcinoma (HCC) compared to cirrhotic and healthy controls [10]. The Child-Turcotte-Pugh (CTP) score is the main score used to assess the hepatic reserve, overall survival and treatment outcomes in patients with CLD [11, 12].

The work aimed to assess IGF1 levels in patients with liver cirrhosis in comparison with healthy controls and to correlate IGF1 levels with CTP score in those patients.

PATIENTS AND METHODS

This is a case-control study that enrolled 170 patients with CLD and 72 healthy controls. CLD (liver cirrhosis) in the study group was caused by chronic hepatitis C virus (HCV) infection. Liver cirrhosis was identified by clinical assessment, abdominal ultrasonography (US), and laboratory assessment.

All subjects in the study were assessed by a thorough history and clinical examination, including residency (urban or rural), smoking history, history of chronic diseases including diabetes mellitus and hypertension, history of previous surgical or dental procedures, and history of anti-bilharzial treatment. Laboratory investigations included CBC, INR, ALT, AST, serum albumin, serum bilirubin, serum creatinine, alpha-fetoprotein and random blood glucose.

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IGF-1 assessment

(3-5 mL) samples from peripheral venous blood were collected. The samples were anticoagulated through addition of ethylene diamine tetraacetic acid (EDTA) then centrifuged at 4°C for 15 minutes at 3000 RPM. Plasma was then extracted from the samples, aliquoted, and snap-frozen at –20 °C until analysis. According to the manufacturer's instructions (Quantikine Human IGF-1 ELISA Kit; R & D Systems, Minneapolis, MN), an enzyme-linked immunosorbent assay (ELISA) was used to test IGF-1. In the MD Anderson validation cohort, plasma IGF-1 levels were measured at a Clinical Laboratory Improvement Amendments (CLIA)–certified facility using the Luminex microsphere technology by Myriad Laboratories (Austin, Texas).

CTP and combined CTP-IGF-1 scores were calculated using the parameters shown in table 1 and 2 respectively stratified as class A (5-6), B (7-9) or C (10-15) [13].

Ethical consent: An approval of the study was obtained from Mansoura University Academic and Ethical Committee. Every patient signed an informed written consent for acceptance of participation in the study. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis

The statistical analysis of the data was performed using excel (Microsoft office 2013) program and SPSS (Statistical Package for Social Science) program (SPSS, Inc., Chicago, IL) version 20. The normality of the data was assessed using Kolmogorov-Smirnov test. Qualitative data were presented as frequency and percentage while quantitative data were presented as median and range, mean and standard deviation. Chi square test was used to compare groups. For comparison between two groups, independent T test (for parametric data) was used. Mann-Whitney test (for non-parametric data) was used. The ROC Curve (receiver operating characteristic) provides a useful way to evaluate the sensitivity and specificity for quantitative diagnostic measures that categorize cases into one of two groups.

RESULTS

This study included 170 patients with chronic HCV-related liver cirrhosis and 72 healthy controls. According to CTP score. The patients were classified as 93 A, 57 B and 20 C. The demographic data of the study group compared to the controls showed that there was no significant difference between both groups regarding residency, occupation, smoking history, hypertension history and surgical or dental procedures.

The age of the study group was older than the controls (controls 49.50 ± 10.961 vs 56.96 ± 6.813 years study group years, $p < 0.001$) and most of the cases were males (controls 50.0%, study group 72.9%, p= 0.007). Diabetes mellitus (controls 0.0%, study group 28.2%, $p < 0.001$) and history of anti-bilharzial treatment (controls 30.6% oral and 5.6% injection, while study group 51.8% oral and 29.4% injection, $p < 0.001$) were significantly higher in the study group compared to controls (Table 1).

Table (1): Demographic characteristics and medical history of the studied patients

		Control group (n= 72)	Study group (n= 170)	95% CI	p
Age (years)		49.50 ± 10.961	53.96 ± 6.813	- 19.3, - 11.6	0.061
Gender	**Male**	50.0% (36)	72.9% (124)	0.05, 0.41	**0.007**
	Female	50.0% (36)	27.1% (46)		
Residency	**Rural**	94.4% (68)	97.1% (165)	-0.05, 0.11	0.608
	Urban	5.6% (4)	2.9% (5)		
Occupation	**Employee**	13.9% (10)	25.9% (44)	-	0.131
	Housewife	41.7% (30)	27.1% (46)		
	Manual worker	44.4% (32)	47.1% (80)		
Smoking	**No**	66.7% (48)	70.4% (119)	-	0.835
	Smoker	27.8% (20)	26.0% (44)		
	Ex-smoker	5.6% (4)	3.6% (6)		
History of DM		0% (0)	28.2% (48)	0.22, 0.35	**< 0.001**
History of HTN		8.3% (6)	14.1% (24)	-0.05, 0.16	0.428
History of Operation		44.4% (28)	53.5% (91)	-0.03, 0.32	0.322
History of Dental		72.2% (52)	75.3% (128)	-0.13, 0.19	0.700
History of Anti-bilharzial	**None**	63.9% (46)	18.8% (32)	-	**< 0.001**
	Oral	30.6% (22)	51.8% (88)		
	Injection	5.6% (4)	29.4% (50)		

Data were expressed as mean and standard deviation or as percentage and frequency. 95% CI: 95% confidence interval of the mean difference between both groups. P is significant when ≤ 0.05.

Regarding the laboratory investigations of the study group compared to controls, IGF-1 showed highly significant low values in the study group compared to controls (42.15 27.976 and 66.31 33.084 ng/ml, respectively, p 0.001). Other laboratory investigations showed significantly lower haemoglobin (12.25 ± 1.792, 13.32 ± 1.649 gm/dl, p 0.001), platelets (115.12 ± 66.981, 215.19 ± 60.221 $10^3/mm^3$, p value <0.001), serum albumin (3.26 ± 0.615, 4.37 ± 0.458 gm/dl, p <0.001) in the study group compared to control respectively and significantly higher white blood cells (6.38 ± 12.816, 6.13 ± 1.816 $10^3/mm^3$, p 0.015), random blood glucose (127.08 ± 54.142, 97.97 ± 14.812 mg/dl, p 0.001), AST (74.51 ± 39.585, 50.03 ± 31.661 IU/l, 0 <0.001), serum bilirubin (1.88 ± 1.679, 0.78 ± 0.247 µmol/l, p <0.001), INR (1.25 ± 0.220, 1.07 ± 0.095, p <0.001) and alpha fetoprotein (356.34 ± 1093.41, 4.85 ± 6.04 ng/ml, p <0.001) in the study group compared to control respectively (Table 2).

Table (2): Laboratory investigations of the studied patients in comparison to controls

	Control group (n= 72)	Study group (n= 170)	95% CI	P
Hb (g/dL)	13.32 ± 1.649	12.25 ± 1.792	0.45, 1.68	**0.001**
WBCs (mcL)	6.13 ± 1.816	6.38 ± 1.816	-2.29, 1.77	**0.015**
Platelets (mcL)	215.19 ± 6.221	115.12 ± 6.981	77.47, 122.67	**< 0.001**
Creatinine (mg)	0.84 ± 0.117	0.96 ± 0.35	-0.21, -0.03	0.064
RBS (mg/dL)	97.97 ± 14.812	127.08 ± 5.142	-38.80, -19.41	**0.001**
IGF1 (ng/ml)	66.31 ± 3.084	42.15 ± 7.976	12.24, 36.06	**< 0.001**
ALT (U/L)	58.40 ± 5.082	55.88 ± 3.115	-14.98, 20.02	0.291
AST (U/L)	50.03 ± 3.661	74.51 ±9.585	-36.69, -12.29	**< 0.001**
Albumin (g/L)	4.37 ± 0.458	3.26 ± 0.615	0.94, 1.30	**< 0.001**
Bilirubin (µmol/L)	0.78 ± 0.14	1.88 ± 0.27	-1.36, -0.83	**< 0.001**
INR	1.07 ± 0.095	1.25 ± 0.220	-0.23, -0.13	**< 0.001**
AFP (ng/mL)	4.85 ± .04	356.34 ± 19.41	-517.05, -185.93	**< 0.001**

Data were expressed as mean and standard deviation or as percentage and frequency. 95% CI: 95% confidence interval of the mean difference between both groups. P is significant when ≤ 0.05, Hb: hemoglobin, WBCs: white blood cells, RBS: random blood sugar, IGF1: insulin like growth factor 1, ALT: alanine transaminase, AST: aspartate transaminase, INR: international normalized ratio, AFP: alpha feto protein.

Assessment of the levels of IGF-1 in relation to CTP score in the study group showed that IGF1 levels were 48.32 ± 28.611, 40.28 ± 25.869 and 18.80 ± 15.953 ng/ml in relation to CTP score groups A, B and C respectively (p value < 0.001) (Table 3).

Table (3): Assessment of IGF-1 levels in study group based on CTP score groups

	CTP A (n= 93)	CTP B (n= 57)	CTP C (n= 20)	P
IGF1 (ng/ml)	48.32 ± 8.611	40.28 ± 5.869	18.80 ± 5.953	**< 0.001**

Data were expressed as mean and standard deviation. P is significant when ≤ 0.05, CTP: Child Turcot Pugh score, IGF1: insulin like growth factor-1

Correlation between IGF-1 and CTP score in the study group using Spearman correlation coefficient revealed that there was highly significant negative correlation between IGF-1 and CTP score in the study group (p < 0.001) (Table 4).

Table (4): Correlation between IGF-1 and CTP score

	Spearman correlation coefficient	P
IGF-1 and CTP score	-0.318	**< 0.001**

P is significant when ≤ 0.05, IGF1: insulin like growth factor-1, CTP: Child Turcot Pugh score

Comparison of IGF-1, CTP score and combined CTP-IGF-1 score in differentiating normal liver in one hand from liver cirrhosis in the other hand showed that the area under the curve was 0.718, 0.848 and 0.854, and the diagnostic point was 55.5 ng/ml, 5.5 and 4.5, sensitivity of 71.2%, 72.2% and 88.8%, specificity of 61.1%, 97.22% and 91.5%, negative predictive value of 31.0%, 41.7% and 53.7%, and accuracy of 69.42%, 75.73% and 83.98% for IGF-1, CTP-IGF-1 score respectively (Table 5).

Table (5): Comparison between IGF-1, CTP score and their combination in evaluation of liver cirrhosis

	IGF-1	CTP score	Combined
Area Under Curve	0.718	0.848	0.854
Diagnostic point	55.50	5.5	4.5
Sensitivity	71.2%	71.2%	88.8%
Specificity	61.1%	97.22%	61.1%
Positive Predictive Value	89.6%	99.2%	91.5%
Negative Predictive Value	31.0%	41.7%	53.7%
False positive	14	1	14
False negative	49	49	19
Accuracy	69.42%	75.73%	83.98%

IGF1: Insulin like growth factor-1, CTP: Child Turcot Pugh Score

DISCUSSION

Liver cirrhosis with or without the development of HCC are the end results of many CLD including non-alcoholic fatty liver diseases, chronic viral hepatitis, alcoholic liver diseases and autoimmune liver diseases [5, 6]. In Egypt, hepatitis C virus (HCV) infection is a major health problem and anti-HCV antibodies were found to be positive in about 20% of Egyptian blood donors [14-15]. IGF system abnormalities were found in patients with liver cirrhosis. These abnormalities include growth hormone resistance and IGF-1 deficiencies with many metabolic abnormalities as a result [5].

In the present study, we enrolled 170 patients with HCV-related cirrhosis and 72 healthy controls. In comparison to the control group, most of the study group were males, which is related to the nature of the disease being is more prevalent in males. Also, because the rate of HCV progression is slower in women, the rate of disease-related complications is higher in men [15, 16]. In the study group, the history of diabetes mellitus was significantly higher (p 0.001) in the study group compared to control. It was found that the risk of DM was four times higher in adults with HCV than in those without HCV [17]. HCV is linked to insulin resistance that is reported to show some improvement after HCV elimination [18, 19]. A previous Egyptian study that included 396 chronic HCV infection patients found that a history of injectable anti-Bilharzial treatment was found in 32.3% of cases [20]. The current study showed that positive anti-bilharzial treatment is significantly higher in the study group compared to the control. Anti-Bilharzial treatment may be linked to a risk of HCV infection through the parenteral route.

In our study, serum IGF-1 levels were found to be significantly (p value 0.001, 95% CI 12.24, 36.06) lower in cases with HCV-related liver cirrhosis in comparison with normal controls (42.15 27.976 and 66.31 33.084 ng/ml, respectively). Similar results are found by **Vyzantiadis and colleagues** [21], who studied 40 patients with liver cirrhosis due to different etiologies and found that serum IGF-1 levels were significantly lower in cases with liver cirrhosis in comparison with 20 controls (57.4 7.0 ng/mL and 198.8 16.3 ng/mL, respectively, p = 0.0000001).

Raslan *et al.* [22] studied 30 patients with chronic HCV infection (19 with cirrhosis) and 11 healthy controls and found that patients with liver cirrhosis had significantly lower IGF-1 levels (p value 0.001). The numbers of both cases and controls in these studies were low, and some of them had mixed etiologies of liver cirrhosis. Low serum IGF-1 levels in patients with liver cirrhosis may be related to the impaired synthetic function of the liver with progressive deterioration with disease progression. Also, growth hormone receptors were found to show lower expression in the hepatic tissue of these patients [23, 24]. Interestingly, we found that serum IGF-1 levels showed progressive reduction with the progression of liver cirrhosis, indicated by higher CTP scores. Our study included 93 CTP A, 57 CTP B, and 20 CTP C patients with serum IGF-1 levels of 48.32 ± 28.611, 40.28 ± 25.869, and 18.80 ± 15.953 ng/ml, respectively (p value 0.001). A highly significant negative correlation (-0.318, p value 0.001) was found between serum IGF-1 levels and CTP scores in our study group.

Ronsoni and colleagues [25] found that serum IGF-1 levels were negatively correlated with CTP score and MELD score in 74 patients with liver cirrhosis and significantly lower values of serum IGF-1 were observed in patients with higher CTP classes (P 0.05). **Vyzantiadis and colleagues** [21] found that serum IGF-1 levels were significantly lower in cases with liver cirrhosis CTP B and C in comparison with cirrhotic with CTP A. Interestingly, comparison of the cases with CTP A (n = 26) in their study showed that there was no significant difference between viral and non-viral cirrhosis regarding serum IGF-1 levels, indicating that the cause of liver cirrhosis has a limited role and it is the stage of cirrhosis and CTP score that significantly affect serum IGF-1 levels. Another study found that there was a statistically non-significant negative correlation between HCV viral load and serum IGF-1 levels [26]. Also, another study revealed that serum IGF-1 levels show progressive decrement with liver cirrhosis progression, namely higher CTP scores [27]. Of importance, **Castro and colleagues** [28] found that serum IGF-1 levels returned to normal 6 months after orthotopic liver transplantation. These data suggest that progression of liver cirrhosis is associated with a decrement in serum IGF-1 levels, probably due to progressive deterioration of hepatic synthetic functions and may be related to growth hormone insensitivity. These abnormalities may be corrected after liver transplantation.

Although CTP score has its drawbacks in the form of incorporation of two variables that are subjective, namely hepatic encephalopathy and ascites, it has been used for decades as the staging and prognostic method for cases of liver cirrhosis [29, 30]. This led to the development of ideas of processing of new scores that can avoid or at least decrease the effect of these subjective variables, hepatic encephalopathy and ascites. In our study, comparison of serum IGF-1, CTP score and combined CTP-IGF-1 score in differentiating normal liver from liver cirrhosis showed that the addition of serum IGF-1 to CTP score in the form of combined score led to improved diagnostic profile of the classical CTP score in the form of improved AUC (0.848 and 0.854), sensitivity (71.2% and 88.8%), negative predictive value (41.7% and 53.7%), false negative results (49 and 19) and accuracy (75.73% and 83.98%) for CTP score and combined CTP-IGF-1 score respectively, but with some drawbacks in the form of reduced specificity (97.22% and 61.1%), positive predictive value (99.2% and 91.5%) and false positive results (1 and 14) for CTP score and combined CTP-IGF-1 score respectively.

CONCLUSION

IGF-1 showed progressive decrements with the progression of liver cirrhosis and is negatively correlated with the CTP score. The addition of IGF-1 to the CTP score to formulate a combined score improved the AUC, sensitivity, negative predictive value, and accuracy of the CTP score and decreased the false negative results.

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Author contribution: Authors contributed equally in the study.

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