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The Crucial Prognostic Role of Serum Cholinesterase in Detecting Liver Disease

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Abstract Liver diseases are considered as the foremost cause of morbidity and mortality around the world, especially in developing countries and classified into acute and chronic liver disease. Further, hepatocytes synthesize the cholinesterase (ChE) and enhances their catalysis through hydrolysis mechanism of the acetylcholine to into choline and acetic acid. This study aims to give a comprehensive account of the vital prognostic and diagnostic marker role of cholinesterase of liver cirrhosis over other known liver function tests (LFTs) like ALT, AST, serum albumin and serum bilirubin. **Subjects and methods:** this study was conducted on 60 livers cirrhotic Egyptian patients, divided into three groups according to their Child-Pugh score and 30 healthy volunteers as a control group. Serum biomarkers for the liver disease were measured (cholinesterase, AST, ALT, Serum Albumin, Serum Bilirubin) in parallel with an abdominal ultrasound examination was made for all participants. **The results:** There was a highly significant decrease in serum cholinesterase levels in all patient groups diagnosed with liver cirrhosis compared to control and more in decompensated patients. **Conclusion:** the present study concluded that the blood cholinesterase can be used as an imaging profile for the degree of liver damage and prognostic level of cirrhosis.

Keywords Liver function tests, Liver cirrhosis, Cholinesterase

1. Introduction

Liver cirrhosis is considered as a noteworthy reason for death worldwide and a particular prickly national issue in Egypt [1]. In developed countries, regular reasons for cirrhosis, including, chronic viral hepatitis B, C [2]. Moreover, hepatitis C, alcoholic and nonalcoholic liver diseases have been considered the most well-known reasons for cirrhosis in the United States and were considered as the fundamental driver for roughly 80 percent of patients of the liver transplantation shortlist somewhere in the range of 2004 and 2013 [3]. Furthermore, individuals share needles for infusing medications and human services laborers or crisis specialists who might be presented to sullied blood are most defenseless and dependably in danger for contracting and spreading hepatitis C in risk for liver cirrhosis [4]. Patients with decompensated cirrhosis develop many serious and life-threatening symptoms and complications with early manifestations of rapid cirrhosis such as fatigue, loss of appetite, weight loss, nausea or abdominal pain and spider navi may develop on the skin [5].

Besides, late phases of cirrhosis improve the progress to a decompensated phase with the development of edema, ascites, Jaundice, Itching (pruritus) developed from the development of bile items, Palmar erythema; in men gynecomastia, or shrinkage of the testicles, simple wounding and excessive bleeding may happen [6]. Patient with liver cirrhosis can be classified according to child score into child A, B and C. Moreover, the Child-Pugh score is still one of the important prevailed prognostic evaluation models for the chronic liver diseases ranging from light damage to cirrhosis that can be used in selecting the treatment quality. Moreover, it was considered as the most indicator of death in spite of the nonappearance of ascites, encephalopathy, and jaundice in the patients with compensated cirrhosis indicating that even subtle abnormalities in laboratory parameters are predictive of death [7]. The Pugh change of the Child-Turcotte characterization utilizes two clinical factors, ascites and encephalopathy, and three laboratory parameters such as serum bilirubin, albumin levels and prothrombin time as in table 1. Every factor is allotted a score from 1 to 3; with the total aggregate score figuring out the CTP score [8].

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Table (1). Proposal of a Modified Child-Turcotte-Pugh Scoring System (8)

	1 point	2 point	3 point	4 point
Original CTP*				
Bilirubin (mg/ dl)	< 2	2-3	>3	
Albumin (g/dl)	> 3.5	2.8- 3.5	< 2.8	
PT prolong (sec)	< 4	4-6	> 6	
Ascites	None	Easily controlled	Poorly controlled	
Encephalopathy	None	Grade 1-2	Grade 3-4	
Modified CTP†				
Bilirubin (mg/ dl)	< 2	2-3	3.1-8	> 8
Albumin (g/dl)	> 3.5	2.8-3.5	2.3-2.7	<2.3
PT prolong (sec)	< 4	4-6	6-11	> 11
Ascites	None	Easily controlled	Poorly controlled	-
Encephalopathy	None	Grade 1-2	Grade 3-4	-

* Original CTP class: A. 5-6 point; B. 7-9 points; C. 10-15 points.

† Modified CTP class: A. 5-6 points; B. 7-9 points; C. 10-15 points; D. 16-18 points

Additionally, the two-fundamental cholinesterase, acetyl-cholinesterase (AChE) and butyryl-cholinesterase (BuChE) differ in their substrates and secretions were inhibited by specific particular inhibitors. In human, for long periods the reduction in serum secretion of BuChE has been correlated to the degree of chronic liver diseases progress [9]. However, the occasional varied secreted levels of AChE in human serum; it has been thought that, it can be used to testify its function in the detection of liver functions. Meng et al., [10] expressed that serum cholinesterase is outstandingly downregulated in patients with liver dysfunction. While normal serum compounds related to the clinical evaluation of liver capacity uncovering noteworthy unregulated in their secretion because of upgrading release because of cellular damage.

Moreover, butryl cholinesterase has a vital role in reflecting the hepatic dysfunction due to its specificity in place secretion; its variations in secretion can be used in early diagnosis of liver cirrhosis and metastases. Additionally, Lampón et al., [11] stated that low plasma BChE levels have also been detected in protein malnutrition acute and chronic diseases, liver damage, obstructive jaundice [11].

Moreover, Garello et al., [12] proposed that estimation of the cholinesterase levels was used to prefigure Parenchymal cirrhosis patients survival rate, graft-*vs*-host outcomes prediction [13], differentiate between liver disease and non-liver disease aberration differentiation [14], and discriminate cirrhosis from non-cirrhosis [15]. Besides, cholinesterase levels have been controlled among patients with enhancement in hepatic capacity [9] at a rate surpassing recover from organophosphate poisoning.

The objective of this study is to assess the recital activity of cholinesterase in predicting liver dysfunction compared to the current common liver function tests and association with scoring models in patients with liver cirrhosis.

2. Subjects and Methods

This study is a case-control study. A total of 60 cirrhotic Egyptian patients with cirrhotic liver, age and sex were matched. The samples were classified as follows: 28 males (46.7%) and 32 females (53.3%) and their ages ranged from (42-59) years with mean±SD (50.45±3.92). All cases were admitted to the internal medicine department at El Zahraa University Hospital from November 2016 to September 2017. 30 apparently healthy volunteers were included in the study as a control group as follows: 15 males (50%) and 15 females (50%) and their ages ranged from (41-57) with mean ±SD (49.2± 4.38) years.

Ethical consideration:

All study participants' have stated oral consent before their enrollment in the study.

Exclusion criteria: the present investigation has utilized some avoidance criteria that will restrain patients portrayed with one of them to be denied from the enrollments, for example, age under 18 years, history of albumin or blood transfusion a month earlier the enrollment, pregnant female, and a history of liver neoplasm or transplantation.

Inclusion criteria for the study were: full history and clinical evaluation, laboratory investigations, including (Complete blood count (CBC) using Sysmex, KN21, liver enzymes (alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, direct bilirubin, serum albumin), Kidney function tests (urea, creatinine), and Na & K. All of them were carried out using Cobas 311 clinical chemistry autoanalyzer, ROCH diagnostic company, Coagulation profile and Serum cholinesterase and abdominal ultrasonography.

Sample collection and storage:

Seven ml of venous blood was collected under complete aseptic technique conditions from patients and control in a sterile vacutainer tube. 1ml has been collected on Ethylenediaminetetraacetic acid (EDTA) solution for complete blood picture., 3ml was used in plain tube and left to clot followed by centrifuged at 2000×g for 10 minutes for serum separation, 2ml of blood was collected on citrate and centrifuged at 2000×g for 5 minutes for plasma separation to be used for PT, PC, and INR estimation. Routine biochemical investigations for liver and kidney have been measured almost immediately. The activity of serum cholinesterase was assessed with 2h of sample separation depending upon the reduction assay of the butyrylthiocholine substrate according to the Boehringer reagent kit protocol (Boehringer Mannheim GmbH, Mannheim, Germany) on an Olympus AU5400 Automatic Analyzer (Olympus Ltd., Tokyo, Japan).

Statistical analysis

SPSS software for Windows (ver. 20.0; SPSS, Chicago, IL, USA) was used for the statistical analysis of database management. Descriptive results were expressed as the mean ± standard deviation (SD). The unpaired t-test was carried out to compare the mean ±SD between every 2 groups and ANOVA to assess the differences between more groups. Additionally, the comparison of cholinesterase, albumin, and serum prothrombin times between the different groups has been calculated using the Pearson correction test. The statistically significant difference was assessed with P<0.05.

3. Results

The present study included a total of 28 male and 32 female patients with a mean age of (50.45±3.92 years). The patient's basic demographic, laboratory analysis and endoscopic structures are summarized in Table 2. Moreover, Child-Pugh score for cirrhosis patients classified them to Child A group with 15 (25%), Child B with 20 (33.3%) and Child C groups in 25 (41.6%) as shown in table 2.

Additionally, there was a highly statistically significant difference in ALT AST, albumin, bilirubin in all groups in comparison to control P<0.001 as shown in table 3.

Table (2). Comparison among all studied groups according to demographic data

	Groups					
	Child A	Child B	Child C	Control	Tests	
					f/X^2	P-value
Sex						
Female	5(33.3%)	13(65.0%)	14(56.0%)	15(50.0%)	3.656	0.301 N S
Male	10(66.7%)	7(35.0%)	11(44.0%)	15(50.0%)		
Age						
Range	45-58	42-56	43-59	41-57	2.184	0.096 NS
Mean±SD 50.66±3.38	50.9±3.64	51.64±4.49	49.2±4.38			

Table (3). Comparison among all groups as regards to liver function test

	Child A		Child B		Child C		Control		ANOVA	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	F	P-value
ALT(IU)	33.47	9.26	48.85	36.63	49.24	20.11	14.77	2.19	16.649	<0.001 HS
Control & Child	0.026 S		<0.001 HS		<0.001 HS					
AST(IU)	40.13	14.86	53.95	24.07	80.24	34.30	23.40	2.33	30.848	<0.001 HS
Control & Child	0.089		<0.001 HS		<0.001 HS					
S. Albumin (g/dl)	3.81	0.46	2.83	0.56	2.56	0.37	4.72	0.14	169.727	<0.001 HS
Control & Child	<0.001 HS		<0.001 HS		<0.001 HS					
T s.bilirubin (mg/dl)	1.00	0.56	2.27	1.66	3.31	1.21	0.81	0.17	30.753	<0.001 HS
Control & Child	0.941		<0.001 HS		<0.001 HS					
D.bilirubin (mg/dl)	0.49	0.28	1.32	1.23	1.83	0.74	0.39	0.14	22.519	<0.001 HS
Control & Child	0.971		<0.001 HS		<0.001 HS					

Table (4). Comparison between Serum Cholinesterase in all groups and control and in each group

Groups	S Cholinesterase						ANOVA	
	Range			Mean	±	SD	F	P-value
Child A	2112	-	4650	3084.33	±	867.52	322.667	<0.001 HS
Child B	1360	-	1960	1603.50	±	197.50		
Child C	390	-	1155	891.28	±	200.87		
Control	4950	-	9775	6281.00	±	1007.54		

Tukey's test					
Control & A	**Control & B**	**Control & C**	**A & B**	**A & C**	**B & C**
<0.001 HS	<0.001 HS	<0.001 HS	<0.001 HS	<0.001 HS	<0.001 H S

Table (5). Comparison between serum cholinesterase in all patients and control

	S Cholinesterase			T-test	
	N	Mean	SD	T	P-value
Patients	60	1676.95	987.18	20.716	<0.001 HS
Control	30	6281.00	1007.54		

On one side, the results of serum cholinesterase comparison between all cirrhotic liver patients and healthy control patients showed a statistically highly significant difference P<0.001 as shown in table 4, 5 and figure 1.

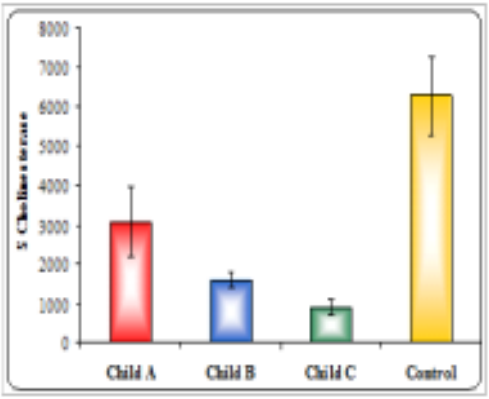

Figure 1. Comparison between Serum cholinesterase in all groups

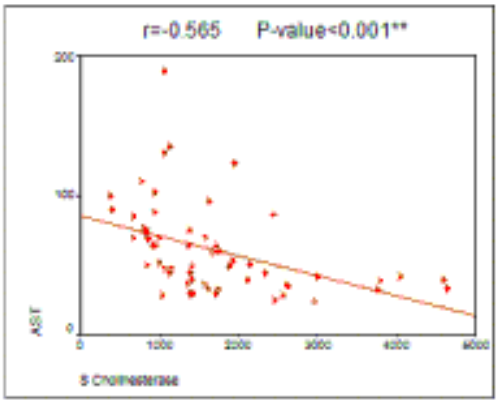

Figure (2). Correlation between serum cholinesterase and AST

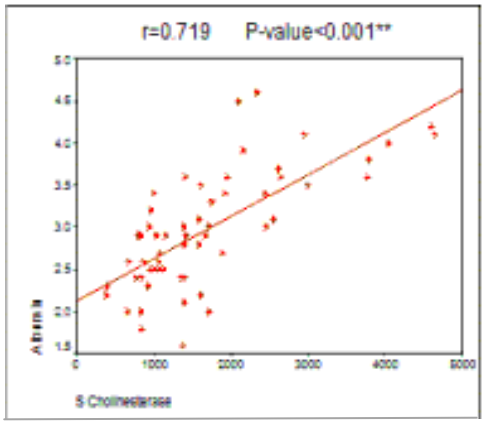

Figure (3). Correlation between Albumin and serum cholinesterase

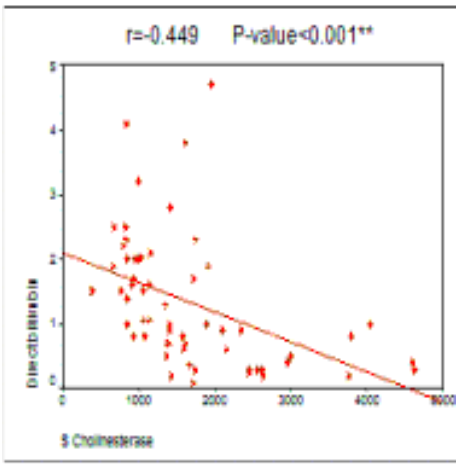

Figure (4). Correlation between Total bilirubin and serum cholinesterase

On the other side, there was a highly significant negative correlation between serum cholinesterase and AST, T. bilirubin, D. bilirubin, (r= -0.445), (r= -0.512), (r=-0.449), with highly significant positive correlation with serum Albumin (r= 0.719), (p<0.001), **(Fig 2, 3, 4)**.

4. Discussion

Cholinesterases are a group of enzymes that habitually considered in relationship with numerous pathological mechanisms. As acetyl-cholinesterase (AChE) is the enzyme responsible for the inactivation of cholinergic neurotransmission and its up-regulation was considered the main triggering factors for Alzheimer's disease [16], neuromuscular disorders, and tumorigenesis [17]. Serum BChE activity levels have been widely used as a test of liver function and only a few studies, including a low number of patients have assessed cholinesterase levels in human liver, but have not included cirrhotic patients [18].

The present study was aimed to use cholinesterase as an another fundamental marker for detecting the liver cirrhosis damaged and severity parallels with the conventional liver diagnosis tests and Child score. The common conventional tests may be abnormal not only in liver dysfunction diseases, but also in illnesses not associated with liver dysfunction, such as non-hepatic disease such as myocardial infarction [19].

This paper is considered as a modest contribution to the ongoing discussions about the vital diagnostic role of cholinesterase in the cirrhotic liver. So, particular attention was paid to the evaluation of serum ChE as a biomarker of liver cirrhosis by studying its levels among patients who were with either compensated or decompensated in comparison to healthy volunteers as controls. Additionally, construct the correlation between ChE and other diagnostic markers of liver function such as serum albumin.

The present study revealed a significantly lower level of serum ChE among cirrhotic patients than control healthy volunteers according to their Child Score. The data obtained

are broadly consistent with Ramachandran et al. [15], who revealed that the main three different grades of liver cirrhosis Child A, Child B, and Child C exposed significantly decreased values of serum cholinesterase. Moreover, the present study also showed that serum cholinesterase was higher in patients with compensated cirrhosis than decompensated cirrhosis patients. These results were matched with the study of Ruchi et al. [20] who concluded that serum cholinesterase can be used as a pivotal marker to distinguish between compensated and decompensated cirrhosis. Furthermore, the present study revealed that the serum levels of ChE were positively correlated with serum albumin levels and negatively with both total and direct bilirubin.

Our results supported the fundamental role of ChE and were consistent with Ramachandran et al. [15] results who proved that ChE levels reflect the functional integrity of the liver. Also, serum level of ChE was negatively correlated with prothrombin time and INR as that was previously reported by Meng et al. [10] and Chromy et al. [21] they showed that cirrhotic patients have bleeding diathesis as blood clotting factors reduced in liver dysfunction.

Additionally, our results were not consistent with Garcı´a-Ayllo´n et al. [18] who observed non-significant changed in the enzyme activity in comparison to controls, but concur with their results in other side, as they detected a significantly increased change in level of protein and mRNA of AChE expression and soluble AChE-R. Therefore, the increase in the level of AChE protein was explained by its association with the decrease in BChE activity in both serum and cirrhotic liver.

5. Conclusions

Based on the results, it can be concluded that the research into the role of cholinesterase has been very successful in detecting the early stages of liver cirrhosis. So, the findings of our research are quite convincing, and thus the following conclusions can be drawn: 1) the severity of liver damage according to the Child-Pugh score can be detected and diagnosed by the serum level of cholinesterase. 2) the amalgamation of supportive results could be used precisely in appraising the liver function degree. Additionally, Serum cholinesterase is higher in compensated than decompensated cirrhosis.

6. Recommendations

Serum cholinesterase levels estimation can be used as a routine diagnostic test besides other traditional liver function tests to precisely evaluate the probable grade of liver damage.

REFERENCES

[1] Hsiang L, Bia O, Roes P, et al., (2015): Epidemiology, disease burden and outcome of cirrhosis in alarge secondary care hospital in South Auckland, New Zealand, Intern Med J; 45:160-169.

[2] Tannapfel, A; Dienes, H; Lohse, A W (2012): The Indications for Liver Biopsy. Dtsch Arztebl Int 2012; 109(27-28): 477-83; DOI: 10.3238/arztebl.2012.0477.

[3] Wong F, Wesley Leung, Mohammed Al Beshir, Max Marquez, Eberhard L. Renner. (2015): Outcomes of patients with cirrhosis and hepatorenal syndrome type 1 treated with liver transplantation. Liver Transpl 21:300–307, 2015. © 2015 AASLD.

[4] Mondelli M, Cerino A and Cividini A (2005): Acute hepatitis C: diagnosis and management. J Hepatol; 42(9):108-14.

[5] Bruha R, Dvorak K and Petrtyl J (2012): Alcoholic liver disease. World Journal of Hepatology; 4:3- 81.

[6] Lim JK and Garcia-Tsao G (2009): Members of Veterans Affairs Hepatitis C Resource Center Program, Management and treatment of patients with cirrhosis and portal hypertension: recommendations from the Department of Veterans Affairs Hepatitis C Resource Center Program and the National Hepatitis C Program. Am J Gastroenterology; 104(7): 1802-29.

[7] D'Amico G, GarciaT and Pagliaro L (2006): Natural history and prognostic indicators of survival in cirrhosis: a systematic review of 118 studies. J Hepatol; 44:217–231.

[8] Huo T, Lin H, Wu J, et al., (2006): Proposal of a Modified Child-Turcotte-Pugh Scoring System and Comparison with the Model for End-Stage Liver Disease for Outcome Prediction in Patients with Cirrhosis. Liver Transpl; 12:65–71.

[9] Brown SS, Kalow W, Pilz W, Whittaker M, Woronick CL (1981): The plasma cholinesteerases: a new perspective. Adv Clin Chem. 22:1-123.

[10] Meng F, Yin X, Ma X' et al., (2013): Assessment of the value of serum cholinesterase as a liver function test for cirrhotic patients. Biomed Rep; 1:265-268.

[11] Lampón N, Hermida-Cadahia E, Riveiro A, et al., (2012): Association between butyrylcholinesterase activity and low-grade systemic inflammation. Ann Hepatol; 11:356–63.

[12] Garello E, Battista S, Bar F, et al., (1999): Evaluation of hepatic function in liver cirrhosis: clinical utility of galactose elimination capacity, hepatic clearance of D-sorbitol, and laboratory investigations. Dig Dis Sci. 44:782-788.

[13] Bacigalupo A, Oneto R, Bruno B, et al, (2001): Serum cholinesterase is an early and sensitive marker of graft-versus host-disease (GVHD) and transplant-related mortality (TRM). Bone Marrow Transplant. 28:1041-1045.

[14] Ogunkeye OO and Roluga AI (2006): Serum cholinesterase activity helps to distinguish between liver disease and non-liver disease aberration in liver function tests. Pathophysiology. 13:91.

[15] Ramachandran J, Sajith K, Priya S, et al., (2014): Serum Cholinesterase is an excellent biomarker of liver cirrhosis. Tropical Gastroenterology; 35(1): 15-20.

[16] Massoulie´ J, Sussman J, Bon S, et al., (1993): Structure and functions ofacetylcholinesterase and butyrylcholinesterase. Prog Brain Res 98:139–146.3.

[17] Grisaru D, Sternfeld M, Eldor A, et al., (1999): Structural roles ofacetylcholinesterase variants in biology and pathology. Eur J Biochem 264:672–686.

[18] Garcı´a-Ayllo´ n MS, Small DH, Avila J, et al., (2011): Revisiting the Roleof Acetylcholinesterase in Alzheimer's Disease: Cross-Talk with P-tau andb-Amyloid. Front Mol Neurosci 4:22.2.

[19] Rej R (1989): Aminotransferases in disease. Clin Lab Med. 9:667-687.

[20] Ruchi G, Pranay J, Nadeem SH, et al., (2014): Serum cholinesterase as diagnostic marker of liver disease. International Journal of Biomedical and Advance Research. IJBAR; 5(9): 439-442.

[21] Chromy V, Sváchová L, Novosád L, et al., (2009): Albumin-based or albumin-linked calibrators cause a positive bias in serum proteins assayed by the biuret method. Clin Chem Lab Med; 47: 91-101.