Evaluation of Coagulation Parameters in Patients with Chronic Liver Diseases

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Abstract

Chronic liver diseases are associated with secondary changes in primary and secondary hemostasis. Recently, many studies have reported that the plasma level of natural anticoagulants , such as antithrombin, are altered in patients with chronic liver diseases and are associated with the severity of the disease. The aim of this study is to evaluate different haemostatic parameters including antithrombin in patients with chronic liver diseases and to define the relationship between antithrombin level and the severity of chronic liver diseases. A case control study was conducted at Ibn Sena Teaching Hospital in Mosul for the period between 1st of October 2012 and 30th of April 2013. A total of 100 subjects were included in this study; 50 patients with chronic liver diseases and 50 age and sex matched healthy controls. Coagulation parameters of cases and controls measured and compared. A total of 50 cases were included in this study, 38 patients with cirrhosis and 12 patients with chronic hepatitis. In comparison with the controls, PT, APTT and showed significant prolongation and INR significantly prolonged ($p < 0.001$). The mean level of platelet count and fibrinogen were significantly reduced in patients with chronic liver disease ($p < 0.001$). The mean levels of antithrombin was significantly reduced in cirrhotic patients ($p = 0.031$) only, and no significant reduction was found in patients with chronic hepatitis. A statistically significant negative correlation were found between antithrombin level and Child-Pugh score (Pearson $r = - 0.414$, $p = 0.01$). In conclusion chronic liver diseases is associated with derangement in all haemostatic parameters. antithrombin reflects hepatocytes synthetic function of the liver and was supported by the negative correlation between antithrombin level and the severity of liver cirrhosis assessed by Child-Pugh score .

key words : chronic liver diseases, antithrombin, Child-Pugh score, cirrhosis, chronic hepatitis

Introduction

Chronic liver diseases (CLDs) represent a major cause of morbidity and mortality worldwide. The major etiologies are chronic infection with hepatitis B (HBV) and C (HCV) viruses, alcoholic and non-alcoholic fatty liver disease. Chronic hepatitis B and C are the leading causes of cirrhosis worldwide.[1]

Chronic liver diseases are commonly associated with several haemostatic defects that include impaired synthesis of clotting factors [2-5] and coagulation inhibitors[6-8] ,abnormalities of fibrinolytic activity,[9] disseminated intravascular coagulation and platelet defects.[10] Consequently, the total effect of chronic liver diseases on haemostasis is complex, and patients with chronic liver diseases can experience both bleeding or thrombotic complications.[11]

Antithrombin (AT) is a natural anticoagulant that is synthesized exclusively in the parenchymal cells of the liver. It

neutralizes thrombin and several other activated serine proteases of the coagulation system.[12] Deficiency of AT occurs in a variety of liver diseases including chronic liver diseases and fulminant liver failure.[13] This reduction may be caused by decreased hepatic synthesis or increased consumption due to fibrinolysis or both.[11,13]
antithrombin level reflects hepatocellular impairment in chronic liver diseases and this is supported by negative correlation between antithrombin level and the clinical stage of liver disease. In mild liver diseases there is no significant reduction in AT, however, a significant reduction occurs in compensated and decompensated liver diseases, and it is severely depressed in cirrhosis. .[13] Consequently, determining the level of AT may be clinically useful in these patients for monitoring coagulopathies and making a differential diagnosis between chronic liver diseases.[13,14]

Based on the above background, the aim of this study is to evaluate different haemostatic parameters including antithrombin in patients with chronic liver diseases and to define the relationship between antithrombin level and the severity of chronic liver diseases to see whether it can be used as a marker of severity in chronic liver diseases.

Patients and methods

To accomplish the objectives of this study, a case -control study was conducted at Ibn Sena Teaching Hospital in Mosul for the period between 1st of October 2012 and 30th of April 2013. A total of 100 subjects were included in this study; 50 patients with chronic liver diseases who were attended Ibn Sena Teaching Hospital in Mosul and 50 age and sex matched healthy controls.

Approval of the study was taken from the local Ethical Committee in Nineveh Directorate of Health and Informed written consent was taken from all the participants in this study. The patients were categorized into two groups; the first group (n = 38) were patients with liver cirrhosis and the second group (n = 12) were patients with chronic hepatitis B and C.

The general exclusion criteria for both groups included: age < 15 years, renal disease from the first, hepatocellular carcinoma and other known malignancies, pregnancy in the preceding six months, and the use of any of the following medications: heparin, warfarin, aspirin and Non Steroidal Anti Inflammatory Drugs (NSAID).
The control groups were 50 age and sex matched healthy subjects who were recruited randomly from blood donors, academic staff, medical staff, and volunteers from general publics.

The medical histories of the patients and the healthy controls was taken and physical examinations was performed. The diagnosis of cases was made by the concerned internist specialist.

A venous blood sample will be taken for CBC , liver function test (TSB, ALT, AST, Albumin), coagulation screen (PT,APTT,INR) fibrinogen and antithrombin levels. All investigations were performed strictly according to the standard technical procedure recommended by the manufacturer information of each kit. Cirrhotic patients were grouped according to Child-Pugh Score and coagulation parameters of the different grades were compared with healthy controls.

Statistical analysis

Data were presented as mean ± standard deviation (SD),range and proportions. Statistical analysis was performed using Student t-test to compare the means of independent groups. One-way analysis of

variance (ANOVA) test was used to evaluate difference between different groups. Correlation Coefficient was evaluated by the Pearson's test. P-value below 0.05 was considered to indicate statistical significance. Statistical analysis was performed using the statistical package 14 SPSS.

Results

A total of 50 patients with chronic liver diseases were enrolled in this study; 30 (60%) were males and 20 (40%) were females. The mean age of patients was (49.56± 2.47) years. More than half (58%) of cases were in age categories 46 years and above.(Figure 1)

Liver cirrhosis was diagnosed in 38 (76%) patients and chronic hepatitis in 12 (24%) patients. (Figure 2)

Table (1) reveals a comparison of coagulation parameters between chronic liver diseases and their healthy controls. The mean level of PT and APTT showed a significant prolongation, and INR significantly higher in patients with chronic hepatitis as well as in patients with cirrhosis compared to healthy controls ($p < 0.001$).The mean fibrinogen level and platelet count were significantly lower in patients with chronic hepatitis and cirrhosis in comparison with healthy controls ($p < 0.001$).The mean levels of antithrombin was significantly reduced in cirrhotic patients ($p = 0.031$) only, and no significant reduction was found in patients with chronic hepatitis.

Table (2) illustrates the coagulation parameters in cirrhotic patients according to Child-Pugh score. The mean platelets count was progressively reduced from Child-Pugh grads A to B and then to C, and in comparison to the controls the difference was statistically significant for grades B and C ($p < 0.001$). There were progressive prolongation in PT and APTT, and increasing INR across Child-Pugh grades from A to C and in comparison with controls the difference in PT and INR were significant for grades B and C and for APTT only grade C showed significant difference ($p < 0.001$). There were progressive reduction in fibrinogen from Child-Pugh Grades A to C and the difference was statistically significant for all grades when compared with healthy controls. Regarding AT there was progressive reduction in AT across Child- Pugh grades from A to C and the difference was statistically significant for grade C only when compared with the controls ($p < 0.001$).

When evaluating antithrombin level with respect to Child-Pugh score, a statistically negative correlation were found between antithrombin level and Child-Pugh score (Pearson $r = - 0.414$, $p = 0.01$). (Figure 3)

Discussion

It is well known that chronic liver diseases is characterized by variable haemostatic defects that affects primary haemostasis, fibrinolysis and coagulation.[15] Coagulation indices because of their association to liver synthetic function are well established as prognostic markers in a variety of settings in both acute and chronic liver diseases.[16]

Previous studies have shown a marked reduction in liver synthesis of coagulation factors and inhibitors in patients with chronic liver diseases.[10] Recently, natural anticoagulation proteins were approved not only to reflect hepatocytes impairment[7,8,17] but also to have predictive value in chronic liver diseases.[18] Consequently it is reasonable to assume that diverse haemostatic assays reflect hepatocyte damage in chronic liver disease and could be

of great value in the assessment of the severity of liver damage.

Thrombocytopenia is a frequent finding in chronic liver diseases. Approximately 30-64% of cirrhotic patients have thrombocytopenia, however, the platelet count is rarely less than 30,000 to 40,000 and spontaneous bleeding is uncommon.[7,19] The present study revealed significant reduction in platelet count in patient with chronic hepatitis and cirrhosis compared with healthy controls. This finding is consistent with that reported by other medical literatures.[7,19,20] In addition this study revealed progressive significant reduction in platelet count from Child-Pugh grades A to C of cirrhotic patients, these finding is in line with that reported by Poordad F. which revealed that the incidence of thrombocytopenia increases in correlation with the severity of chronic liver diseases.[20]

The present research revealed significant prolongation of PT and APTT, and increasing INR in patients with chronic liver diseases. These findings are consistent with that reported in other medical literatures,[7,21,22] and PT has kept its place as one of the parameters of common prognostic indices in advanced liver disease. Moreover, this study showed progressive prolongation of coagulation parameters (PT and APTT) and increasing INR across Child-Pugh grades A to C of cirrhotic patients. Similar findings were reported by Cong YL *et al* who founds that PT and APTT were progressively prolonged from Child-Pugh grades A to B and then to C.[23]

In consistency with other medical literatures,[17,24,25] this study showed that fibrinogen level was significantly reduced in patients with chronic hepatitis and cirrhosis. In addition cirrhotic patients showed progressive reduction in the mean fibrinogen level across Child-Pugh grades A to C and this finding is in line with that reported by another study done in China.[23] Fibrinogen is synthesized almost exclusively in the liver and low levels in cirrhotics are generally attributed to decreased liver synthetic capacity, extravascular loss (ascites) or concomitant DIC.[20]

Chronic liver diseases are usually accompanied by decreases in levels of naturally occurring anticoagulants. Decreased synthesis accounts for the majority of the deficiency,[26,27] however increased consumption during a process of intravascular coagulation ,that may complicate end stage liver diseases, may also contributes to such deficiencies.[28]

The current study showed that the mean level of antithrombin exhibited significant reduction in cirrhotic patients in comparison with healthy controls, however, there was no significant reduction in patients with chronic hepatitis. This can be interpreted as antithrombin was shown to be a good marker of cell synthetic function in cirrhosis and acute hepatitis,[29,30] but less sensitive protein reflecting hepatocytes malfunction in chronic hepatitis.[17]

The present study showed progressive reduction in the mean antithrombin level from Child-Pugh grades A to B and then to C in cirrhotic patients with significant correlation between Child-Pugh score and antithrombin level. These findings are consistent with that reported by other medical literatures [23,29,31] which stated that there is a relationship between the degree of liver function impairment that assessed by Child- Pugh score, and coagulation inhibitors which are significantly lower in Child C.

Conclusion

On the basis of the results of this study, we concluded that chronic liver diseases are associated with derangement in all haemostatic parameters. antithrombin reflects hepatocytes synthetic function of the liver and this was supported by the negative correlation between antithrombin level and

the severity of liver cirrhosis assessed by Child-Pugh score .

Further studies is needed to confirm whether antithrombin could be used in the clinical practice as a marker of the severity of chronic liver diseases.

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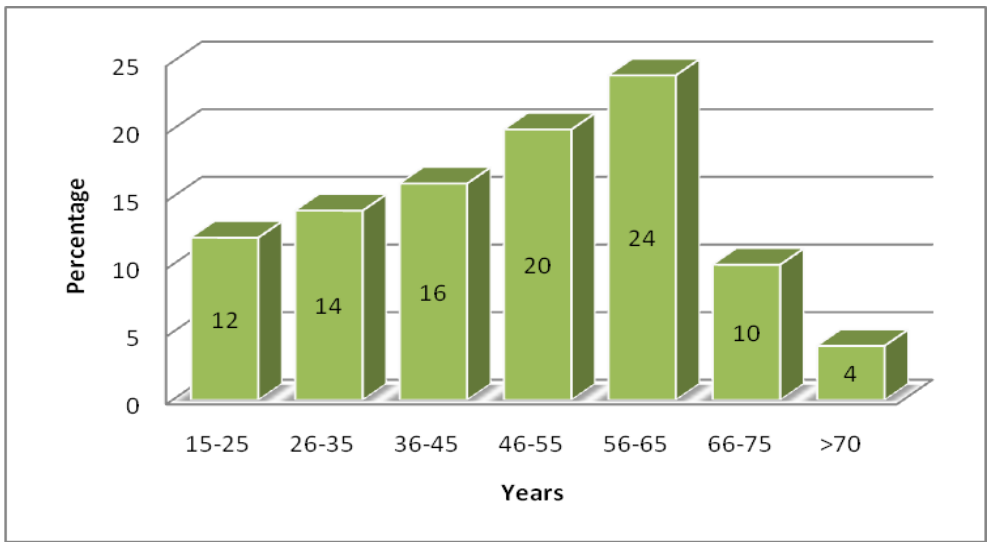


Figure (1): Age distribution of patients with chronic liver diseases.

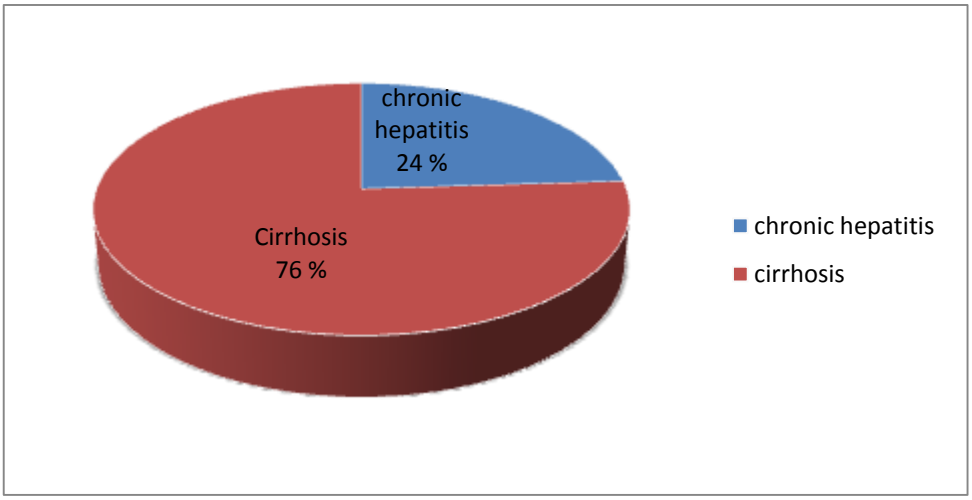


Figure (2): Categories of chronic liver diseases.

Table (1): Comparison between coagulation parameters of chronic liver diseases patients and controls

Parameter	Chronic hepatitis (n = 12)	Cirrhosis (n = 38)	Controls (n = 50)
	X±SD	X±SD	X±SD
Platelet × 10^9	151.9 ± 54.78*	132.6 ± 100.56*	219.3 ± 42.3
PT sec.	23.4 ± 10.69*	23.0 ±7.77*	13.02 ± 0.42
APTT sec.	55.5 ± 14.23*	50.5 ± 23.96*	38.4 ± 6.55
INR	2.6 ± 1.74*	2.4 ± 1.25*	1.0 ± 0.0
Fibrinogen g/L	1.98 ± 0.55*	1.93 ± 0.50*	2.96 ± 0.7
AT mg/dl	7.1 ± 7.46	7.53 ± 6.44**	10.58 ± 4.97

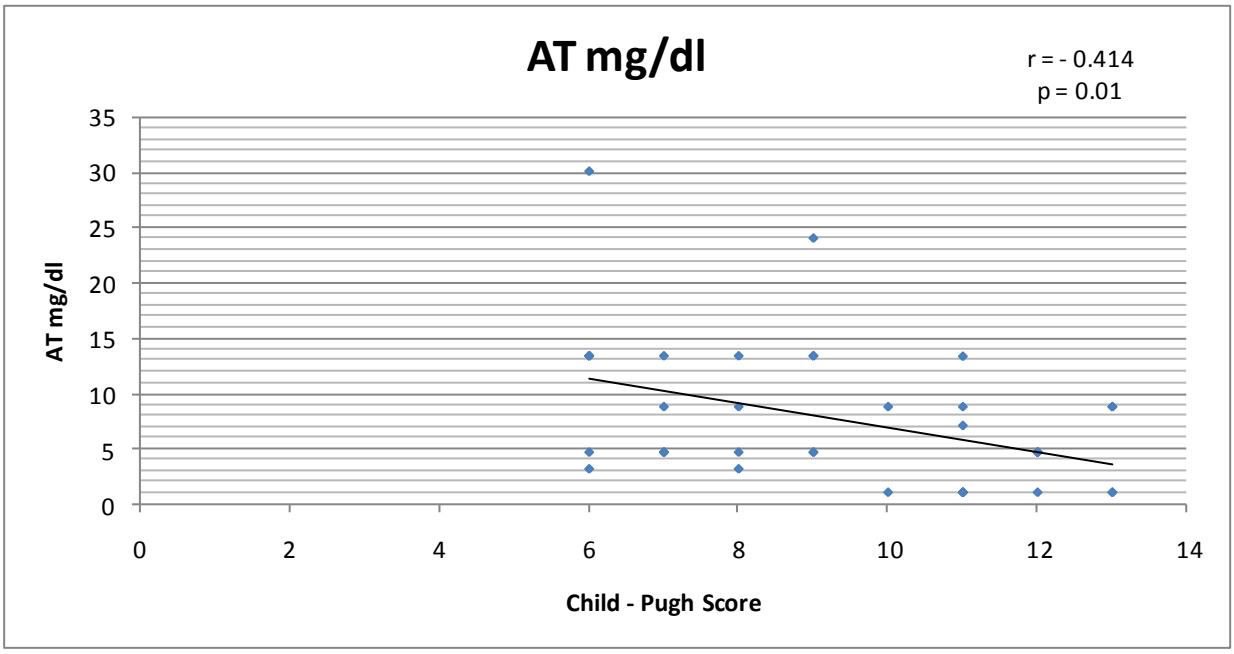
*significant difference ($p < 0.001$) in comparison with controls using one way ANOVA test to evaluate the difference between different groups.

** significant difference ($p = 0.031$) in comparison with controls using one way ANOVA test to evaluate the difference between different groups

Table (2): Coagulation parameters in patients with cirrhosis according to Child-Pugh Score

Parameter	Child-Pugh's A Grade (n= 6)	Child-Pugh's B Grade (n = 14)	Child-Pugh's C Grade (n = 18)	Controls (n = 50)
	X±SD	X±SD	X±SD	X±SD
Platelet × 10^9	156 ± 108	141.9 ± 106.3*	117.5 ± 97.1*	219.3 ± 42.3
PT sec.	17.75 ± 2.35	20.89 ± 5.62*	26.39 ± 8.95*	13.02 ± 0.42
APTT sec.	43.17 ± 3.49	43.29 ± 10.04	58.56 ± 32.23*	38.4 ± 6.55
INR	1.62 ± 0.27	2.07 ± 0.86*	3.00 ± 1.47*	1.0 ± 0.0
Fibrinogen g/L	1.94 ± 0.64*	1.93 ± 0.5*	1.91 ± 0.42*	2.96 ± 0.7
AT mg/dl	13.0 ± 9.59	9.0 ± 5.89	4.56 ± 3.87*	10.58 ± 4.97

*significant difference ($p < 0.001$) in comparison with controls using one way ANOVA test to evaluate the difference between different groups.



Figure(3): Correlation between Child-Pugh Score and AT levels in 38 patients with liver cirrhosis.