TAJ June 2023; Volume 36 Number-1

ISSN 1019-8555
The Journal of
Teachers Association
RMC, Rajshahi

Original Article

Serum Cholinesterase Level in Patients with Cirrhosis of Liver and Its Correlation with the Severity of the Disease

Md. Mamun-ur Rashid,[1] Md. Shafiqul Islam,[2] Most. Firoza Parvin,[3] ANM Saifullah,[4] Bimal Chandra Shil,[5] Md. Habibur Rahman,[6] Mst. Musarrat Sultana [7]

Abstract

Background: Serum cholinesterase mainly comes from the liver, a sensitive indicator of the synthetic capacity of the liver. It can be used as a prognostic marker for cirrhosis.

Objectives: To measure the serum cholinesterase level in cirrhotic patients and to correlate its level with the severity of the disease as per the Child-Pugh score.

Methodology: This cross-sectional study was conducted in the Department of Gastroenterology, Sir Salimullah Medical College Mitford Hospital, Dhaka, Bangladesh, from January 2018 to December 2018. Fifty adult patients with cirrhosis of the liver were enrolled. Fifty healthy individuals were also taken to compare serum cholinesterase levels. Cirrhotic patients were grouped strictly into A, B, and C classes, as per the Child-Pugh score. Serum cholinesterase level was measured in all participants. The correlation between cholinesterase level and the severity of the disease was analyzed.

Result: Mean age of the patients was 47.42 ± 12.40 years and 47.22 ± 11.99 years in cirrhotic patients and healthy group, respectively. The number of patients in the Child-Pugh A, B, and C subgroups was 12 (24%), 20 (40%), and 18 (36%), respectively. The mean serum cholinesterase level was 2938 ± 1561 U/L in cirrhotic patients and 9036 ± 2024 U/L in the healthy group. Serum cholinesterase level in different Child-Pugh class was 4740 ± 1046 U/l (Child A), 3157 ± 1161 U/l (Child B), and 1493 ± 500 U/l (Child C). Serum Cholinesterase was positively correlated with serum albumin and negatively correlated with bilirubin, prothrombin time, and INR. A negative correlation was found between serum Cholinesterase level and the severity of the disease.

Conclusion: Serum cholinesterase level was low in cirrhotic patients, and its level was inversely correlated with the severity of the disease. Thus it can be used as a prognostic marker of cirrhosis. However, further study with a large sample size could explain this more precisely.

Keywords: Cirrhosis, serum cholinesterase, Child-Pugh class.

TAJ 2023; 36: No-1: 33-40

Introduction

Cirrhosis is the widespread disruption of the normal liver structure by fibrosis and the formation of regenerative nodules that is caused by any of various chronic progressive conditions affecting the liver.[1] According to the WHO Report 2004, cirrhosis of the liver was the 18th leading cause of death worldwide and responsible for

[1] Junior Consultant (Medicine), Upazilla Health Complex, Godagari, Rajshahi, Bangladesh.
[2] Assistant Professor, Department of Gastroenterology, Rajshahi Medical College, Rajshahi, Bangladesh..
[3] Junior Consultant (Paediatrics), Upazilla Health Complex, Godagari, Rajshahi, Bangladesh.
[4] Assistant Professor, Department of Gastroenterology, Sir Salimullah Medical College, Dhaka.
[5] Professor(Retd), Department of Gastroenterology, Sir Salimullah Medical College, Dhaka.
[6] Professor (Retd), Department of Gastroenterology, Sir Salimullah Medical College, Dhaka.
[7] Resident Physician (Pediatrics), OPD, Rajshahi Medical College Hospital, Rajshahi, Bangladesh.

1.3% of all deaths.[2] Management of hepatic cirrhosis includes many tests like serum bilirubin, aminotransferases, serum albumin levels, prothrombin time (PT), and INR. These are collectively known as liver function tests (LFTs).

LFTs usually reflect hepatocyte integrity and cholestasis but may be abnormal in many non-hepatic diseases.[3] Serum albumin may be abnormal in extrahepatic causes like intestinal malabsorption, renal loss, and secondary to albumin/blood transfusions. PT and INR values may be affected by vitamin K deficiency, therapeutic anticoagulation, and fresh frozen plasma (FFP) transfusions. Serum bilirubin may be raised in hemolysis and extrahepatic causes. Similarly, aminotransferase LDH levels can also be abnormal secondary to extrahepatic cell membrane damage. So, these conventional tests can't individually confirm liver dysfunction.[4] Due to recent advances in the understanding of the aetiopathogenesis of cirrhosis, various newer effective treatment modalities are emerging. Although the Child-Pugh score is widely used as a simple indicator of severity and prognosis at the bedside, it has some limitations.

It requires multiple clinical and laboratory parameters to evaluate liver reserves and predict outcomes. Encephalopathy and ascites must be subjectively interpreted. Moreover, albumin, blood, or FFP transfusion may affect the actual value of serum albumin and prothrombin time, which in turn affects the Child-Pugh score. Therefore, the evaluation of new markers is important for patients with liver cirrhosis.

In this regard, serum cholinesterase has been studied as a test of synthetic liver function since the early 1950s. Cholinesterase refers to two enzymes; acetylcholinesterase, found in the RBCs and CSF, and butyrylcholinesterase, found in serum. Both of the enzymes catalyze the hydrolysis of the neurotransmitter acetylcholine into choline and acetic acid.[5] The main source of serum cholinesterase is the liver and therefore reflects synthetic hepatic function. Its level is lowered in cirrhosis of the liver and can be normalized following recovery from liver injury. In a study, Ramachandran et al. found serum cholinesterase levels below 3506 had 98.7% sensitivity and 80.3% specificity in predicting cirrhosis.[6] They also mentioned that it is useful in assessing the prognosis of cirrhosis. Meng et al. found that the combination of cholinesterase with the Child-Pugh score may be more subjective and accurate in evaluating the liver reserve function of cirrhotic patients.[5]

Despite many studies, the usefulness of serum cholinesterase in the evaluation and management of cirrhosis is still a matter of some controversy. No such study has been carried out in our country to see the utility of serum cholinesterase levels in liver diseases. So further studies will be necessary to assess the potential value of serum cholinesterase in measuring severity.

Materials and Methods

This was a cross-sectional study performed in the Department of Gastroenterology, Sir Salimullah Medical College Mitford Hospital, from January 2018 to December 2018, after obtaining the clearance of the institutional ethical committee. All participants were enrolled after written informed consent. The sampling technique was convenient sampling. Patients with cirrhosis of the liver due to any cause and age over 18 years were included. The healthy (Comparison) group was an equal number of age-sex-matched healthy individuals with normal LFTs, including hospital staff and patients' relatives. Patients with a history of acute and chronic exposure to organophosphate, carbamate, diabetes, hyperthyroidism, uremia, hyperlipidemia, protein-energy malnutrition, albumin, or blood transfusion within four weeks of enrolment in the study and history or clinical evidence of UGI bleeding at the time of enrolment in the study were excluded from the study.

Fifty cirrhotic patients were included, and an equal number of age and sex-matched healthy individuals with normal LFTs were also included as a comparison group. All patients were subjected to thorough history taking and clinical examination. LFTs, complete blood count, renal function tests, ultrasonography of the abdomen, fibroscan of the liver, and endoscopy of upper GIT

were done in all cirrhotic patients. Hepatic encephalopathy was graded clinically. Ascites were detected clinically and by ultrasonography. Cirrhotic patients were sub-grouped into A, B, and C by Child-Pugh score. Serum cholinesterase level was measured in all patients as well as in healthy individuals.

Serum cholinesterase was analyzed by commercially available reagents and kits on a fully automated analyzer (ADVIA – 1800 chemistry analyzer, origin – SIEMENS, Germany) in the Department of Biochemistry, BIRDEM, Dhaka. Manuals given with the kits for procedures were strictly followed. A fresh and non-hemolyzed serum was used for the assay. The normal value of serum cholinesterase is 5400-13200 U/L. (Laboratory ref.). The correlation between the values of serum cholinesterase level and serum bilirubin, ALT, serum albumin, PT&INR, and various Child-Pugh classes was analyzed.

All data were recorded systematically in a preformed data collection form (questionnaire). Statistical analysis was performed by using window-based computer software devised with Statistical Packages for Social Sciences (SPSS-22) (SPSS Inc, Chicago, IL, USA). Quantitative data were expressed as mean, and standard deviation, and qualitative data were expressed as frequency distribution and percentage. Categorical data were tested with the Chi-square test, and continuous data were tested with an unpaired t-test Mann Whitney U test. Spearman's correlation test was used to evaluate correlations between S. cholinesterase level and severity of cirrhosis. A P value of ≤ 0.05 was considered statistically significant. The summarized data was interpreted accordingly and was then presented in the form of tables and figures.

Results

This hospital-based cross-sectional study was conducted in the Gastroenterology Department, Sir Salimullah Medical College Mitford Hospital, over a period of one year. The results are as follows:

Table I: Distribution of the study subjects according to age in the cirrhotic and healthy groups (n=100)

Age (years)	Cirrhotic (n=50)	Healthy group (n=50)	p-value
<=30	4 (8.0)	5 (10.0)	
31 - 40	12 (24.0)	12 (24.0)	
41 - 50	15 (30.0)	14 (28.0)	
>50	19 (38.0)	19 (38.0)	
Mean ± SD	47.42 ± 12.40	47.22 ± 11.99	0.935

An unpaired t-test was done to measure the level of significance

The mean age was 47.42 ± 12.40 years and 47.22 ± 11.99 years in cirrhotic and healthy subjects, respectively. There was no statistically significant difference in mean age between the two groups

Table II: Distribution of the study subjects according to gender in cirrhotic and healthy groups (n=100)

Gender	Cirrhotic (n=50)	Healthy group (n=50)	p-value
Male	37 (74.0)	29 (58.0)	0.091
Female	13 (26.0)	21 (42.0)	

A chi-square test was done to measure the level of significance.

Males were predominant in both the cirrhotic and healthy groups, with a male-to-female ratio of 2.8:1 and 1.4:1 in the cirrhotic and healthy groups, respectively. There was no statistically significant difference in sex distribution between the two groups.

Table III: Comparison of laboratory findings between cirrhotic and healthy groups (n=100)

	Cirrhotic (n=50)	Healthy group (n=50)	p-value
Bilirubin	1.96 ± 1.75	0.88 ± 0.10	0.001[#]
ALT	47.32 ± 24.67	29.20 ± 13.94	<0.001[#]
PT	18.02 ± 4.77	13.23 ± 1.16	<0.001[*]
INR	1.70 ± 0.53	1.10 ± 0.09	<0.001[*]
Albumin	2.79 ± 0.79	3.91 ± 0.22	<0.001[*]

[*]Unpaired t-test and [#]Mann Whitney U test

Bilirubin, PT, and INR were significantly higher, and albumin was significantly lower in cirrhotic patients than that in the healthy group. The difference between each parameter of the cirrhotic and healthy groups was statistically significant.

Table IV: Comparison of serum cholinesterase level between cirrhotic and healthy groups (n=100)

	Cirrhotic (n=50)	Healthy group (n=50)	p-value
S. Cholinesterase (U/L)	2938 ± 1561	9036 ± 2024	<0.001

An unpaired t-test was done to measure the level of significance.

Serum cholinesterase was lower in cirrhotic patients than that in healthy subjects. The difference between the two groups was statistically significant.

Table V: Serum cholinesterase level of cirrhotic patients in different Child-Pugh classes (n=50)

Group	n (%)	S. Cholinesterase (U/I) (Mean±SD)	p-value
Child A	12 (24.0)	4740 ± 1046	
Child B	20 (40.0)	3157 ± 1161	<0.001
Child C	18 (36.0)	1493 ± 500	
Total	50 (100.0)	2938 ± 1561	

Analysis

Group	n (%)
Child A vs Child B	<0.001
Child A vs Child C	<0.001
Child B vs Child C	<0.001

ANOVA test was done among the groups, and Bonferroni was done between the groups to measure the level of significance. Table V shows S. Cholinesterase levels in different Child-Pugh groups. S. Cholinesterase was reduced significantly with the severity of the disease

Table VI: Correlation of serum cholinesterase level with S. bilirubin, ALT, PT, and INR in cirrhotic patients (n=50)

	Parameters	r	p
S. Cholinesterase	Albumin	+0.596	<0.001
	Bilirubin	-0.507	<0.001
	ALT	-0.241	0.092
	PT	-0.451	<0.001
	INR	-0.659	<0.001

Pearson's correlation test was used to evaluate correlations

Serum albumin had a positive, and bilirubin, PT, and INR had a negative correlation with serum cholinesterase. ALT had no significant correlation with serum cholinesterase.

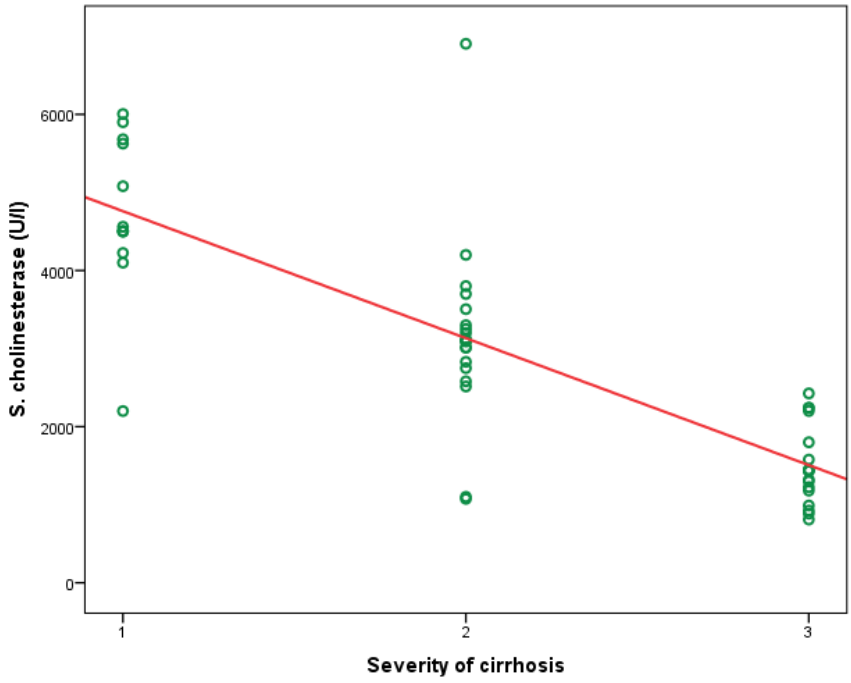

Figure 1 Scattered diagram showing a correlation between serum cholinesterase level and severity of cirrhosis based on CP class.

Spearman's correlation test was used to evaluate correlations. The correlation was statistically significant (r_s = -0.810; p = <0.001).

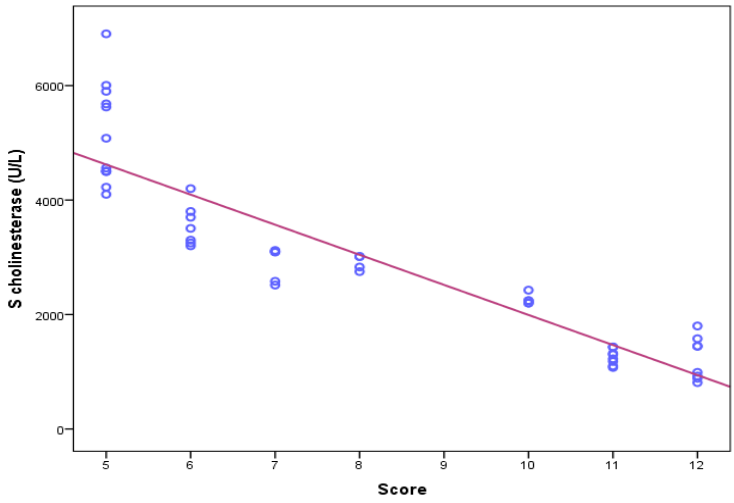

Figure II: Scattered diagram of S. Cholinesterase with CP score (r = -0.066; p = 0.668)

Discussion

Cirrhosis of the liver is quite prevalent throughout the world. Its early and correct diagnosis is always a concern among physicians. A liver function test is a good tool, but it is usually difficult to screen patients exhibiting or concealing signs of liver disease. Serum cholinesterase is an enzyme

synthesized mainly in the liver. This study was done to estimate the level of serum cholinesterase in cirrhotic patients and to correlate its level with the severity of the disease. The study was conducted on 50 cirrhotic patients and 50 healthy individuals.

In this study, the mean age of the cirrhotic patients was 47.42 ± 12.40 years and 47.22 ± 11.99 years in the healthy group. In the study of Meng et al., the mean age of the cirrhotic patients was 53.2 ± 11.2 years.[5] Males were predominant in both cirrhotic (74.0%) and healthy groups (58.0%). There was no significant difference in gender between cirrhotic and healthy subjects. Male to female ratio in cirrhotic patients was 2.8:1, and in the healthy group was 1.4:1. Meng et al. found male predominance in their study.[5] This may be due to the greater chance of exposure of males to environmental and occupational risk factors like hepatitis viruses.

This study showed that there was a significant decrease in serum cholinesterase in cirrhotic patients compared to the healthy subjects (2938 ± 1561 U/L vs 9036 ± 2024 U/L). The result was statistically significant (p<.001). This was in agreement with the findings of Mohamed et al.[6], Thathiya et al.[7], and Ramachandran et al.[8]. Mohamed et al. found mean serum cholinesterase 2519.58 ± 3.2 U/L in cirrhotic patients and 5984.0 ± 1.9 U/L in controls.[6] In Ramachandran et al., median serum cholinesterase in cirrhotic patients was 1590 U/L (110-8143U/L) compared to controls 7886 U/L (2022- 21673U/L), p < 0.001.[8] In the study of Thathiya et al., the level of serum cholinesterase was significantly lower in chronic liver disease patients (2314 ± 1413 U/L) when compared to controls (7883 ± 1012 U/L).[7] This may be a result of liver cirrhosis that directly affects its function leading to deficient liver production. Strahl and Maier found that the synthetic function of the liver is reflected by the levels of serum cholinesterase, which is synthesized by hepatocytes .[9]

The cirrhotic patients were strictly grouped into the A, B, and C groups based on their Child-Pugh scores. The highest numbers of patients were in Child Class B (40%). In a study, Sujatha and Ramanathan also found Child class B (41%) predominance in their study.[10] The serum cholinesterase in the Child A, Child B, and Child C groups was (4740 ± 1046 U/l), (3157 ± 1161 U/l), and (1493 ± 500 U/l), respectively. The difference between the mean serum cholinesterase level in the Child A, B, and C groups was statistically significant (p<0.001). Meng et al. observed similar findings in their study. In their study, they found mean serum cholinesterase level was 5368.04±1657.32 U/l, 2943.06±1212.84 U/l, and 1832.51±710.68 U/l in Child A, Child B, and Child C groups respectively.[5] The difference among the groups was statistically significant. This study result was also in agreement with the findings of Gu and Zhong.[11] They demonstrated that cholinesterase levels in the three grades were: Child A (5978±535 U/l), Child B (3957±454 U/l), and Child C (2267±332 U/l).[11]

In this study, serum albumin was significantly decreased in cirrhotic patients, whereas prothrombin time, INR, and bilirubin were significantly increased in cirrhotic patients. In the study of Mohamed et al., a similar finding was observed in albumin level and prothrombin time.[6] Serum albumin level and prothrombin time are useful tools for monitoring the synthetic activity of the liver. Thus, albumin levels decrease when cirrhosis occurs, and they have prognostic value in cirrhotic patients.[12]

Serum cholinesterase was positively correlated with serum Albumin (r=+0.596; p=<0.001) and negatively correlated with bilirubin (r=-0.507; p=<0.001), prothrombin time (r=-0.451; p=<0.001) and INR (r=-0.659; p=<0.001). There was no significant correlation between serum cholinesterase and ALT (p=0.092). Meng et al. revealed a positive correlation of serum cholinesterase with albumin (r=0.633, p=0.000) and a negative correlation with plasma prothrombin time (r=-0.571, p=0.000) in the cirrhotic patients.[5] Serum cholinesterase had a positive correlation with albumin (r=0.617, p=0.000) and negative correlation with prothrombin time (r=-0.580, p=0.000) in the study of Mohamed et al..[6] Amin et al. found a positive

correlation of albumin (r=0.582, p=0.000) and negative correlation of INR (r=-0.520, p=0.000) with serum cholinesterase.[13]

In this study, it was found that serum cholinesterase level had a negative correlation with the severity of cirrhosis based on the Child-Pugh class (r_s = - 0.810; p = <0.001). Amin et al. found a strong negative correlation between serum cholinesterase level and Child score (r=-0.9, P<0.001).[13] Sujatha and Ramanathan also found a similar negative correlation (-0.850; p = <0.01) between serum cholinesterase and the Child-Pugh class.[10] It may be due to progressive loss of hepatocyte residual functional capacity as the disease progresses.

Conclusion

According to this study finding, the level of serum cholinesterase was low in cirrhotic patients. Its level is inversely correlated with other routinely performed liver function tests and with the severity of liver damage as per the Child-Pugh score. Compared with the Child-Pugh score, serum cholinesterase is less complex, has no subjective error, requires a single laboratory test, and is not easily affected by treatments for decompensated cirrhosis. Hence, the estimation of serum cholinesterase will prove useful in the management of liver cirrhosis. However, The study was done in a single referral center, and only a small number of cirrhosis patients and healthy individuals were enrolled – hence it is not representative of the whole population of the country. Further nationwide multicenter studies with a large sample size should be done.

Conflict of interest: None declared

References

1. Dooley JS, Lok AS, Garcia-Tsao G, Pinzani M, editors. Sherlock's diseases of the liver and biliary system. John Wiley & Sons; 2018 Aug 6.
2. World Health Organization. The World health report: changing history. World health organization; 2004.Retrieved August 05, 2019, Available:*https://www.who.int/healthinfo/global_burden_disease/2004_report_update/en.*
3. Winkel P, Ramsoe K, Lyngbye J, Tygstrup N. Diagnostic value of routine liver tests. Clin chem. 1975;21 (1),71-75.
4. Ogunkeye OO, Roluga AI. Serum cholinesterase activity helps to distinguish between liver disease and non-liver disease aberration in liver function tests. Pathophysiology. 2006;13(2):91-93. doi:10.1016/j.pathophys.2006.01.002.
5. Meng F, Yin X, Ma X, Guo XD, Jin B, Li H. Assessment of the value of serum cholinesterase as a liver function test for cirrhotic patients. Biomedical rep. 2013;*1*(2),265-268. doi: 10.3892/br.2013.60.
6. Mohamed NA, Amanullah M, Amanvermez R, Ibrahim MA, Abbas M. Serum cholinesterase as liver function test in cirrhotic patients at Soba Teaching hospital, Khartoum, Sudan. Int Res J Med Med Sci. 2017;5(3):44-9.
7. Thathiya M, Thamarai R, Sivakumar K.. Evaluation of serum cholinesterase levels in patients with chronic liver diseases. Int J of Sci Res. 2018; 7(7):24-25.
8. Ramachandran J, Sajith KG, Priya S, Dutta AK, Balasubramanian KA. Serum cholinesterase is an excellent biomarker of liver cirrhosis. Trop Gastroenterol. 2014;35(1):15-20. doi:10.7869/tg.158.
9. Strahl S, Maier KP. Risk-classification in liver cirrhosis. Praxis. 2006 Aug 1;95(34):1275-81.
10. Sujatha N, Ramanathan K. A Study on Serum Cholinesterase as a Biomarker for Cirrhosis of the Liver. J of Med Sci and Clin Res. 2017; 5(8), 26820-26827
11. Gu YJ, Zhong YB. Cholinesterase determination of evaluation of patients with liver cirrhosis of the liver reserves significance. Chin J Med Guide. 2010;12:649-50.
12. Green RM, Flamm S. AGA technical review on the evaluation of liver chemistry tests. Gastroenterology. 2002 Oct 1;123(4):1367-84.
13. Amin MA. Assessment of serum level cholinesterase as a biomarker of liver cirrhosis in Egyptian cirrhotic patients. Gastroenterology Insights. 2017 May;8(1):1-5.

All correspondence to
Md. Mamun-ur Rashid
Junior Consultant (Medicine)
Upazilla health complex
Godagari, Rajshahi.
E-mail: drmurashid@gmail.com.