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Correlations between the value of serum cholinesterase and Child-Pugh and Meld-Na scores in cirrhotic patients

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ABSTRACT

To determine the degree of the liver failure in cirrhotic patients we use serum liver function tests In contrast with tests, serum cholinesterase values are low in liver failure. Purpose of the study is to establish if serum cholinesterase corelates with the level of liver disfunction. According to the Child-Pugh Score, 70 patients with chronic liver disease were selected and grouped into 3 categories. Serum cholinesterase, serum albumin and International Normalized Ratio were analyzed and correlations between them were calculated. We observed that the cholinesterase levels tend to decrease according to the Child-Pugh score, lowest in the C group and highest in the A group. The cholinesterase correlated with the albumin serum levels, value of MELD-Na score and Child-Pugh score and did not corelate to INR. In conclusion, serum cholinesterase can be used as an indicator of the liver disfunction grade.

Keywords: serum cholinesterase, liver cirrhosis, Child-Pugh Score, albumin, MELD-Na score

Abbreviations:
LFTs iver function tests;
INR International Normalized Ratio
BCHE cholinesterase

INTRODUCTION

The patients with liver disease are evaluated by using liver function tests (LFTs), a set of laboratory blood tests. These tests are used also in the treatment decisions for the patients with liver disease. These tests are albumin, alkaline phosphatase, bilirubin, coagulation factors and serum aspartate and alanine transaminases [1]. The result of these tests can be altered by the presence of concomitant pathologies and then the abnormal results doesn't reflect only the liver dysfunction [2]. The proteins synthetised by the liver include ceruloplasmin, serum albumin, alfa1-antitrypsin, ferritin, lipoproteins and blood clotting factors. These proteins are synthetised in the liver but the serum levels can be influenced by other pathologies. Serum cholinesterase is also synthetised in the liver cell and then released in the blood stream [5]. As other proteins, in liver failure due to reduced synthesis, the serum cholinesterase activity is reduced also. In contrast with other serum proteins used in the estimation of liver function whose level rise secondary to increased re-

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lease from liver cells induced by altered membrane permeability [3] or secondary to exposure to medication or other treatments. In the evaluation of the patient, the Child-Pugh score is used to estimate the prognosis of liver disease. Initially was utilised to predict surgery related mortality, the Child Pugh score is now utilised to predict prognosis and the need to adjust the treatment intensity, and the necessity for liver transplantation. In the Child-Pugh score, blood-clotting factors and serum protein are very important in estimation of the functional liver reserve [4]. In the case of patients with cirrhosis, especially the patients with advanced liver disease, with Child grades B and C with complications (ascites or coagulopathies), the treatment include human albumin or transfusions, which alter the LFT when calculating the Child-Pugh Score [5]. As an advantage, serum cholinesterase level is not altered by these treatments. We compared Child-Pugh score and MELD-NA score with the serum cholinesterase activity to estimate the liver reserve function of cirrhotic patients. We monitored the correlation between cholinesterase, albumin and INR because these proteins are synthesized by the liver with different half-life [6].

PATIENTS AND METHODS

Patients

We selected 70 patients admitted to the Fundeni Clinical Institute (Bucharest, Romania), 28 male medium age and 42 females between 2017 and 2018 were included in the present study. The inclusion criteria was: a diagnosis of cirrhosis (based on clinical examination or ultrasound signs or transient elastography evaluations or histology data). Exclusion criteria were recent treatment with blood transfusion or albumin in the last month prior to enrolment, clinical evidence of recent variceal bleeding, known diagnosis of hepatocellular carcinoma and history of liver transplantation. We obtained the informed consent from all patients.

Measurement of biochemical serum markers

Minimal stasis was used when we obtained blood samples. Serum was obtained from clotted blood by centrifugation within 1 h from sampling. Serum albumin, total bilirubin, creatinine, Na, ALAT, INR and complete blood count were carried out. Serum cholinesterase activity was determined using a chemiluminescent method using a Cobas e601 Roche automatic analyser in 2 hours of sample separation.

Statistical analysis

Statistical analysis and database management were performed using JASP 0.16.3 Software for Windows [11]. Descriptive results were presented as the mean ± standard deviation (SD) or number (percentage) of patients. We used multiple comparisons for the ANOVA test to compare the mean data. We applied The Pearson correction test for comparison of serum cholinesterase, serum albumin and serum prothrombin times (INR). The tests were two-tailed and $P<0.05$ was considered to indicate a statistically significant difference.

RESULTS

Patient characteristics

A total of 70 patients mean age 66.47±10.41 years were included. 28 patients were male with a mean age of 63,64±12,74 Years and 42 females with a mean age of 68.35±8,15 years. The main demographic data of the patients are summarized in Table 1 and the clinical and laboratory data in Table 2.

Child-Pugh class A group was present in 43 patients (61,42%), class B in 13 patients (18,57%) and class C in 14 patients (20%) (Table 3).

Serum cholinesterase in various Child-Pugh score groups

The results indicated that serum cholinesterase tends to decrease significantly in the three grades: Child A (8055.465±1709.092U/l), Child B (5415.769 ± 1109.270 U/l) and Child C (2543.643±838.512 U/l) (Table 4). Difference between the mean serum cholinesterase activity in the Child A, B and C groups was statistically significant, as was the difference between the mean values for the Child B and C groups (Table 3, Figure 1, Figure 2).

Correlation between the serum cholinesterase, albumin and INR

Cholinesterase was positively correlated with albumin ($r=0.633$, $P<0.001$) and negatively correlated with INR ($r=-0.404$, $P<0.001$) in these patients. This aspect confirms that those substances were synthesized in the liver and reduced in the liver disfunction due to reduced synthesis. Cholinesterase and INR ($r=-0.404$, $p=0.001$) have a negative strong correlation. Albumin and INR ($r=0.782$, $p=0.001$) have a strong positive correlation (Table 4, Table 5, Table 6).

TABLE 1. Demographic characteristics of the study population

Descriptive Statistics							
		Valid	Missing	Mean	Std. Deviation	Minimum	Maximum
Age	female	42	0	68.357	8.150	46.000	84.000
Age	male	28	0	63.643	12.749	33.000	82.000

TABLE 2. Clinical and laboratory characteristics of the study population

Descriptive Statistics						
	Valid	**Missing**	**Mean**	**Std. Deviation**	**Minimum**	**Maximum**
Age	70	0	66.471	10.416	33.000	84.000
Sex	70	0				
Albumin	70	0	3.471	1.046	1.800	5.200
Cholinesterase activity	70	0	6462.871	2651.086	1131.000	11982.000
Child Pugh Score	70	0	7.157	3.264	5.000	16.000
MELD-Na Score	70	0	11.129	7.089	6.000	32.000
Total Bilirubin	70	0	2.572	5.592	0.270	30.900
Encephalopathy grade	70	0	0.371	0.705	0.000	2.000
Ascites grade	70	0	0.300	0.667	0.000	2.000
Creatinine	70	0	0.950	0.402	0.400	3.300
ALAT	70	0	63.029	38.464	11.000	190.000
INR	70	0	1.243	0.434	0.890	3.010
Na	70	0	137.971	5.217	122.000	147.000
Hb	70	0	13.523	2.261	3.500	17.200
PLT	70	0	176.443	75.188	31.000	348.000
Leu	70	0	6.599	2.473	3.100	18.000
Note. Not all values are available for *Nominal Text* variables						

TABLE 3. Cholinesterase activity in the Child-Pugh groups of cirrhotic patients

Descriptive Statistics			
	Cholinesterase activity		
	A	**B**	**C**
Valid	43	13	14
Missing	0	0	0
Mean	8055.465	5415.769	2543.643
Std. Deviation	1709.092	1109.270	838.512
Range	6719.000	2950.000	2820.000
Minimum	5263.000	4342.000	1131.000
Maximum	11982.000	7292.000	3951.000

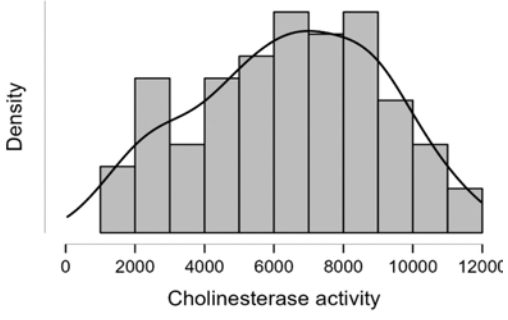

FIGURE 1. Distribution Plots of cholinesterase activity

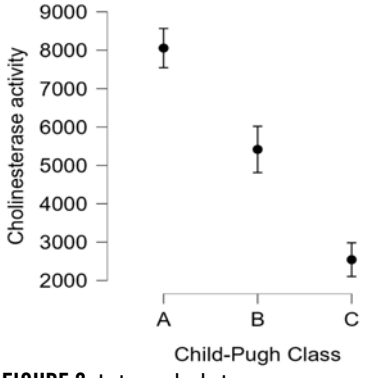

FIGURE 2. Interval plots

TABLE 4. Correlations between cholinesterase, albumin and INR in the Child A group of cirrhotic patients

Related pairs	Correlation index	P-value
BCHE: Alb	r=0.153	0.328
BCHE: INR	r=-0.027	0.862
Alb: INR	r=-0.114	0.357
BCHE, cholinesterase; Alb, albumin; INR International Normalized Ratio		

TABLE 5. Correlations between cholinesterase, albumin and INR in the Child B group of cirrhotic patients

Related pairs	Correlation index	P-value
BCHE: Alb	r=0.881	0.001
BCHE: INR	r=0.564	0.045
Alb: INR	r=0.732	0.004
BCHE, cholinesterase; Alb, albumin; INR International Normalized Ratio		

TABLE 6. Correlations between cholinesterase, albumin and INR in the Child C group of cirrhotic patients

Related pairs	Correlation index	P-value
BCHE: Alb	r=0.169	0.564
BCHE: INR	r=-0345	0.227
Alb: INR	r=0.716	0.004
BCHE, cholinesterase; Alb, albumin; INR International Normalized Ratio		

Correlation between the serum cholinesterase, Child-Pugh Score and MELD-Na

Cholinesterase and Child-Pugh Score have a negative, strong correlation (r=-0.696, p=0.001). Cholinesterase and MELD-Na score (r=-0.548, p=0.001) have the same negative strong correlation. Between the Child-Pugh score and MELD-Na score (r=-0.783, p=0.001) we have a strong significative correlation that validates the data (Table 4, Table 5, Table 6, Table 7).

TABLE 7. Correlations between cholinesterase, albumin and INR in all patients

Related pairs	Correlation index	P-value
BCHE: Alb	r=0.663	0.001
BCHE: INR	r=-0.404	0.001
Alb: INR	r=0.782	0.001
BCHE: Child-Pugh Score	r=-0.696	0.001
BCHE: Meld NA	r=-0.584	0.001
Child-Pugh Score: Meld-Na score	r=0.783	0.001
BCHE, cholinesterase; Alb, albumin; INR International Normalized Ratio		

Serum cholinesterase in Child-Pugh score groups in patients with Virus C

We selected 52 patients with virus C and grouped them into A, B and C groups, based on their Child-Pugh score. The results indicated that serum cholinesterase levels have a tendency to decrease significantly in the three grades: Child A (8237.541 ± 1572.758U/l), Child B (5390.111±1167.291 U/l) and Child C (2702.667±1011.552 U/l) (Table 8), similar to the results from all the patients. The difference between the mean serum cholinesterase activity in the Child A, B and C groups was statistically significant, as was the difference between the mean values for the Child B and C groups (Table 8, Figure 3). The values are similar to the values obtained for the entire group.

TABLE 8. Cholinesterase activity in the Child-Pugh groups of cirrhotic patients with virus C

Descriptive Statistics			
	Cholinesterase activity		
	A	**B**	**C**
Valid	37	9	6
Missing	0	0	0
Mean	8237.541	5390.111	2702.667
Std. Deviation	1572.758	1167.291	1011.552
Range	6389.000	2950.000	2820.000
Minimum	5593.000	4342.000	1131.000
Maximum	11982.000	7292.000	3951.000

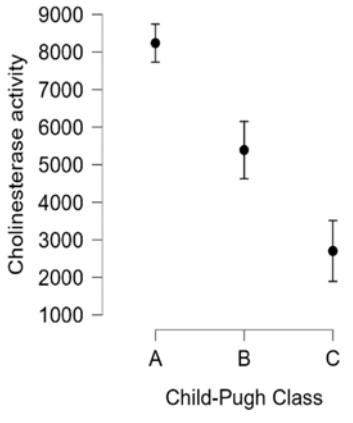

FIGURE 3. Interval plots – Cholinesterase activity in selected patients with virus C liver cirrhosis

DISCUSSION

The cholinesterases are part of a family of enzymes that process acetylcholine, a neurotransmitter, into choline and acetic acid. This reaction is important because allows a cholinergic neuron to return to its resting state after activation [7]. There are two types of cholinesterases: acetylcholinesterase (AChE) and butyrylcholinesterase (BChE).

Acetylcholinesterase (AchE) also known as erythrocyte cholinesterases or acethylcholine acetylhydrolase, which is found mainly in the blood and neural synapses. Butyrylcholinesterase (BCHE), also termed as plasma cholinesterase or pseudocholinesterase or acylcholine acylhydrolase, is found mainly in the liver [8,9].

The determination of the serum cholinesterase activity was first studied by McArdle in 1940 (10), as a potentially useful tool for differentiating jaundice of hepatic cause from obstructive jaundice. The data suggested that cholinesterase activity is an useful indicator for liver dysfunction grade in patients with liver disease. Serum cholinesterase is used in scores to distinguish hepatitis severity by Chinese National Society of liver disease [11]. However, there are still not enough studies to sustain the general use of serum cholinesterase level in the assessment of liver functional reserve. The Child-Turcotte-Pugh scoring system is the first score used in the evaluation of end-stage liver disease [12]. Our 70 patients were grouped according to Child-Pugh score groups. Serum cholinesterase level tended to significantly decrease in all the three grades. In the Child A group, the serum cholinesterase value was 8055.46U/l with a SD of 1709.09U/l, in the Child B group the mean value of serum cholinesterase was 5415.76U/l with SD of 1109.27 and in the Child C the mean value of serum cholinesterase was 2543.64U/l with a SD of 838.51U/l. The result are similar with the data published by Gu and Zhong [13]. Their findings showed that the levels of cholinesterase were: Child A (5978±535U/l), Child B (3957±454U/l) and Child C (2267±332U/l). The Child-Pugh score is calculated from five clinical items of liver disease. Two of them, ascites and encephalopathy, are subjective measures [14]. Liver cirrhosis is stratified into three Child-Pugh class A, b and C, utilising the added score from above. Cholinesterase compared with the Child-Pugh score, has the advantage that is easier to obtain (only one blood test to determine), more objective in evaluating the liver reserve of cirrhotic patients and has a low cost.

Protein biosynthesis is done mainly by the liver. Serum cholinesterase, serum albumin and blood-clothing factors are synthetised in the liver and then released into the blood stream. Thus, LFT's include albumin, cholinesterase and prothrombin time (INR) and may provide useful information concerning the liver function reserve of a patient with liver cirrhosis. Cholinesterase was positively correlated with albumin and negatively corelated with INR, confirming that those proteins were produced by the liver and reduced in liver disfunction due to re-

duced synthesis. In patients with decompensated liver disease (Grade B and C of Child-Pugh score), albumin and blood transfusions are usually used as a standard treatment, which may alter or create a false improvement of the value of the albumin and INR that are used to calculate the Child-Pugh score [15]. If surgery is needed as a treatment, the risk calculated with the Child-Pugh score may be inaccurate if the patient received intravenous treatment with human albumin and blood transfusions [16]. In their study, Gu and Zhong [13] demonstrated that three cirrhotic patients (two Child B and one Child A score patient) suffered hepatic encephalopathy following portal azygos disconective operation, with cholinesterase levels of under 2000 U/l [6]. Thus, those authors suggested that cirrhotic patients with cholinesterase <2000 U/l may have higher risk for liver failure, if undergoing abdominal surgery. Thus, the combination of Child-Pugh score with serum cholinesterase levels may be more objective and accurate in evaluating the liver reserve function of cirrhotic patients, which is useful for surgeons to decide on surgery timing or for gastroenterologists to adjust the intensity of the liver treatment.

CONCLUSIONS

Our study demonstrates that the severity of the liver cells disfunction is correlated with the value of serum cholinesterase. Also the value of serum cholinesterase can estimate the liver reserve function of cirrhotic patients. Compared with the current scores (Child-Pugh score and MELD-Na score), serum cholinesterase is less complex, cheaper, easy to obtain available in all emergency units and not easily affected by treatment for decompensated cirrhosis or other disease. The combination of cholinesterase with Child-Pugh score or MELD-Na score may be more subjective and accurate in evaluating the liver reserve function of cirrhotic patients, but more research is needed.

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