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Evaluation of Serum Cholinesterase as an Early Diagnostic Marker of Liver Cirrhosis

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ABSTRACT

Background: Hepatocytes are the primary source of acetyl cholinesterase, which is released into the bloodstream and has a lower activity in liver dysfunction.

Objective: The aim of this study was to assess the value of serum cholinesterase in early diagnosis of cases with liver cirrhosis.

Patients and Methods: This study included a total of 111 patients with liver cirrhosis, attending at Internal Medicine Department, Zagazig University Hospitals and at Al-Ahrar Teaching Hospital. This study was conducted between April 2021 to October 2021. Patients were classified into 4 groups:1st group: 24 Child A score liver cirrhosis cases, 2nd group:25 Child B score liver cirrhosis case,3rd group: 25 Child C score liver cirrhosis cases. And 4th group: Matching control persons of a healthy 37 years old. Fibroscan and measurement of serum cholinesterase were done for all subjects.

Results: The serum cholinesterase levels drop rapidly in each of the three cirrhosis grades, Child A, Child B, and Child C. In compensated cirrhosis, serum cholinesterase is higher than in decompensated cirrhosis. Blood albumin and cholinesterase levels were found to be strongly linked. Serum bilirubin and serum cholinesterase levels have a strong negative correlation. Patients with higher MELD scores have lower cholinesterase levels.

Conclusion: It could be concluded that serum cholinesterase levels can help in liver cirrhosis diagnosis and prognosis. Serum cholinesterase concentration is strongly linked to the severity of cirrhosis.

Keywords: Cholinesterase, Liver Cirrhosis.

INTRODUCTION

One of the leading causes of death in the globe is liver cirrhosis **(1).** Excessive extracellular matrix components (ECM), histological remodeling, and structural microenvironment shifts are among these modifications. A wound in the parenchyma of the hepatic stellate cells is required for the production of collagen, matrix proteins and a wide spectrum of proliferative, anti-inflammatory and growth factors **(2).** Patients with cirrhosis face a lowered life expectancy and an increased risk of various complications **(3)**.

The fact that many patients with liver cirrhosis are asymptomatic in the early stages and that the vast majority of patients with liver cirrhosis are admitted to the hospital owing to complications from the disease may lead to an underreporting of cases. Liver cirrhosis has a mortality rate between 1% and 57% in a year, depending on the severity of complications that emerge **(4).**

Gastroenterologists use the Child-Pugh score to evaluate patients with chronic liver disease, including cirrhosis. Besides predicting surgical mortality, this score is used to determine prognosis and the intensity of treatment required **(5).**

The prognosis of cirrhotic patients has long been predicted using the Child–Pugh and MELD scores. This does have certain disadvantages. Whether or not to alter the Child–Pugh scores for ascites and HE, two criteria that can change, is the doctor's decision. In individuals with cirrhosis, the INR components of the Child-Pugh and MELD scores do not effectively represent coagulopathy and liver function. To make matters more complicated, the INR varies from one laboratory to the other **(6).**

To hydrolyze acetylcholine, an enzyme known as Cholinesterase is required **(7).** Two forms of cholinesterase are present: acetyl cholinesterase, or erythrocyte cholinesterase, and pseudocholinesterase, or plasma cholinesterase, which is produced in the liver and released into the blood; its activity is lowered in liver failure due to diminished synthesis in these cells**(8).**

The aim of this study was to assess the value of serum cholinesterase in early diagnosis of cases with liver cirrhosis.

PATIENTS AND METHODS

This study included a total of 111 patients with liver cirrhosis, attending at Internal Medicine Department, Zagazig University Hospitals and at Al-Ahrar Teaching Hospital. This study was conducted between April 2021 to October 2021.

The included subjects were divided into four groups **according to the following inclusion criteria**;
criteria: Group 1: 24 Child A score liver cirrhosis cases, **Group 2:** 25 Child B score liver cirrhosis cases, **Group 3:** 25 Child C score liver cirrhosis cases, and **Group 4 (control):** Matching control persons of a healthy 37 years old.

Exclusion criteria: patients aged under eighteen, a four-week history of blood or albumin transfusion, patients with history or indication of variceal hemorrhage on

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admission, hepatocellular carcinoma in the past or present, and transplantation of the liver.

All patients underwent the following:

1- A complete medical history and clinical assessment.
2- Laboratory investigations: Liver function tests, kidney function tests, complete blood count (CBC), and serum cholinesterase measured by colorimetric kinetic method.
3- Abdominal ultrasonography. (There are several ultrasonic features that can be used to identify the presence of diseased tissue in the liver such as nodules with a circular edge and hypoechoic nodules in the liver parenchyma. Early detection of hepatocellular cancer requires the detection of hypoechoic nodules larger than 10 millimeters. Ultrasound can be used to detect splenomegaly, ascites, and portosystemic collaterals)
4- Fibroscan for liver cirrhosis.

***Ethical Consideration*:**

An approval of the study was obtained from Zagazig University academic and ethical committee. Written informed consent of all the subjects was obtained. 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 collected data were coded, processed and analyzed using the SPSS (Statistical Package for Social Sciences) version 22 for Windows® (IBM SPSS Inc, Chicago, IL, USA). Data were tested for normal distribution using the Shapiro Walk test. Qualitative data were represented as frequencies and relative percentages. Chi square test ($\chi 2$) to calculate difference between two or more groups of qualitative variables. Quantitative data were expressed as mean ± SD (Standard deviation). Independent samples t-test was used to compare between two independent groups of normally distributed variables (parametric data). These tests included the mean, standard deviation, t-tests (student and chi-square), Linear Correlation Coefficient, and Analysis of variance [ANOVA]. P value < 0.05 was considered significant.

RESULTS

Regarding to age and gender, no statistically significant differences were found. Each group had a higher percentage of males than females **(Table 1)**.

(Table 2) shows that cholinesterase levels differ significantly among the groups studied.

(Table 3) reveals that the relationship between cholinesterase and age is statistically insignificant. MELD and ALIBI, on the other hand, have a strong negative relationship with the enzyme cholinesterase.

(Table 4) shows that cholinesterase levels are positively correlated with both hemoglobin and platelet count. In contrast, cholinesterase has a strong negative correlation with white blood cells.

(Table 5) shows that Cholinesterase and salt have a statistically significant positive correlation. On the other hand, cholinesterase and both prothrombin time and INR have a substantial negative correlation.

(Table 6) shows that Cholinesterase and albumin have a statistically significant positive correlation. Contrarily, strong negative correlations exist between cholinesterase and all three of these bilirubin markers as well as with the ALT and AST tests.

(Table 7) shows that Cholinesterase and both serum urea and creatinine have a statistically significant negative correlation. The correlation between cholinesterase and portal vein diameter is statistically significant.

The best cutoff of serum cholinesterase in prediction of Child C is ≤2072.05 with area under curve 0.975 and sensitivity 96%, specificity 95.3%, positive predictive value (PPV) 85.7%, negative predictive value (NPV) 98.8% and accuracy 95.5%, The best cutoff of serum cholinesterase in prediction of Child B is ≤2885.65 to <2072.05 with area under curve 0.984 and sensitivity 96%, specificity 98.4%, positive predictive value (PPV) 96%, negative predictive value (NPV) 98.4% and accuracy 97.7%, The best cutoff of serum cholinesterase in prediction of Child A is ≤4922.55 to <2885.65 with area under curve 1 and sensitivity 95.8%, specificity 100%, positive predictive value (PPV) 100%, negative predictive value (NPV) 97.4% and accuracy 98.4% **(Figures 1, 2, 3).**

Table (1): Comparison between the studied groups regarding demographic data:

Parameter	Groups				Test	
	Control group	Child A group	Child B group	Child C group	χ^2/F	P
	N=37(%)	N=37(%)	N=37(%)	N=26(%)		
Gender						
Female	16 (43.2%)	6 (25%)	6 (24%)	9 (3%)	0.651	0.419
Male	21 (56.8%)	18 (75%)	19 (76%)	17 (64%)		
Age (year):						
Mean ± SD	54.95±4.61	55.33±3.29	53.12±4.4	54.28±2.59	1.583	0.198
Range	45 – 65	50 – 60	48 – 62	50 – 61		

Table (2): Comparison between the studied groups regarding serum cholinesterase:

Parameter	Groups				Test	
	Control group	Child A group	Child B group	Child C group	χ^2	p
	N=37(%)	N=37(%)	N=37(%)	N=26(%)		
Cholinesterase Mean ± SD	7353.03±1152.4	3928.95±896.8	2283.48±495.8	1565.38±380.02	299.211	<0.001**
HSD	P_1<0.001**	P_2<0.001**	$P_3$0.016*	P_4<0.001**	P_5<0.001**	P6<0.001**

P1 the difference between control group and Child A group P2 the difference between Child A and B groups P3 the difference between Child B and C groups P4 the difference between Child A and C groups P5 the difference between Child B and control groups P6 the difference between control and child C groups HSD Turkey highest significant difference group F One Way ANOVA **p≤0.001 is statistically highly significant *p<0.05 is statistically significant

Table (3): Correlation between serum cholinesterase and both age, MELD and ALBI scores among the studied patients

Parameter	Cholinesterase	
	r	p
Age	0.087	0.363
MELD	-0.948	<0.001**
ALIBI	-0.831	<0.001**

Table (4) Correlation between serum cholinesterase and CBC data among the studied patients

Parameter	Cholinesterase	
	r	p
Hemoglobin (g/dL)	0.798	<0.001**
WBCs (mcL)	-0.262	0.005*
Platelet count (mcL)	0.833	<0.001**

Table (5) Correlation between serum cholinesterase and both bleeding profile and sodium among the studied patients:

Parameter	Cholinesterase	
	r	p
PT	-0.923	<0.001**
INR	-0.877	<0.001**
Sodium (mEq/L)	0.65	<0.001**

Table (6) Correlation between serum cholinesterase and liver function test among the studied patients:

Parameter	Cholinesterase	
	r	p
Albumin (g/L)	0.818	<0.001**
T. bilirubin (µmol/L)	-0.589	<0.001**
AST (U/L)	-0.778	<0.001**
ALT (U/L)	-0.731	<0.001**

Table (7) Correlation between serum cholinesterase and kidney function tests, portal vein diameter and spleen diameter among the studied patients:

Parameter	Cholinesterase	
	r	p
Urea (mg/dl)	-0.837	<0.001**
Creatinine (mg/dl)	-0.87	<0.001**
PV	-0.306	0.008*
Spleen diameter	-0.251	0.008*

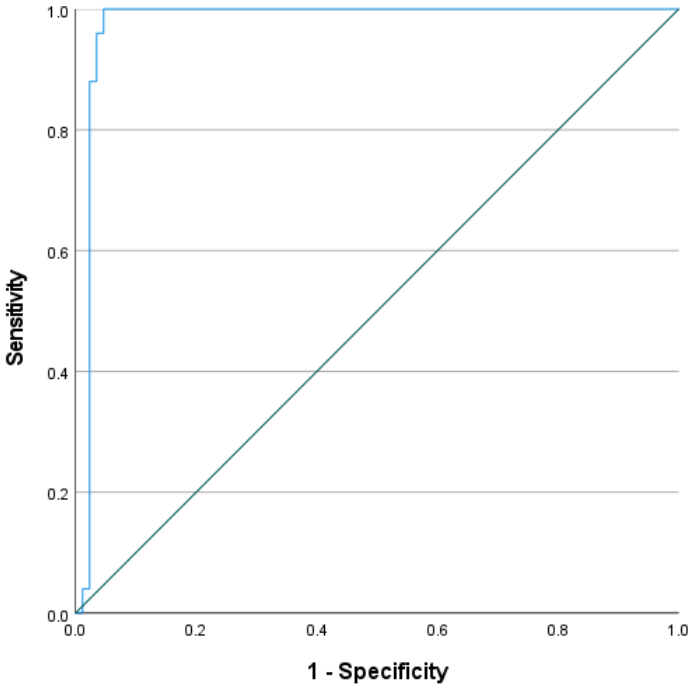

Figure (1): ROC curve showing performance of cholinesterase in prediction of Child C class among the studied participants

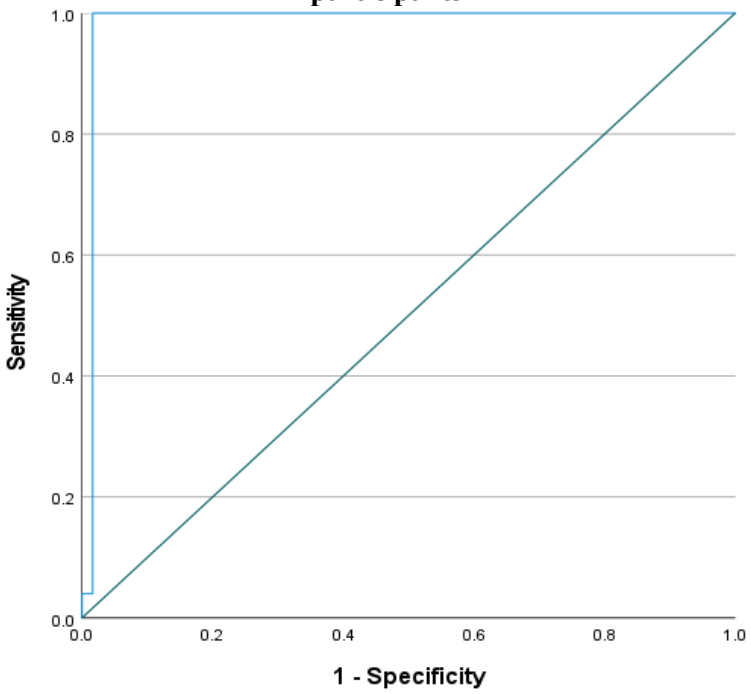

Figure (2): ROC curve showing performance of cholinesterase in prediction of Child C class among the studied participants

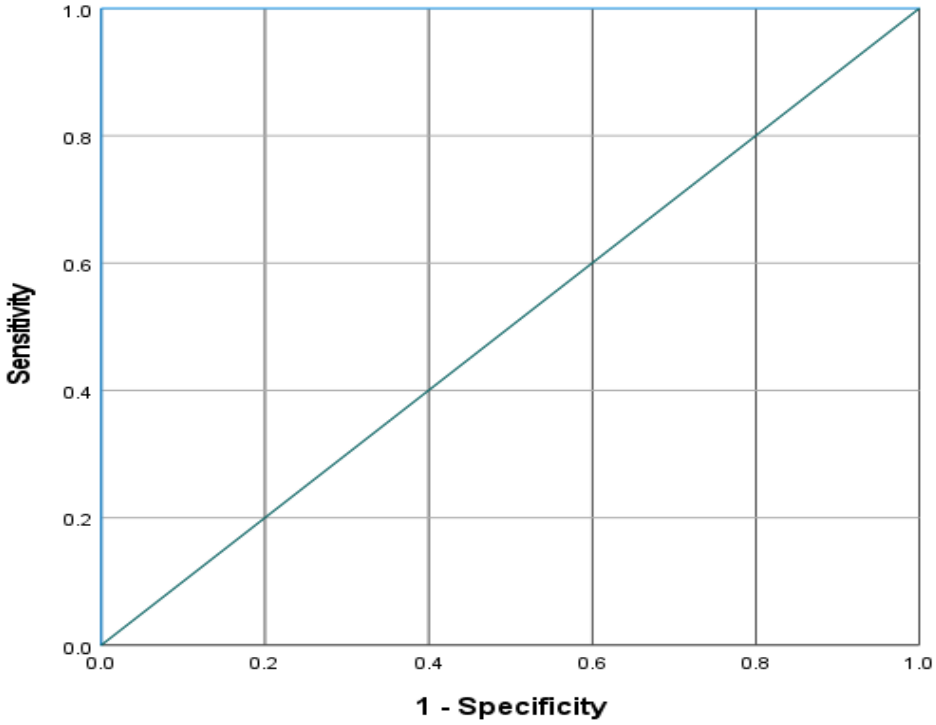

Figure (3): ROC curve showing performance of cholinesterase in prediction of Child A class among the studied participants

DISCUSSION

Cirrhosis-related complications cause 1 million deaths annually, while viral hepatitis and hepatocellular cancer cause 1 million each. This disease is responsible for a whopping 3.5 per cent of all global deaths, making liver cancer the 16th most common cause of death overall [(9)].

Few researches have been done on the role of cholinesterase in assessing hepatic reserve function in cirrhotic individuals. First of its kind, the Child Pugh scoring system ranks the severity of end-stage liver disease, primarily cirrhosis [(10)].

This study was conducted on 111 subjects divided into 4 groups; 37 apparently healthy control subjects, 74 cirrhotic patients divided into child A B C groups.

As a new method for assessing liver damage and severity, the current study used cholinesterase as an additional fundamental marker in addition to conventional liver diagnostic and Child score.

A statistically insignificant difference in age or gender was found in this investigation. According to **Salama *et al.*[(11)]** finding's men constituted a bigger proportion of each group.

Ramachandran *et al.*[(12)] showed that Serum cholinesterase levels showed significant decrease in patients with liver cirrhosis Child A (mean, SD: 3928.95±896.8), Child B (mean, SD: 2283.48±495.8), Child C (mean, SD: 1565.38±380.02) compared to healthy controls (mean, SD: 7353.03±1152.4) with p value ≤ 0.001, Researchers found that a decrease in serum cholinesterase is linked to an increase in the severity of liver cirrhosis and the decline in liver function.

According to the findings of this study, blood cholinesterase levels drop dramatically in children with cirrhosis grades A, B, and C. This agreed with **Gu and his colleagues[(13)]** findings.

Cholinesterase levels were higher in patients with compensated and decompensated disease, respectively. Serum cholinesterase can differentiate between cirrhosis that is well-controlled and cirrhosis that is not well-controlled [(12)].

P 0.001 was found for the association between ChE and serum albumin levels in our investigation. ChE levels represent the liver's functional integrity, according to **Ramachandran *et al.*[(12)]** who also found similar results.

Serum bilirubin and serum cholinesterase showed a negative relationship, with a p value of less than 0.001, making the finding statistically significant. According to **Ramachandran *et al.*[(12)]**.

Our study found a negative correlation between INR and serum cholinesterase levels, with a p value less than 0.01 indicating statistical significance. This was in line with the findings of **Mohamed *et al.* [(7)]**.

In liver cirrhotic patients, we found a link between serum cholinesterase and MELD Score, with lower cholinesterase levels in those with a higher MELD Score. The correlation coefficient between serum cholinesterase and the MELD score was similar to that found by **Ramachandran *et al.* [(12)]**.

As opposed to the controls' median serum ChE concentration of 7886 IU/L (2022-21673), the median serum ChE concentration in patients with cirrhosis was 1590 IU/L (110-8143) (p0.001). Researchers observed that serum ChE levels below 3506 have high sensitivity

and specificity in diagnosing cirrhosis 98.7 %, 80.3 % respectively.

CONCLUSION

It could be concluded that both the diagnosis and prognosis of liver cirrhosis can be improved by determining the serum cholinesterase level. A strong association may be shown between cirrhosis degree and the concentration of serum cholinesterase.

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