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RESEARCH ARTICLE

A Comparative Study in Assessing the Usefulness of Serum Cholinesterase, High Sensitivity C-reactive Protein with Liver Function Tests in Alcoholic Liver Disease

[1]Hemantha Kumara DS, [2]Muralidhara Krishna CS, [3]HL Vishwanath

ABSTRACT

Introduction: Chronic alcohol ingestion is one of the major causes of liver disease. The pathology of alcoholic liver disease consists of three major lesions (1) fatty liver; (2) alcoholic hepatitis; and (3) cirrhosis. Fatty liver is present in >90% of binge and chronic drinkers with a smaller percentage of heavy drinkers progressing to alcoholic hepatitis thought to be a precursor to cirrhosis. A lot of studies have been conducted in the past but requires further studies to prove its usefulness in the diagnosis of liver diseases. The present study has been planned to find out the use of assay of serum cholinesterase and high-sensitivity C-reactive protein (hs-CRP) in the diagnosis of alcoholic liver disease.

Materials and methods: Thirty male cases diagnosed with the alcoholic liver disease were compared with 30 male normal subjects as controls and 30 male non-alcoholic liver disease patients as an additional study group. The diagnosis was based on interview and questionnaire, clinical signs of liver disease and supporting laboratory tests [bilirubin, total protein, serum albumin, albumin:globulin (A:G), aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase (ALP), and gamma-glutamyl transferase (GGT)] and ultrasound.

Results and discussion: The study showed deranged liver function tests in both alcoholic and non-alcoholic cirrhosis patients compared to controls and normal liver function tests in controls. The serum cholinesterase levels were significantly decreased in alcoholic cirrhosis patients (2112.43 ± 1195.94) compared to non-alcoholic cirrhosis (4004.73 ± 971.03) patients with p-value <0.001 whereas hs-CRP levels were significantly increased in non-alcoholic cirrhosis patients (1.79 ± 0.28) compared to alcoholic cirrhosis patients (1.23 ± 0.42) with p-value <0.001.

Conclusion: To conclude, the marked decrease in serum cholinesterase in alcoholic cirrhosis patients suggest that its activity might be a specific indicator of liver dysfunction and may be used for the diagnosis of alcoholic cirrhosis patients and the hs-CRP can be used as a strong predictor of non-alcoholic cirrhosis.

Keywords: Alcoholic cirrhosis, Hs-CRP, Non-alcoholic cirrhosis, Serum Cholinesterase.

[1]Tutor, [2]Assistant Professor, [3]Professor and HOD

[1]Department of Biochemistry, Shimoga Institute of Medical Sciences, Shimoga, Karnataka, India

[2,3]Department of Biochemistry, Bengaluru Medical College and Research Institute, Bengaluru, Karnataka, India

Corresponding Author: Muralidhara Krishna CS, Assistant Professor, Department of Biochemistry, Bengaluru Medical College and Research Institute, Bengaluru, Karnataka, India, e-mail: muralidharakrishna@yahoo.com

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INTRODUCTION

The alcoholic liver disease is a term that encompasses the hepatic manifestations of alcohol overconsumption which includes fatty liver, alcoholic hepatitis and chronic hepatitis with hepatic fibrosis.[1] Alcohol is a common cause of cirrhosis all over the world including India, and alcoholic liver disease is among the ten most common causes of death worldwide. The consumption of alcohol has been steadily increasing in India during the last decade because of the rise in socio-economic status. Chronic and excessive alcohol ingestion is one of the major causes of liver disease.[2] Liver cirrhosis is most commonly caused by alcoholism and hepatitis B or C but has many other possible causes. Epidemiology of liver cirrhosis varies in gender, ethnic groups, and geographical distribution.[3] Quantity and duration of alcohol intake are the most important risk factor involved in the development of an alcoholic liver disease. The threshold of developing the alcoholic liver disease in men is an intake of >60 to 80 g/day of alcohol for 10 years while in women are at increased risk of developing similar degrees of liver injury by consuming 20 to 40 g/day. Ingestion of 160 g/day is associated with 25 fold increased risk of developing alcoholic cirrhosis. Chronic infection with hepatitis C is an important comorbidity in the progression of the alcoholic liver disease to cirrhosis among chronic excessive drinkers.[2]

The alcoholic liver disease has a wide spectrum, varying from asymptomatic liver enlargement to severe liver failure and/or portal hypertension with high mortality rate. The three main types of liver involvement are: (a) alcoholic fatty liver; (b) alcoholic hepatitis; (c) alcoholic cirrhosis. In men, 40 to 80 g/day of ethanol produces fatty liver, 160 g/day for 10 years causes hepatitis or cirrhosis. Only 15% of alcoholics developed alcoholic liver disease. Hepatitis C virus (HCV) infection concurrent with the alcoholic liver disease

is associated with younger age of severity, more advanced histology, decreased survival.[2] In the early phase of inflammation cell products, proteinases and reactive oxygen radicals may initiate hepatocellular necrosis with consecutive releasing of numerous cytokines. Following hepatic injury, there is the increase in the extracellular matrix, the activation of stellate cells, the increase in rough endoplasmic reticulum and expression of smooth muscle-specific alpha chain.[4] Activated stellate cells are influenced by numerous cytokines. Some of them have a proliferative effect on stellate cells while other stimulate fibrogenesis.[5]

Most of the non-alcoholic liver disease constitutes non-alcoholic fatty liver disease (NAFLD). NAFLD is a common cause of chronic liver disease, and its incidence is rising worldwide. Understanding its pathogenesis, biochemical parameters, histological grading and staging, and its management is a vital issue in today's clinical practice. The exact causes responsible for the development of NAFLD have not been established yet. However, some researchers consider that a cluster of disorders that increases the risk of developing heart diseases, diabetes and stroke may be the factor behind the development of NAFLD.

Most patients with NAFLD have no symptoms or signs of liver disease at the time of diagnosis. In these patients, abnormal liver function tests are often discovered incidentally. Non-alcoholic steatohepatitis (NASH) is that stage of the spectrum that involves fat accumulation (steatosis), inflammation (hepatitis) and scarring (fibrosis) in the liver. Most patients with NAFLD have no symptoms or signs of liver disease at the time of diagnosis. In these patients, abnormal liver function tests are often discovered incidentally. Non-alcoholic steatohepatitis (NASH) is that stage of the spectrum that involves fat accumulation (steatosis), inflammation (hepatitis) and scarring (fibrosis) in the liver. In our study, non-alcoholic cirrhosis patients were included as additional study group along with controls.[6]

OBJECTIVES OF THE STUDY

To study the levels of serum cholinesterase and hs-CRP in alcoholic cirrhotics and healthy controls.

To study the levels of serum cholinesterase and hs-CRP in alcoholic cirrhotics and non-alcoholic cirrhotics.

To study the efficacy of serum cholinesterase and hs-CRP levels to differentiate alcoholic cirrhosis from non-alcoholic cirrhotics.

MATERIALS AND METHODS

The study was done in Victoria Hospital, and Bowring and Lady Curzon Hospital attached to Bangalore Medical College and Research Institute. Institutional ethical committee approval has been taken. The study period is from July 2015 to June 2016. The case-control study involved 90 subjects. Based on inclusion and exclusion criteria a total number of 60 subjects (30 cases and 30 controls) were selected for the present study.

Thirty males who are diagnosed with the alcoholic liver disease with a history of consumption of alcohol spirits of >60 g in males on a daily basis for a duration of more than 8 to 10 years, clinical signs of liver disease, supporting biochemical tests and ultrasonographic features were included in the study. Controls are 30 males who are non-alcoholic, normal, healthy individuals. Patients with clinical evidence of hypertension, diabetes mellitus, pancreatitis, and renal failure, documented evidence of organophosphorus poisoning, history of intake of hepatotoxic drugs, history of any inflammatory diseases and other causes of cirrhosis were excluded in the study. Thirty non-alcoholic cirrhosis cases confirmed by ultrasonography were included in this study as an additional study group.

Based on the inclusion and exclusion criteria, age-matched cases and controls were included in the present study after obtaining informed consent. A proforma was used to record relevant information and patient's data. Alcohol drinking history was assessed by interview and questionnaire. Data from the questionnaire was used to establish consumed duration type and pattern of alcohol intake.

Method of Analysis

Following selection of subjects and after obtaining informed consent about the proposed study, clinical history was taken from subjects, and examination findings were noted down. About 5 mL of venous blood sample was collected from the median cubital vein by venipuncture with aseptic precautions. Serum was separated by centrifugation, and separated serum was used for estimation of γ-GT, serum cholinesterase (CHE), hs-CRP, total and direct bilirubin, albumin, total protein, AST, ALT, and ALP. The fully automated clinical chemistry analyzer Beckman Coulter AU480 was used to analyze those parameters.

Statistical Analysis

The results were tabulated. Results on continuous measurements are presented on mean ± standard deviation (SD). The statistical analysis of data was done by using software namely statistical analysis system (SAS) 9.2, Statistical Package for Social Sciences (SPSS) 20.0, Stata 10.1, MedCalc 9.0.1, Systat 12.0 and R environment version 2.1.1. The results of cases and controls were compared by student 't' test. A 'p' value of < 0.05 was considered significant. A 'p' value of <0.0001 was considered as highly significant. Pearson correlation between study variables is performed to find the degree of relationship.

RESULTS AND DISCUSSION

The alcoholic liver disease is considered to be a major cause of morbidity and mortality, with an increased rate of incidence daily, especially in developing countries like India. Chronic alcohol intake remains the major cause of cirrhosis. Excessive consumption of alcohol by a large section of the population is still a medical and social problem in many countries.

In Table 1, the age of the cases was ranged from 31 to 60 years which was similar in controls and non-ALC groups. The mean ± SD age of cases was 45.03 ± 8.45 and controls were 46.9 ± 7.21 with p-value equals 0.3603, this is in accordance with the study by Diana C which suggests that alcoholic cirrhosis is typically encountered at ages between 30 and 50 years. According to Paula et al., age-specific mortality was highest in 45 to 64 years of age. The mean ± SD age of the non-ALC group was 45.66 ± 8.17. There were significant elevation in serum bilirubin (both total and direct) levels in alcoholic cirrhosis cases when compared to controls with significant p-value of < 0.001.

In Tables 2 and 3, the values of mean ± SD of total bilirubin and direct bilirubin in cases and controls were 8.37 ± 7.97 and 3.83 ± 3.79 and 0.49 ± 0.26 and 0.02 ± 0.04 respectively. This shows that the excretory function of liver in alcoholic cirrhosis cases is impaired. The values of mean ± SD of total bilirubin and direct bilirubin in cases and the non-ALC group were 8.37 ± 7.97 and 3.83 ± 3.79 and 2.33 ± 0.78 and 0.55 ± 0.45 respectively. There was a significant elevation in both total and direct bilirubin levels in alcoholic cirrhosis cases compared to non-ALC group with a statistically significant p-value of < 0.001.

In this study, the serum total protein was decreased in alcoholic cirrhosis cases compared to controls. The mean ± SD of total protein in cases and controls were 6.43 ± 1.19 and 7.48 ± 0.47 respectively. The decrease in serum total protein in cases is statistically very

Table 1: Age distribution of patients studied

	Cases		*Controls*		*Non-ALC*	
Age in years	*No.*	*%*	*No.*	*%*	*No.*	*%*
31–40	10	33.33	7	23.33	9	30.00
41–50	11	36.67	15	50.00	12	40.00
51–60	9	30.00	8	26.67	9	30.00
Total	30	100.00	30	100.00	30	100.00
Mean ± SD	45.03 ± 8.45		46.9 ± 7.21		45.66 ± 8.17	

Table 2: Comparison of study variables in cases and controls

Parameters	*Cases*	*Controls*	*p-value*
Total bilirubin	8.37 ± 7.97	0.49 ± 0.26	< 0.001
Direct bilirubin	3.83 ± 3.79	0.02 ± 0.04	< 0.001
Total protein	6.43 ± 1.19	7.48 ± 0.47	< 0.001
Albumin	2.07 ± 0.66	4.25 ± 0.34	< 0.001
A:G	0.48 ± 0.17	1.29 ± 0.18	< 0.001
AST	127.23 ± 97.01	29.3 ± 7.57	<0.001
ALT	41.33 ± 36.49	23.63 ± 8.82	0.0112
ALP	166.16 ± 73.53	87.86 ± 19.29	< 0.001
GGT	90.7 ± 48.61	22.56 ± 9.06	< 0.001
hs-CRP	1.23 ± 0.42	0.17 ± 0.10	< 0.001
Serum cholinesterase	2112.43 ± 1195.94	7652.1 ± 586.16	< 0.001

Table 3: Comparison of study variables in cases and non-ALC group

Parameters	*Cases*	*Non-ALC*	*p-value*
Total bilirubin	8.37 ± 7.97	2.33 ± 0.78	< 0.001
Direct bilirubin	3.83 ± 3.79	0.55 ± 0.45	< 0.001
Total protein	6.43 ± 1.19	5.65 ± 0.86	0.051
Albumin	2.07 ± 0.66	2.88 ± 0.63	< 0.001
A:G	0.48 ± 0.17	1.02 ± 0.17	< 0.001
AST	127.23 ± 91.01	142.4 ± 52.11	0.4536
ALT	41.33 ± 36.49	86.3 ± 33.09	< 0.001
ALP	166.16 ± 73.53	118.7 ± 27.17	0.016
GGT	90.7 ± 48.61	30.43 ± 8.13	< 0.001
hs-CRP	1.23 ± 0.42	1.79 ± 0.28	< 0.001
Serum cholinesterase	2112.43 ± 1195.94	4004.73 ± 971.03	< 0.001

highly significant with p-value <0.001. This result is in accordance with Gopinath et al. study which showed a significant decrease in total protein levels in alcoholic liver disease. The serum total protein was much more decreased in non-ALC group compared to alcoholic cirrhosis cases. The mean ± SD of total protein in cases and the non-ALC groups were 6.43 ± 1.19 and 5.65 ± 0.86 respectively. The decrease in serum total protein in the non-ALC group is statistically highly significant with p-value = 0.005. This shows the synthetic function of the liver is getting impaired. The liver is the primary site of synthesis of plasma proteins. Disturbance of protein synthesis occurs as a result of an impaired hepatic function. The causes include the decreased availability of amino acids, increased catabolic states which are present in cirrhosis.

Serum albumin levels in this study were significantly decreased in cases compared to controls with a significant p-value of <0.001. The mean ± SD of serum albumin levels in cases and controls were 2.07 ± 0.66 and 4.25 ± 0.34 respectively. Whereas, the serum albumin levels were decreased in both alcoholic cases and non-ALC group with a significant p-value of <0.001. The mean ± SD of serum albumin levels in cases and the non-ALC group were 2.07 ± 0.66 and 2.88 ± 0.63 respectively. Decreased hepatic synthesis of albumin and loss of albumin in the ascitic fluid are the main causes of hypoalbuminemia in cirrhosis.

In this study, albumin/globulin ratio was significantly decreased in cases compared to controls with a mean of 0.48 and 1.29 in cases and controls and SD of 0.17 and 0.18 respectively with a significant p-value of <0.001. Whereas, when compared to the non-ALC group, the A:G ratio was still lower in alcoholic cases than the non-ALC group with a significant p-value of <0.001. There is a reversal of A:G ratio in this study.

Aspartate transaminase (AST) estimated in this study had significantly elevated in alcoholic cirrhosis cases when compared to controls with a highly significant p-value of <0.001. The mean and SD of AST in cases and controls were 127.23 ± 97.01 and 29.3 ± 7.57 respectively. But there was no significant rise in ALT in cases compared to controls with significant p-value equals 0.0112. The mean and SD of ALT in cases was 41.33 and 36.49 respectively and in controls was 23.63 and 8.82 respectively. In alcoholic cirrhosis, AST is higher than ALT, the cause may be increased appearance of mitochondrial AST, a decrease in ALT production and damage to other tissues that release AST and not ALT. The mean ± SD of AST in cases and the non-ALC group were 127.23 ± 97.01 and 142.4 ± 52.11 respectively with p = 0.4526. The ALT levels were slightly elevated in non-alcoholic cirrhosis than alcoholic cirrhosis cases with a highly significant p-value of <0.001. The mean ± SD of ALT in cases and non-ALC were 41.33 ± 36.49 and 86.3 ± 33.09 respectively.

In this study, the mean ALP level in cases was 166.16 and SD 73.53 when compared to controls with mean 87.86 and SD 19.29. The elevation of ALP levels in cases compared to controls were very highly significant with a p-value of <0.001. The mean ± SD of ALP in cases and the non-ALC group were 166.16 ± 73.53 and 118.7 ± 27.17 respectively. There was a slight elevation of ALP level in cases compared to non-alcoholic cirrhosis group with significant p = 0.0016.

The mean GGT level in cases was 90.7 and SD 48.61. In controls, the mean GGT level was 22.56 and SD 9.06. In the non-ALC group, the mean GGT level was 30.43 and SD 8.13. Serum GGT levels were significantly elevated in alcoholic cirrhosis cases when compared to controls and non-ALC group with a significant p-value <0.001. Alcohol causes the microsomal induction thereby increasing the serum levels of GGT.

In this study, the serum cholinesterase levels were decreased in alcoholic compared to controls with a highly significant p-value of <0.001. The mean ± SD of serum cholinesterase in cases and controls were 2112.43 ± 1195.94 and 7652.1 ± 586.16 respectively, and this is in accordance with the study by Jeyamani Ramachandran. The mean serum cholinesterase level in non-ALC group was 4004.73 and SD 971.03. The serum cholinesterase levels were decreased in both alcoholic cirrhosis and non-alcoholic cirrhosis groups, but the levels were very much reduced in alcoholic cirrhosis cases compared to non-alcoholic cirrhosis with a significant p-value <0.001.

In this study, the hs-CRP level was increased in cases compared to controls with a p-value of <0.001. The mean ± SD in cases were 1.23 ± 0.42 and in controls were 0.17 ± 0.10. The hs-CRP levels were increased in both alcoholic cases, and non-alcoholic group whereas the levels were higher in the non-ALC group compared to alcoholic cases with a significant p-value of <0.001. The mean ± SD in the non-ALC group was 1.79 ± 0.28. Several studies showed that there was an increase in hs-CRP levels in non-alcoholic liver disease and can be used as a biomarker.

As shown in Table 4, serum cholinesterase correlated positively with total protein, albumin, GGT and hs-CRP with an R-value of 0.2779, 0.4075, 0.1073, and 0.1334 respectively and negatively with AST, ALT and ALP with an R-value of –0.1936, –0.1547, and –0.1331 respectively in alcoholic cirrhosis patients. Whereas, In Non- alcoholic cirrhosis patients, the Serum cholinesterase showed a negative correlation with total protein and albumin with an R-value of –0.2538 and –0.2891 respectively and positive correlation with AST, ALT, ALP, GGT, and hs-CRP with the R-value of 0.3018, 0.3094, 0.0373, 0.032, and 0.0964 respectively.

Table 4: Comparison of serum cholinesterase with liver function tests

	Cases		*Controls*		*Non-ALC*	
Pair	*R-value*	*p-value*	*R-value*	*p-value*	*R-value*	*p-value*
CHE *vs* TP	0.2779	0.1370	–0.027	0.8873	–0.2154	0.2538
CHE *vs* Alb	0.4075	0.025	0.0637	0.7380	–0.2891	0.1214
CHE *vs* AST	–0.1936	0.3068	–0.0065	0.9748	0.3018	0.1050
CHE *vs* ALT	–0.1547	0.4164	0.0681	0.7206	0.3094	0.096
CHE *vs* ALP	–0.1331	0.4835	0.203	0.2819	0.0373	0.8448
CHE *vs* GGT	0.1703	0.3682	0.246	0.1900	0.032	0.8666
CHE *vs* hs-CRP	0.1334	0.4822	–0.2229	0.2383	0.0964	0.9598

Table 5: Comparison of hs-CRP with liver function tests

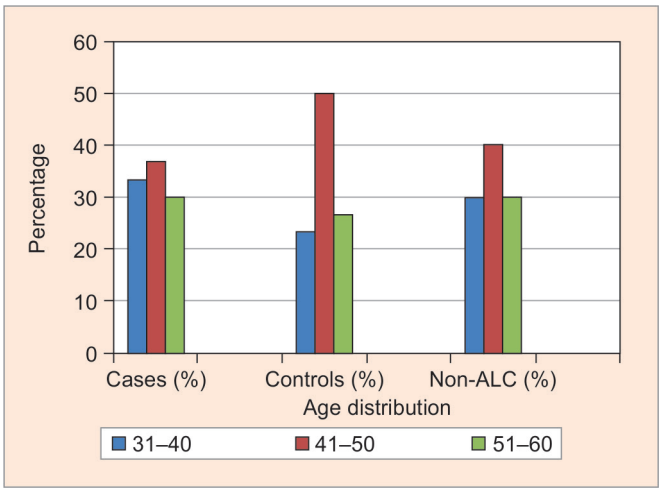
	Cases		*Controls*		*Non-ALC*	
Pair	*R-value*	*p-value*	*R-value*	*p-value*	*R-value*	*p-value*
hs-CRP *vs* TP	–0.0977	0.6101	0.0598	0.7535	–0.1826	0.3357
hs-CRP *vs* Alb	0.1424	0.4528	0.1576	0.4055	–0.1847	0.3303
hs-CRP *vs* AST	0.2634	0.1596	–0.2068	0.2747	0.2411	0.1993
hs-CRP *vs* ALT	–0.0111	0.9539	–0.0821	0.6666	0.0745	0.6956
hs-CRP *vs* ALP	0.1195	0.5293	0.2116	0.2616	–0.2766	0.1398
hs-CRP *vs* GGT	0.1682	0.3742	–0.0275	0.8873	–0.0334	0.8620

Table 6: Analysis of variance (ANOVA) results of CHE and hs-CRP among study groups

		Sum of squares	*df*	*Mean square*	*F*	*Sig.*
Serum cholinesterase (IU/L)	Between groups	475719896.689	2	237859948.344	262.656	0.000
	Within groups	78786693.933	87	905594.183	–	–
	Total	554506590.622	89	–	–	–
hs-CRP (mg/dL)	Between groups	29.283	2	14.641	23.902	0.000
	Within groups	52.679	86	0.613	–	–
	Total	81.961	88	–	–	–

As shown in Table 5, the hs-CRP correlated positively with albumin, AST, ALP and GGT with the R-value of 0.1424, 0.2634, 0.1195 and 0.1682 respectively and negatively with total protein and ALT with the R-value of –0.0997 and –0.0111 respectively in alcoholic cirrhosis patients. Whereas, In non-alcoholic cirrhosis patients, hs-CRP showed a positive correlation with AST and ALT with the R-value of 0.2411 and 0.0745 respectively and negative correlation with total protein, albumin, ALP and GGT with the R-value of –0.1826, –0.1847, –0.2766, and –0.0334 respectively.

Analysis of variance (ANOVA) results are shown in Table 6. Using this procedure, both serum cholinesterase and hs-CRP were showing the significance level with a value of 0.000 between the study groups.



Graph 1: Age distribution of patients and controls studied

Das et al. shows that alcohol is one of the main causes of end-stage liver diseases. Five to 15% of patients with alcoholic fatty liver develop cirrhosis. Alcohol is associated with spectrum disease, especially liver cirrhosis. Alcoholic liver disease occurs in patients who consume an excessive amount of alcohol for many decades.[7,8] Meng et al. showed that serum cholinesterase might provide useful information concerning the state of a cirrhotic patient's liver. It is closely correlated with the severity of liver cells and can be used as a liver function test.[9] Wilson et al. showed that, compared with normal subjects and convalescent patients, there is a significant difference in the plasma cholinesterase activity of patients with liver disease.[10] Rao et al. showed that Pseudocholinesterase enzyme is a more specific and better marker of liver disorder than serum glutamic pyruvic transaminase (SGPT) itself. The pseudocholinesterase concentration decreases correspondingly and specifically with more functional liver cell damage and may be used as a diagnostic marker for cirrhosis of the liver.[11] Galanti et al. showed that serum cholinesterase levels were more lowered in alcoholic liver disease than nonalcoholic

patients.[12] Ramachandran et al. and Ogunkeye et al. showed that serum cholinesterase levels decreased in cirrhotics as compared to healthy controls and it is an excellent biomarker of cirrhosis with good sensitivity and specificity.[13,14] Ndumele et al. provides an association between hepatic damage and elevated levels of hs-CRP, a protein produced predominantly by the liver under conditions of inflammation.[15] Yeniova et al. and Kogiso et al. showed that high sensitivity C-reactive protein is a strong predictor of non-alcoholic liver disease.[16,17]

To conclude, the marked decrease in serum cholinesterase in alcoholic cirrhosis patients suggest that its activity might be a specific indicator of liver dysfunction and may be helpful in diagnosing alcoholic cirrhosis patients and the hs-CRP can be used as a strong predictor of non-alcoholic cirrhosis. Similar studies on a large study group of alcoholic and non-alcoholic cirrhosis patients with results of the outcome of the liver diseases are needed to establish their usefulness as reliable and cost-effective biomarkers in alcoholic and non-alcoholic liver disease.

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