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Coagulation Profiles of Patients with Chronic Liver Disease

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Abstract

Background: The liver has a vital role in the hemostatic system. It is the site of synthesis of proteins responsible for clotting factors and their inhibitors. Liver infections/ diseases pose the effective functioning of the liver enzymes and clotting profiles. ***Objective of Study***: This retrospective study aims to determine the plasma level of APTT, PT, in patients with chronic disease state in the University of Abuja Teaching Hospital, Gwagwalada, Nigeria. ***Materials and Methods:*** A total of 144 participants were enrolled for this study; both PT and APTT were analyzed using Quick and kaolin methods, respectively. ***Results:*** 144 candidates who met the inclusion criteria were recruited for this study. table 1.0 and 2.0 showed relationship between PT and APTT in liver infections/ diseases respectively, among the subjects, 81 subjects had Asymptomatic HBV Infection with mean ± SD of 15.3704± 3.0391, 18 Asymptomatic HCV infection, 2 HBV and HCV coinfection, 34 Chronic HBV, 6 Chronic HCV, 1 HCV/HIV coinfection, 1 Chronic HCV /HIV coinfection, 1 HBV/HIV coinfection, and Liver cirrhosis. They was non-statistically significant decrease in the level of PT among patients with both asymptomatic and chronic HBV, HCV, HBV and HCV co-infection, HBV co-infection with HIV, HCV co-infection with HIV and patients with liver cirrhosis with P-value of 0.229. ***Conclusion*:** Findings from this study demonstrated that coagulation profile has an association with liver disease.

Keyword: Chronic liver disease, Coagulopathy, Hematopathy, Nigeria.

INTRODUCTION

The liver play an important role in the hemostatic system it serves as the site of synthesis of all clotting factors and their inhibitors. Other function of the liver include: immunological, digestive and endocrine functions. The liver is responsible for synthesis of proteins such as clotting factors and their inhibitors (Pahwa *et al.*, 2019). The liver is also responsible for the synthesis of thrombopoietin. Thromboplastin is also known as c-Mpl ligand, and it is the primary physiological growth factor for the megakaryocyte lineage which serve as progenitor cells responsible for the production of platelet (Varda and Aaron, 2006).

Liver disease over the period of 6 months is termed chronic liver disease. It is characterized with the gradual and continuous destruction and regeneration of the hepatic parenchyma giving rise to fibrosis and cirrhosis. Liver diseases such as inflammation (chronic hepatitis), liver cirrhosis, and hepatocellular carcinoma may give rise to chronic liver diseases (Pahwa *et al.*, 2019). Thus liver damage from chronic liver disease can develop multiple coagulation abnormalities that can interrupt the balance in hemostasis (balance between clotting and fibrinolysis). This is consequent on the inability of the liver to execute it hemostatic activities thereby causing multiple: quantitative and qualitative platelet defects; decrease production of coagulation and inhibitor factors; vitamin K deficiency; synthesis of abnormal clotting factors; decreased clearance of activated factors; hyperfibrinolysis and disseminated intravascular coagulation (Amitrano *et al.*, 2002), (Sohail *et al.*, 2011).

Viral hepatitis remains a leading cause of chronic liver diseases giving rise to morbidity and mortality affecting millions of individuals worldwide. By World Health Organization record, over 2 billion people have been infected with the hepatitis B virus (HBV), and more than 350 million have chronic HBV infection. More so, it has been estimated that up to 3% of the world's population have been infected with hepatitis C virus (HCV) of which 170 million people are chronically infected (WHO, 2008 (1 & 2)). In Nigeria, the prevalence of CLD as noted by Basharo and Maier in their meta-analysis showed that the prevalence depends on a range of factors such as cultural practices and traditions. The north central Nigeria has higher cases prevalence of hepatitis B ranging from 2 to 25%. This may be related to some cultural practices such as drinking from same cup, tribal marks or the practice of circumcision. More so, it was noted that the north central state of Nasarawa has the highest prevalence of hepatitis c range from 0.7 % to 15% (Nwokediuko *et al.,* 2013), (Maisanda and Manfred 2018).

Coagulation abnormalities in chronic liver disease are usually measured through the prolongation of first-line global screening tests such as the prothrombin time (PT) and the activated partial thromboplastin time (aPTT) (Rverter, 2006). PT measures the time needed for the platelet-poor plasma to clot after the addition of tissue extracts (thromboplastin) and calcium chloride. While aPTT is the time needed for the platelet-poor plasma to clot when mixed with a particulate or soluble activator of the contact coagulation factors (factor XII, pre-kallikrein and high-molecular- weight kininogen) and negatively charged phospholipids such as platelet substitutes (Shah and Jansari, 2014). PT determines vitamin K dependent extrinsic factors VII, X, II, V and fibrinogen. The aPTT measures the activities of intrinsic and common pathways of coagulation cascade most sensitive to factor VIII, IX, XI, XII and those of the contact system (Thachil, 2008) The clotting factors measured by the common screening test are in the normal range until plasma levels of procoagulants would be reduced below 30 to 40% (Sohail *et al.,* 2011).

Cirrhosis, which is an end stage of many liver diseases, is known to be associated with a number of hematological complications, especially thrombocytopenia and coagulation disorders. Chronic hepatitis, especially viral, constitutes a major health problem and can be caused by different etiological agents. In chronic liver diseases, the levels of anticoagulant proteins like antithrombin III, protein S, protein C, and alpha-2 macroglobulin are reduced (Devrajani *et al.,* 2012) Therefore, the coagulopathy pattern in liver disease is not limited to being anticoagulation. Rather, this group of disorders (resulting from cirrhosis of liver) encompasses procoagulant as well as anticoagulation tendencies (Bhatia *et al.,* 2017).

In this study coagulation abnormalities among patients with chronic liver disease were investigated using PT, aPTT and INR. This study also reported the relationship between hemostatic parameters with the gender and age among patients with chronic liver disease in a tertiary health institution in Nigeria.

MATERIALS AND METHOD

Study Design

The study was a retrospective study of confirmed cases of patients with chronic liver disease to be part of the study, age and gender- was matched monitored.

Study Area

This study was conducted in university of Abuja Teaching Hospital gwagwalada, Federal Capital Territory (FCT) Abuja, Gwagwalada is about 62 km away from the FCT. It is one of the settler's towns of the FCT. The town is close to the Nnamdi Azikwe international airport along the Abuja –Lokoja Express way, it is located between latitude 8°55' and 9°00'N and longitudinal 7°00' and 7°05'E.

The centrality of this town in relation to other area councils' headquarters makes it influential and important in various socio-economic activities. The climate condition of this town is not far-fetched from that of the tropics having several climatic elements in common; most especially the wet and dry season characteristic. The temperature of the area ranges from 30°C to 38°C yearly, with the highest temperature experienced in the month of March and mean total rainfall of approximately 1650 mm/annum.

About 60% of this rain falls between the months of May to August. The area council is an industrial zone of FCT that stands out as the second most cosmopolitan city of the FCT, after the capital city with 10 political wards. These have brought about the inflow of people into the council. 75% of the residents live in close proximity with poor drainage system, several pot-holes on their streets and indiscriminate environmental dumpsites.

Study Population

The study population includes 144 confirmed cases of chronic liver disease (subject) and ages-matched were recruited university of Abuja Teaching Hospital North-Central Nigeria.

Study Subjects/ Selection

Exclusion Criteria

- All confirm cases of chronic liver disease.

The following were excluded from participating as subjects in the study:

- Non liver disease cases.

Ethical Clearance and Informed Consent

Ethical clearance was obtained from the ethical committee of university of Abuja teaching Hospital. Informed consent will also be obtained from all participating subjects in accordance with the standards of human experimentation and with the Helsinki Declaration of 1975, as revised in 70. This will be done via informed consent from study participants.

Sample Size Determination

The sample size was determined using the standard formula for calculation of minimum sample size:

($n= z^2 pq/d^2$)

n =minimum sample size

z =standard normal deviation and probability.

p=prevalence of value to be estimated from previous studies.

q=Proportion of failure (= 1 - p)

d=precision, tolerance limit, the minimum is 0.05.

Therefore $n= z^2 pq/d^2$

Where; Z =95% (1.96)

P=9.9% (0.099) (Aliyu *et al*., 2011).

q=1 - 0.099 (=0.901)

d=5% (0.05)

Therefore, $n= (1.96)^2 (0.099) (0.901) / (0.05)^2$

n=144

Laboratory Analytical Protocol

Activated Partial Thromboplastin Time (aPTT), Prothrombin Time (PT)

APTT and PT were analyzed using Quick and kaolin method respectively, while hemoglobin electrophoresis was analyzed using standard cellulose acetate paper technique as described by Dacie and Lewis.

Statistical Analysis

Data obtained was entered into a statistical package (such as SPSS version 22) on a computer to define the nature of the distribution of data for each group. Statistical differences of data were analyzed using series of statistical analysis such as mean, standard deviation, Chi –square, student's t-test, ANOVA depending on the nature (categorical or continuous) and distribution of data (normal or non-normal). Pearson's correlation was used to determine the relationship between sets of data. Probability ($p \leq 0.05$) was used to determine the level of significant for all statistical analysis.

RESULTS

Table 1: Relationship between PT and liver infections/ diseases of subject

Clinical Diagnosis	No. of Subject tested	Prothrombin Time	F ratio	P value
		Mean ± SD		
Asymptomatic HBV Infection	81	15.3704± 3.0391		
Asymptomatic HCV infection	18	14.1111± 2.9283		
HBV and HCV coinfection	2	16.0000± 0.0		
Chronic HBV	34	16.2353± 3.3760		
Chronic HCV	6	17.6667± 4.0825		
HCV/HIV coinfection	1	20.0000± 0.0		
Chronic HCV /HIV coinfection	1	14 ± 0.0		
HBV/HIV coinfection	1	15 ± 0.0		
Liver cirrhosis	1	15± 0.0		
Total	**144**	**-**	**1.340**	**0.229**

Table 2: Relationship between PTTK and liver infections/ diseases of subjects

Clinical Diagnosis	No. of Subject tested	PTTK	F ratio	P value
		Mean ± SD		
Asymptomatic HBV Infection	81	32.8765± 9.1820		
Asymptomatic HCV infection	18	31.8889± 8.7910		
HBV and HCV coinfection	2	42.0000± 16.9706		
Chronic HBV	34	16.2353 ± 3.3760		
Chronic HCV	6	39.5000± 13.0652		
HCV/HIV coinfection	1	42.0000 ± 0.0		
Chronic HCV /HIV oinfection	1	34 ± 0.0		
HBV/HIV coinfection	1	34 ± 0.0		
Liver cirrhosis	1	34± 0.0		
Total	**144**	-	1.073	0.386

Table 3: Relationship between INR and liver infections/ diseases of subjects

Clinical Diagnosis	No. of Subject tested	INR	F ratio	P value
		Mean ± SD		
Asymptomatic HBV Infection	81	1.4951± 1.3344		
Asymptomatic HCV infection	18	1.2389± 0.1819		
HBV and HCV coinfection	2	1.3000± 0.0		
Chronic HBV	34	1.3794± 0.3497		
Chronic HCV	6	1.5667± 0.4033		
HCV/HIV coinfection	1	1.4000± 0.0		
Chronic HCV /HIV oinfection	1	1.1 ± 0.0		
HBV/HIV coinfection	1	1.3± 0.0		
Liver cirrhosis	1	1.3± 0.0		
Total	**144**	-	0.158	0.996

Table 4: Relationship between PTTK and age of subjects

Age (years)	No. of Subject tested	PTTK	F ratio	P value
		Mean ± SD		
≤ 14	6	34.3± 9.2		
15 – 25	26	31.6± 3.53		
26 – 35	38	37.3± 13.4		
36 – 45	44	33.2± 10.8		
46 – 55	19	31.1± 5.1		
> 55	12	37.3± 1.37		
Total	**144**	-	1.9019	0.0978

Table 5: Relationship between PT, PTTK, INR and gender of subjects

Gender	No. of Subject tested	PT	F ratio	P value	PTTK	F ratio	P value	INR	F ratio	P value
		Mean ± SD			Mean ± SD			Mean ± SD		
Male	95	15.8632± 3.4568			37.0421±14.4126			1.5158±1.2366		
Female	50	14.9200± 2.4648			30.3000±7.0689	9.690	0.002	1.2680±0.2668	1.954	0.164
Total	**145**	-	2.933	0.089						

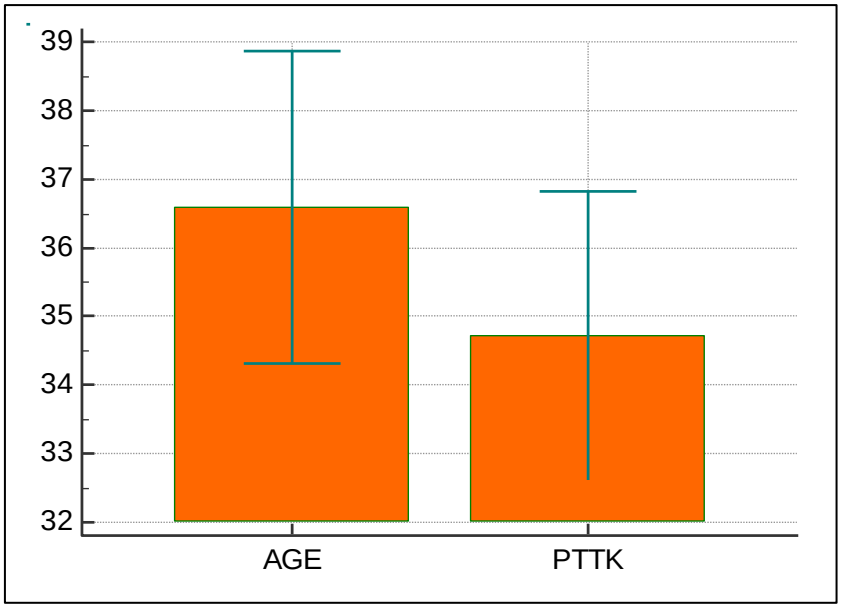

Figure 1: Bar char correlation of PTTK and Age of subjects
P = 0.033, F value = 1.594

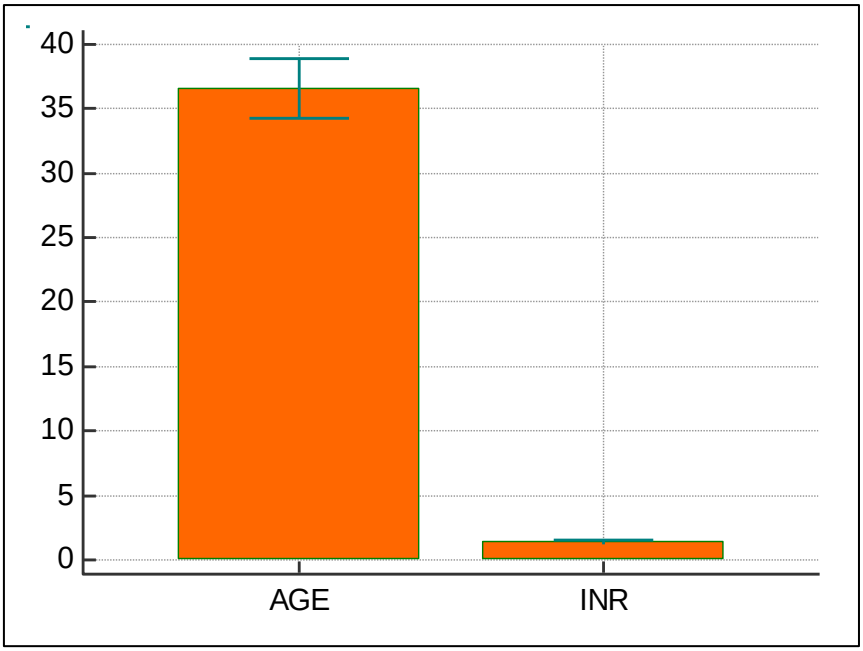

Figure 2: Bar char correlation of INR and Age of subjects
P = 0.228, F value = 1.280

DISCUSSION

The liver has a vital role in the hemostatic system. It is the site of synthesis of proteins responsible for clotting factors and their inhibitors. Liver infections/ diseases pose the effective functioning of the liver enzymes and clotting profiles at large. In this study, first-line global screening tests (PT), (aPTT) and the (INR) were employed as bio-markers for assessing the liver physiologic functioning (Devrajani *et al.,* 2012).

144 candidates who met the inclusion criterial were recruited for this study. table 1.0 and 2.0 showed relationship between PT and APTT in liver infections/ diseases respectively, among the subjects, 81 subjects had Asymptomatic HBV Infection with mean ± SD of 15.3704± 3.0391, 18 Asymptomatic HCV infection, 2 HBV and HCV coinfection, 34 Chronic HBV, 6 Chronic HCV, 1 HCV/HIV coinfection, 1 Chronic HCV /HIV coinfection, 1 HBV/HIV coinfection, and Liver cirrhosis. They was non-statistically significant decrease in the level of PT among patients with both asymptomatic and chronic HBV, HCV, HBV and HCV co-infection, HBV co-infection with HIV, HCV co-infection with HIV and patients with liver cirrhosis with P-value of 0.229. Our findings were in keeping with an earlier report from Archna *et al.,* who noted statistically non-significant difference in mean values of PT and aPTT in patients with or without cirrhosis (Pahwa *et al.,* 2019). Lack of significant prolongation of PT in chronic liver disease may be consequent upon the fact that, significantly increased PT is not seen in early stages until that of cirrhosis and the liver fibrosis. As CLD progresses, both PT and aPTT levels are prolonged; however, in cases, where compensatory mechanisms are intact, increase in factor VIII may suppress the increase in aPTT (Forns *et al.,* 2002). Our finding were in opposition to previous report by Sohail *et al.,* who reported 72% prolongation in PT among CLD subjects (Sohail *et al.,* 2011) and Gautam *et al.,* who reported 62% (186/300) and 39.3% (118/300) patients having prolonged PT and APTT respectively in liver diseases. Their findings agree with the study of Malik *et al.,* (Gautam *et al.,* 2017and Malik *et al.,* 1999). Okoroiwu *et al.,* also noted statistical change in all the coagulation factors (APTT, PT and INR) In Hepatitis B virus infection (HBV), infection of the liver by virus causes virus-induced tumor necrosis factor production which mediates a significant liver pathology and this changes can therefore be explained based on the state of the diseased liver which is saddled with the responsibility of clotting factors synthesis (Yang-Mei *et al.,* 2008).

The loss of hepatic function following HBV infection could arise also from hepatic inflammation caused by HBX (hepatitis B virus x protein) which is pro-inflammatory cytokines including inter-leukin – 18. (IL-18). The IL-18 in turn increases the expression of Fasl (Fas-Ligand) which leads to increased susceptibility to fas-mediated cell apoptosis (Okoroiwu *et al.,* 2014). Prolongation of PT and APTT in advancing liver cirrhosis as noted in their findings indicates damage of liver parenchyma resulting in decreased production of coagulation proteins with increased risk of bleeding tendencies (Gautam *et al.,* 2017).

Our study showed statistically non-significant decreases in PT and APTT in both chronic HBV and HCV. Our findings are in conflict with the findings from Sajjadieh and Viunytska where PT values in patients with chronic hepatitis C without fibrosis and in

patients with cirrhosis were significantly different with those in healthy participants (P<0.01) and (P<0.001) respectively. Also statistically significant increase in prolonged aPTT, PT and TT among hepatitis C virus infected patients were observed with decrease in fibrinogen and platelet levels (Okoroiwu *et al.,* 2014). Previous researches suggest that patients with HCV infection fail to clear the virus during the acute phase of the disease and as result become chronic carriers. This is consequent upon the production of envelop protein E1 and E2 whose hypervariable regions prevent the antibodies from clearing the disease. It is therefore the chronic exposure to activation of the humoral immune system to HCV and the failure to clear the infection that results to repeated exposure to self- reactive antibody with consequent organ damage (Sy and Jamah, 2006).

In addition, patients with chronic hepatitis tend to have cirrhosis leading to decreased levels of AT III, a marker that was suggested for fibrosis. In hemostasis testing in chronic liver disease, PT does not adequately reflect coagulation abnormalities in patients with chronic hepatitis C. Nevertheless, this parameter does give a good estimate of the synthetic function of the liver and, thus, may be used as a prognostic marker for fibrosis (Sajjadieh and Viunytska, 2008 and Shaikh, 2008). Varnika *et al.,* also noted prolongation in PT and aPTT of conventional coagulation screening tests appears in advanced liver disease (Varnika *et al.,* 2017). Nevertheless it was believed that these parameters are not sensitive markers of liver damage (Saja *et al.,* 2013). Furthermore, recent studies have shown that these global tests are not predictive of bleeding in patients with cirrhosis however PT has kept its place as one of the parameters of common prognostic indices in advanced liver disease (Tripodi *et al.,* 2007).

Table 3.0 showed Relationship between INR and liver infections/ diseases among the subjects. They were non- statistical significant increase in INR among patients with asymptomatic and chronic HBV and HCV virus with p-value of 0.996. Our findings were in contrast with earlier report from Gautam *et al.,* which out of 156 patients of cirrhosis in his studies, noted 66% (103/156) prolonged PT and APTT in 47.4% (74/156) derangement in patients with cirrhosis. INR, which is a ratio of the patient's PT as compared to a laboratory normative PT value, was designed as a method of monitoring individual patient responses to anticoagulation therapy with a vitamin-K antagonist such as warfarin, INR is believed to be particularly elevated in patients with chronic liver disease and cirrhosis, but holds to the view that its elevation does not correlate with bleeding tendency as opined by previous literature (Michael, 2018). Statistical non-significant increase in INR among patients in our findings could also be attributed to compensatory mechanisms such as the increase in factor VIII, which may suppress the increase in aPTT (Forns *et al.,* 2002).

Table 4.0 shows a statistically non-significant relationship between PTTK and age of subjects with the p-value of 0.0978, while Table 5.0 expressed relationship between PT, PTTK, INR and gender of subjects.

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