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A Study on Serum Cholinesterase as a Biomarker for Cirrhosis of the Liver

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ABSTRACT

Background – *Cirrhosis of the liver is a frequently encountered disease. The commonly available tests used in assessing the severity of cirrhosis have certain drawbacks. The estimation of serum cholinesterase is useful to assess the severity and prognosis of the disease.*

Aim *– The aim of the study is to compare the level of serum cholinesterase in patients with cirrhosis with other tests of liver function like serum albumin, serum bilirubin, PT INR, MELD and Child Pugh score.*

Materials and Methods – *This was a hospital based observational study conducted for six months between March to August 2015. Patients who were diagnosed with cirrhosis both clinically and by ultrasound were included in the study. The assay for serum cholinesterase was done in all patients.The correlation between the values of serum cholinesterase and serum albumin, bilirubin, INR, Child Pugh and MELD score were analysed.*

Results *– A total of 100 patients were studied. The majority were males (80%) in the age group of 41to 50 years.(40%). The most common aetiological factor in this study was alcohol(68%). Of the clinical signs studied 83% had ascites, 72% had icterus, 63% had splenomegaly and 31% had hepatic encephalopathy. On analysis of the laboratory parameters, 71% had a bilirubin level more than 3 and 73% had an INR less than 1.7. The majority of the patients were in Child Pugh class B (41%) and 64% had MELD score greater than 15. On analysing the correlation between serum cholinesterase and other tests of liver function, it was found that there was significant correlation with albumin, bilirubin, INR levels, Child Pugh and MELD score.*

Conclusion – *A significant correlation was found between serum cholinesterase levels and the severity of Cirrhosis.*

Keywords: *serum cholinesterase- reduced levels in chronic liver disease- biomarker for cirrhosis.*

INTRODUCTION

Hepatic cirrhosis is a commonly encountered clinical entity. Its management includes an array of tests like serum albumin levels, PT INR, serum bilirubin, aminotransferases. Various classification systems have also been developed including the MELD and Child Pugh scores for assessing its severity and prognosis. However, the routinely used tests have certain shortcomings.

Serum albumin, may be abnormal due to extrahepatic causes like intestinal malabsorptive states, malnutrition, renal disease and albumin transfusions, thereby interfering with its usage as a marker of liver synthetic capacity and severity of cirrhosis.The PT INR values may be abnormal secondary to vitamin K deficiency, therapeutic anticoagulation, congenital clotting factor deficiencies and its values are altered following fresh frozen plasma transfusions in the treatment of coagulopathy which occurs in decompensated liver disease. Serum bilirubin may be raised in hemolysis and extrahepatic causes, Serum ALP altered in disorders of placenta, bone, intestinal mucosa and similarly aminotransferase and LDH levels can be abnormal secondary to their release from extrahepatic sources following cell membrane damage.

In this regard, serum cholinesterase has been studied as a test of liver function since the early 1950 s. It was found that the source of serum cholinesterase is the liver and hence reflects hepatic function. Its levels are lowered in chronic liver disease and cirrhosis and can normalize following recovery of liver injury. It can overcome some of the shortcomings of the commonly measured tests of liver function. A lot of studies have shown that it helps in assessing the severity and prognosis of cirrhosis.

Studies have also shown that it shows good correlation with the routinely performed tests of liver function like serum albumin, PT INR, Child Pugh and MELD scores.

OBJECTIVE

The objective of this study is to compare the level of serum cholinesterase in patients with cirrhosis with other tests of liver function like serum albumin, serum bilirubin, PT INR, MELD and Child Pugh scoring.

MATERIAL AND METHODS

This was a prospective observational study of 100 patients presenting to a tertiary care hospital in Chennai between March to August 2015. The patients with cirrhosis which was diagnosed clinically and by ultrasound were included in the study. Patients with history of Organophosphate, carbamate poisoning, exposure to succinyl choline, cocaine, codeine and morphine, those who had albumin or blood transfusion 4 weeks prior to enrolment in the study, patients with history of clinical evidence of UGI bleed at the time of enrolment and liver transplanted individuals were excluded from the study.

Sampling method used was purposive. After selection, patients were subjected to thorough history taking and clinical examination. Liver function tests, Complete blood count, Renal function tests,Viral markers, PT INR, Ultrasonography of the abdomen and serum cholinesterase were done in all patients.

The assay for serum cholinesterase was done using propionylthiocholine as substrate, by the kineticpropionylthiocholine method. The reagents used included propionylthiocholine, 2-nitrobenzoic acid, buffer and stabilizers. Cholinesterase caused the hydrolysis of propionylthiocholine to propionic acid and thiocholine. This thiocholine reacted with 2-nitrobenzoic acid to result in the formation of 5-thio-2-nitrobenzoic acid, which is yellow in colour.

Fresh and non hemolysed serum was used for the assay.About 20 microliters of the sample was used with 1 ml of the reagent and the and the absorbance was first read at 15 seconds and then at 45 seconds and the results were calculated by the instrument automatically using the following formula:

Activity in U/L = Absorbance/30 seconds × factor

Factor = [TV×1000×2] ÷ [14.64 × SV × P]

Where:

TV= total reaction volume in ml

SV= sample volume in ml

14.64= millimolar absorption coefficient of 5-thio-2-nitrobenzoic acid at 405 nm.

P=cuvette pathlength in cm

2=conversion from absorbance/second to absorbance/minute.

The normal values at 37 degree Celsius: 4900 – 11900 U/L.

The calculator in the UNOS website was used to calculate MELD scores. Ascites was detected clinically and by ultrasonography. Hepatic encephalopathy was graded clinically. The correlation between the values of Serum cholinesterase and Serum albumin, Serum bilirubin, INR, Child Pugh score and MELD score were analysed.

Statistical method used – The data was analysed using SPSS software. Pearsons correlation coefficient and p value were calculated to find the statistical significance. Variables were considered to be significant if p value <0.05.

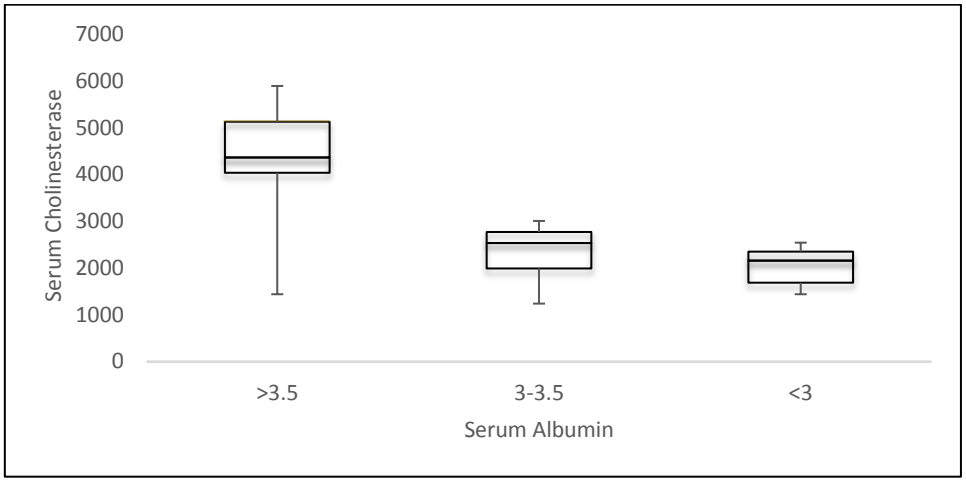
RESULTS

Most cases of cirrhosis (40 patients) occur in the 41 – 50 years age group (40%). Among the 100 patients in our study, 80 patients(80%) were males and 20 patients (20%) were females.The most common cause for cirrhosis among the patients in our study was alcohol, seen in 68 patients (68%). 83 patients (83%) presented with ascites and 72(72%) presented with icterus while the remaining patients did not have icterus clinically. In our study, 31 patients (31%) presented with hepatic encephalopathy, of which 10 patients were in grade I (10%), 13 patients (13%) in grade II, 7 patients (7%) in grade III and 1 patient (1%) in grade IV. 37 patients (37%) had splenomegaly, as detected by ultrasonography.

92 patients(92%) had a serum cholinesterase level less than 4900U/ L. 71 patients (71%) had bilrubin levels greater then 3 mg/dl, 12 patients (12%) had bilirubin levels between 2 to 3 mg/dl and 17 patients (17%) had bilirubin levels less than 2 mg/dl. 73 patients (73%) had INR levels less than 1.7, 21 patients (21%) had values between 1.7 – 2.3 and 6 patients (6%) had values >2.3. 41 patients (41%) belonged to Child Pugh class B, 35 patients (35%) belonged to Child Pugh class C and 24 patients (24%) belonged to Child Pugh class A.64 patients (64%) had MELD score greater 15 and 36 patients (36%) had a MELD score less than or equal to 15.

TABLE 1: Correlation between Serum Albumin and Serum Cholinesterase

Serum Albumin	S.che Mean	Min	Max	Std	Range	Correlation	P Value
>3.5	4360.269231	1437	6101	1053.098	4664	0.52124	<0.01
3-3.5	2531.509434	1237	5125	815.0791	3888		
<3	2155.619048	1437	4800	756.957	3363		

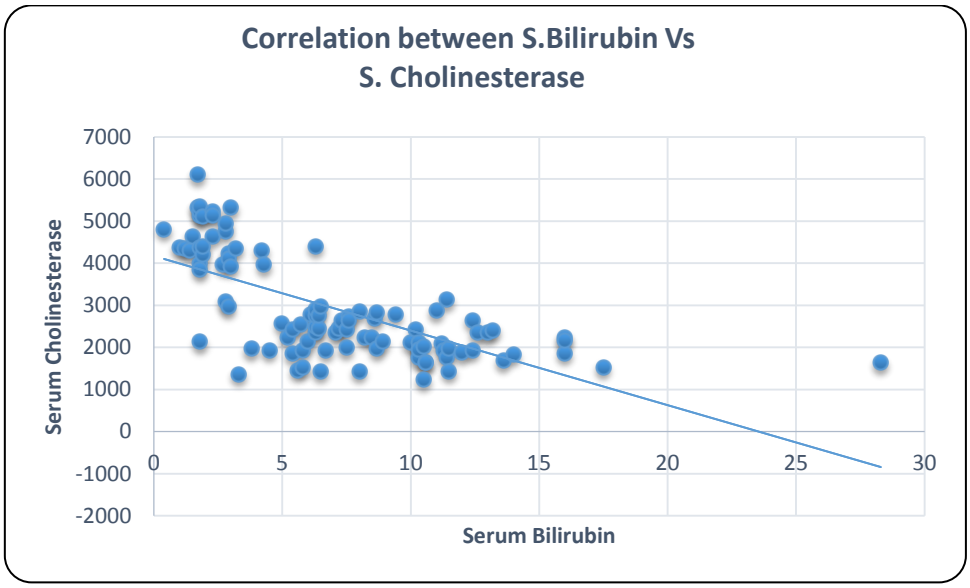


In our study, serum albumin levels were compared with the serum cholinesterase levels. It was found that the serum cholinesterase levels were lower in patients with lower values of serum albumin (positively correlated) which was statistically significant with p value < 0.01.

TABLE 2: Correlation between Serum Bilirubin and Serum Cholinesterase

Bilirubin Range	Frequency	Percentage
<2	17	17
2 to 3	12	12
>3	71	71
Total	100	100

	Serum Cholinesterase					
Bilirubin Range	**Mean**	**Min**	**Max**	**Range**	**Correlation**	**P Value**
<2	4567.2353	2131	6101	3970	-0.675	<0.01
2 to 3	4361.4167	2963	5318	2355		
>3	2293.3099	1237	4396	3159		

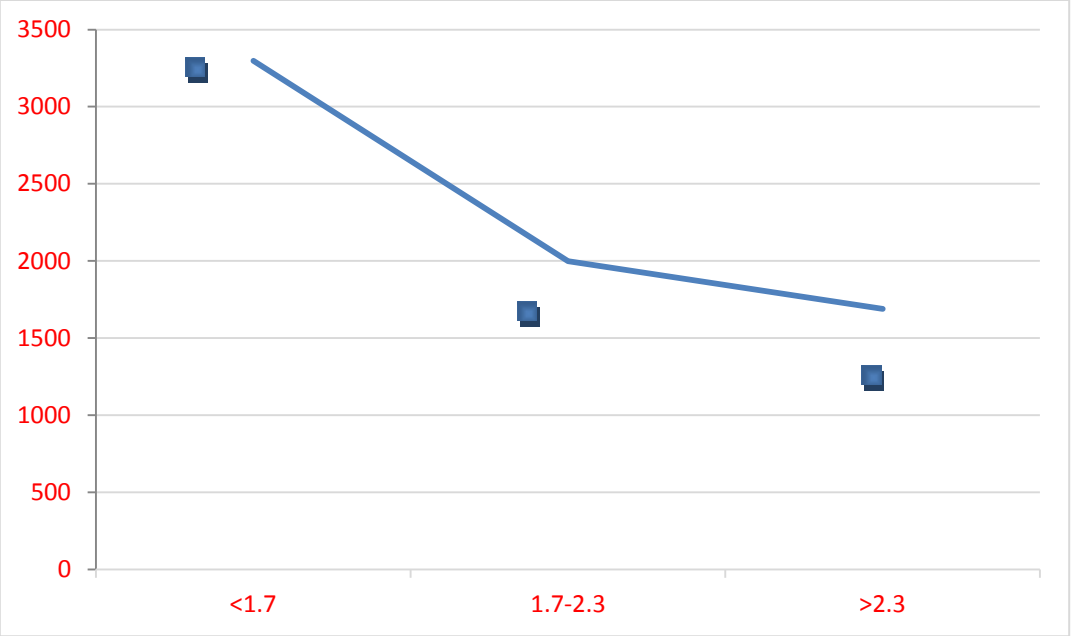


In our study, serum bilirubin levels were negatively correlated with serum cholinesterase levels and the p value was <0.01 which was statistically significant.

TABLE 3: Correlation Between INR (International Normalised Ratio) and Serum Cholinesterase

INR Range	Frequency	Percentage
<1.7	73	73
1.7-2.3	21	21
>2.3	6	6
Total	100	100

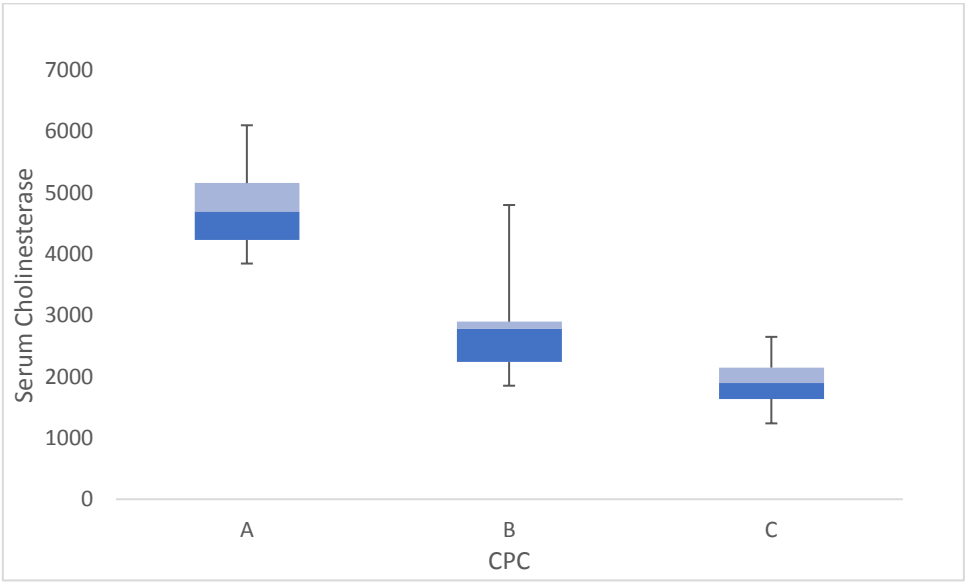
	Serum Cholinesterase					
INR RANGE	Mean	Min	Max	Range	Correlation	P Value
<1.7	3297.438	1237	6101	4864	-0.49565	<0.01
1.7-2.3	1998.286	1437	4296	2859		
>2.3	1688	1356	1967	611		



In our study, it was found that INR value was negatively correlated with the values of serum cholinesterase and it was statistically significant with p value <0.01.

TABLE 4: Correlation Between Child Pugh Class and Serum Cholinesterase

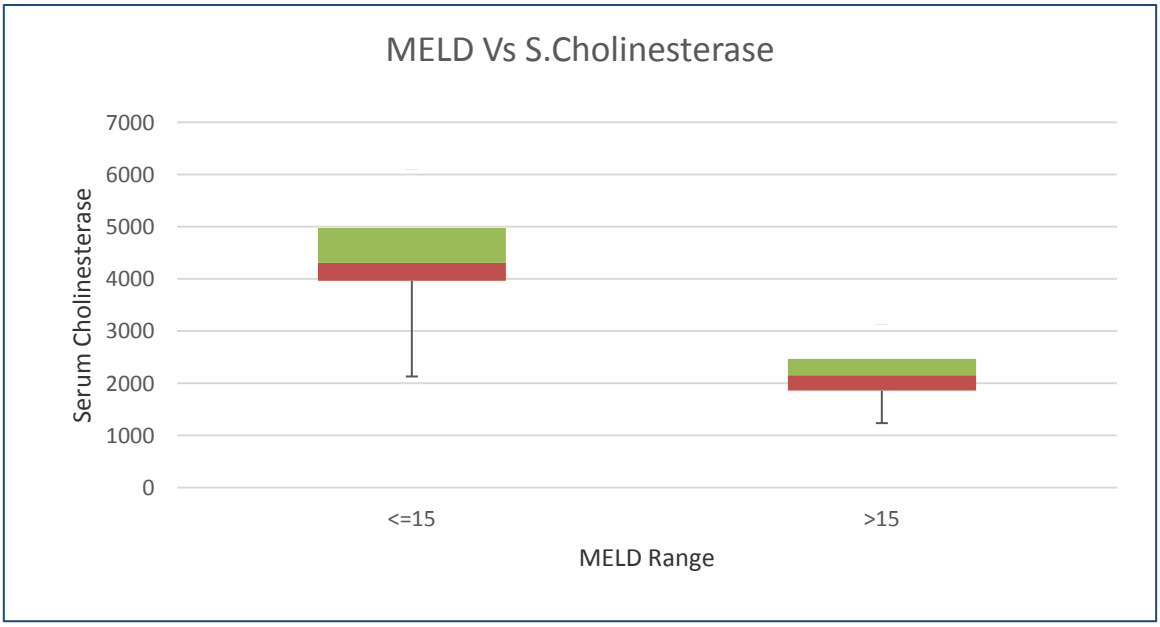
	Serum Cholinesterase				Correlation	P Value
CPC	**Mean**	**Min**	**Max**	**Range**		
A	4692.25	3845	6101	2256	-0.850087	<0.01
B	2779.682927	1852	4800	2948		
C	1892.114286	1237	2649	1412		



In our study, it was found that serum cholinesterase values were higher among Child Pugh class A patients than class B patients, in whom the values of serum cholinesterase were higher than class C patients. Thus, higher Child Pugh grading correlated negatively with the serum cholinesterase values and it was statistically significant with p value <0.01

TABLE 5: Correlation between Meld Score and Serum Cholinesterase

	Serum Cholinesterase					
MELD Score	**Mean**	**Min**	**Max**	**Range**	**Correlation**	**P Value**
<=15	4304.833	2131	6101	3970	-0.7927219	<0.01
>15	2153.609	1237	3125	1888		



In our study, it was found that MELD scores were inversely correlated with the seum cholinesterase levels and it was statistically significant p value <0.01.

DISCUSSION

This study was conducted to compare the levels of serum cholinesterase among patients with cirrhosis with other tests of liver function like serum albumin, serum bilirubin, PT INR, MELD and Child Pugh scores.Our study population consisted of 100 patients who were diagnosed with cirrhosis of liver clinically and by ultrasonography. Serum cholinesterase levels were measured in all the 100 patients along with routinely performed tests like serum bilirubin, serum albumin, PT INR.

Analysis was done to study the correlation between levels of serum cholinesterase and levels of serum albumin, serum bilirubin, INR and severity of cirrhosis of liver using Pearson's correlation coefficient. Following observations were made from our study.

Age distribution

Out of 100 patients, majority were in the 41 – 50 years age group (40%) .In our study cirrhosis was most commonly seen in the middle age group.

Sex distribution

Out of 100 patients, 80 patients were males (80%) and the remaining 20 patients (20%) were females. The male to female ratio is 4:1.

Etiology

Among 100 patients with liver cirrhosis, the most common etiological cause for cirrhosis in this study was alcohol in 68 patients (68%) followed by other causes in 19 patients (19%).

Clinical signs

Out of the 100 patients in the study, 83 patients (83%) had ascites, 72 patients (72%) had icterus,63 patients (63%) had splenomegaly and 31 patients (31%) had hepatic encephalopathy.

Among the 31 patients with hepatic encephalopathy, 10 patients (10%) had grade I, 13 patients (13%) had grade II, 7 patients (7%) had grade III, 1 patient (1%) had grade IV hepatic encephalopathy. Among the 100 patients, 63 patients (63%) had splenomegaly which was indicative of the presence of portal hypertension.

Cholinesterase levels

Among the 100 patients with cirrhosis, 92 patients (92%) had a serum cholinesterase level less than 4900U/L.[1]

Bilirubin levels

Among the 100 patients, 71 patients (71%) had a bilirubin level greater than 3 mg/dl and 12 patients (12%) had bilirubin levels between 2 to 3. A bilirubin level equal to or greater than 3 can be detected clinically as scleral icterus.

Coagulopathy

In our study, 73 patients (73%) had INR levels less than 1.7. Thus the majority of patients in our study did not have coagulopathy.

Child-Pugh class

In our study, out of 100 patients, 41 patients (41%) belonged to class B, 35 patients (35%) to class C and 24 patients (24%) belonged to class A. Thus the majority of patients belonged to class B. Child-Pugh class is used in the assessment of patients for liver transplantation and is a good indicator of liver disease severity.

MELD score

In our study, 64 patients (64%) had MELD score greater than 15 and 36 patients (36%) had MELD score less than or equal to 15. MELD score predicts the prognosis of patients with portal hypertension and liver disease and is used for forming the priority list for liver transplant.

Correlation between Serum Albumin and Serum Cholinesterase

In our study the correlation between serum albumin levels and the levels of serum cholinesterase were studied. It was found that they were positively correlated with a p value <0.01 This was comparable with the observations in the study by FanpingMeng et al.[2] and Ramachandran J[3]. et al.

Correlation between Serum Bilirubin and Serum Cholinesterase

In our study, it was found that the serum bilirubin levels were negatively correlated with serum cholinesterase levels and the p value was <0.01 which was statistically significant. This is similar to the observations made in the study by Ramachandran J et al.[3] and O.O. Ogunkeye et al[5].

Correlation between INR Levels and Serum Cholinesterase

In our study, it was found that INR value was negatively correlated with the values of serum cholinesterase and it was statistically significant with p value <0.01. This was comparable to the observations made in the study by Eassam M. Hafez.[4]

Correlation between Child Pugh Class and Serum Cholinesterase

In our study, it was found that the serum cholinesterase values were lower in patients with Child Pugh class C and B compared to those with Child Pugh class A. This was found to be statistically significant with a p value <0.01. This was similar to the observations made in the study by FanpingMeng[2] et al who noted in their study that values of serum cholinesterase were lower among patients with decompensated cirrhosis than patients with compensated cirrhosis .

Correlation Between Meld Score and Serum Cholinesterase

In our study, it was found that MELD scores were inversely correlated with the seum cholinesterase levels and it was statistically significant with p value <0.01. It was similar to the findings noted by Ramachandran J[3] et al.

CONCLUSION

The estimation of serum cholinesterase levels has several implications in the assessment and management of patients with cirrhosis of liver.Serum cholinesterase activity levels have shown good correlation with the other routinely performed tests of liver function. It is a relatively inexpensive test and can be easily measured on a outpatient basis and among inpatients. Its value is altered according to the liver disease severity which helps assess prognosis and further management.

Thus serum cholinesterase levels are comparable to other routinely performed tests of liver function and serves as a biomarker for cirrhosis of the liver.

Grants: Nil.

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