ORIGINAL ARTICLE

Determine the Prevalence of Acquired Dysfibrinogenemia in Patients Presented with Chronic Liver Disease

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ABSTRACT

Aim: To examine the prevalence of acquired dysfibrinogenemia in patients presented with chronic liver disease.
Study Design: Cross-sectional
Place and Duration of Study: Department of Hematology, Shaikh Zayed Hospital Lahore from 1st September 2019 to 29th February 2020.
Methods: One hundred and thirty patients of both genders presented with chronic liver disease having ages 20 to 65 years were enrolled. Patients detailed demographics including age, sex and causes of chronic liver disease were recorded after written consent. Blood sample was taken from all the patients to measure fibrinogen level, prothrombin time, activated partial thromboplastin time, serum albumin and bilirubin. Severity of chronic liver disease was graded by Child-Pugh score.
Results: Ninety (69.23%) were males while 40 (30.77%) were females with mean age 46.26±15.47 years. Hepatitis C virus was the most common etiology in 98 (75.48%) patients followed by hepatitis B virus in 24 (18.46%) and hepatitis B virus and hepatitis C virus both in 8 (6.15%) patients. Acquired dysfibrinogenemia was found in 70 (53.85%) patients. A significant association of increased prevalence of acquired dysfibrinogenemia with severity of disease was observed according to Child-Pugh score graded ($p<0.05$).
Conclusion: The prevalence of acquired dysfibrinogenemia was quite high in patients with chronic liver disease.
Keywords: Chronic liver disease, Fibrinogen level, Thrombin time, Thrombosis

INTRODUCTION

Dysfibrinogenemia is a coagulation disorder caused by a variety of structural abnormalities in the fibrinogen molecule that result in abnormal fibrinogen function.[1] It can be inherited or acquired. The inherited form is associated with increased risk of bleeding, thrombosis, or both in the same patient or family.[2] Traditionally, dysfibrinogenemia is diagnosed by abnormal tests of fibrin clot formation; the thrombin time and reptilase time are the screening tests, and the fibrinogen clotting activity–antigen ratio is the confirmatory test.[3] The inherited form is diagnosed by demonstrating similar laboratory test abnormalities in family members, and if necessary by analysis of the fibrinogen protein or fibrinogen genes in the patient.[4]

The prevalence of inherited dysfibrinogenemia among the general population is unknown; however, the prevalence among patients with a history of venous thrombosis is 0.8%[4]. The pattern of inheritance is almost always autosomal dominant[5]. Most patients have no history of bleeding or thrombosis (55%), while others develop bleeding (25%) or thrombosis (20%)[5].

Acquired dysfibrinogenemia is usually caused by disease of the liver or biliary tract. The specific disease associations include cirrhosis, chronic active liver disease, acute liver failure, acetaminophen overdose, choledochal cyst of the bile duct, and miscellaneous causes of obstructive jaundice[6,7,8]. The mechanism of acquired dysfibrinogenemia involves increased sialylation of carbohydrate side chains of the fibrinogen molecule[9]. The additional sialic acid residues are localized to the β and γ chains.[10] This chemical change increases the net negative charge of fibrinogen, which promotes charge repulsion between fibrin monomers and decreases the rate of fibrin polymerization. The prevalence of dysfibrinogenemia is higher in patients with liver disease (76% to 86%) than in those with obstructive jaundice (8%).[11,12] The present study was conducted aimed to examine the acquired dysfibrinogenemia in patients presented with chronic liver disease. This study will be helpful for the management of morbidities associated with chronic liver disease.

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MATERIALS AND METHODS

This cross-sectional/observational study was conducted at Department of Hematology, Shaikh Zayed Hospital Lahore from 1st September 2019 to 29th February 2020. A total of 130 patients of both genders having ages 20 to 65 years presented with chronic liver disease were enrolled. Patients detailed demographics including age, sex and causes of chronic liver disease were recorded. Patients with history of blood disorder and those on drug therapy were excluded. 5ml blood sample was taken from all the patients and sent to laboratory to examine the fibrinogen level, prothrombin time, thrombin time, APTT, serum albumin and bilirubin. The reference range for PT was 12-15 sec and APTT was 26-33 sec. The Thrombin time was measured using Thrombin timekit provided by Weiner Laboratory. Reagent (bovine thrombin) was prepared and added to centrifuged plasma sample. The starting time of clot formation was

measured as the thrombin time. The normal reference range was 13-17sec. In cases where thrombin time was found prolonged, its correction was checked using a reagent toluidine blue provided by British Drug House Ltd for diagnosis of acquired dysfibrinogenemia. Hemostat fibrinogen kit was used to examine the fibrinogen level and reference rages 200 to 400 mg/dl. Severity of liver disease was examined and graded by Child-Pugh score A, B and C. Data was analyzed by SPSS 24. Chi-square test was applied to examine the association of dysfibrinogenemia with severity of disease. P-value <0.05 was set as significant.

RESULTS

Ninety (69.23%) were males while 40(30.77%) were females with mean age 46.26±15.47 years. Hepatitis C virus (HCV) was the most common etiology in 98(75.48%) patients followed by hepatitis B virus (HBV) in 24(18.46%) and HBV and HCV both in 8(6.15%) patients (Table 1). According to the severity of disease graded by Child-Pugh score, 40(30.77%) patients had score A, 48(36.92%) had score B and 42 (32.31%) patients had score C (Table 2).

According to the fibrinogen level, 12(9.23%) patients had fibrinogen level >400 mg/dl, 70(53.85%) patients had fibrinogen level 200 to 400 mg/dl and 48(36.92%) patients had fibrinogen level <200mg/dl (Table 3). According to the thrombin time 54(41.54%) patients had normal while 76 (58.46%) patients had prolonged thrombin time. As per correction of prolonged thrombin time with toluidine blue 70(53.85%) patients had corrected thrombin time and considered as acquired dysfibrinogenemia (Table 4).

According to the association of acquired dysfubrinogenemia with severity of disease, among patients with Child-Pugh score A 9(22.5%) had acquired dysfibrinogenemia, in score B 16(33.33%) had acquired dysfibrinogenemia and among patients with score C the prevalence of acquired dysfibrinogenemia was 35(83.33%). A significant increased in acquired dysfibrinogenemia with increases the severity of disease was observed with p-value <0.0001 (Table 5).

Table 1: Demographic information of the patients

Variable	**No.**	**%**
Age (years)	46.26±15.47	
Gender		
Male	90	69.23
Female	40	30.77
Etiology		
HBV	24	18.46
HCV	98	75.48
HBV & HCV	8	6.15

Table 2: Severity of disease by Child-Pugh score

Variable	**No.**	**%**
Grade A	40	30.77
Grade B	48	36.92
Grade C	42	32.31

Table 3: Fibrinogen level among all the patients

Fibrinogen Level	**No.**	**%**
<200mg/dl	48	36.92
200-400mg/dl	70	53.85
>400mg/dl	12	9.23

Table 4: Prevalence of acquired dysfibrinogenemia

Prevalence of ADF	No.	%
Yes	54	41.54
No	76	58.46

Table 5: Association of severity of disease with acquired dysfibrinogenemia (ADF)

Child-Pugh score	**ADF**		**P-value**
	Yes	**No**	
A (n=40)	9 (22.5)	31 (77.5)	<0.0001
B (n=48)	16 (33.33)	32 (66.67)	
C (n=42)	35 (83.33)	7 (16.67)	

DISCUSSION

Chronic liver disease demonstrated one of the common life threatening disorders with high morbidity and mortality rate. Bleeding is the commonly found disorder in patients with chronic liver diseases and acquired dysfibrinogenemia is the most important risk factor of bleeding in patients with CLD.[13,14] We conducted this study aimed to examine the prevalence of acquired dysfibrinogenemia in patients presented with chronic liver disease. In this regard 130 patients were enrolled. Majority of patients in our study was male 69.23% as compared to females accounted 30.77% with mean age 46.26±15.47. These results showed similarity to the many of other studies conducted regarding chronic liver diseases in these study majority of patients with CLD were males 70% to 85% as compared to females and age group 40 to 60 years was the most common age group found in these patients.[13,15]

In the present study we found that HCV was the most common etiology of CLD in 98 (75.48%) patients followed by HBV in 24 (18.46%) and HBV and HCV both in 8 (6.15%) patients. A study conducted by Noor et al[16] reported similarity, in which the most common cause of CLD was HCV found in 98%. Some other studies showed similarity in which HCV was the most frequent cause of chronic liver disease accounted 70% to 90%[17,18].

In the current study we found that the prevalence of acquired dysfibrinogenemia was 70 (53.85%). A study conducted by Casini et al[19] reported that acquired abnormalities of fibrinogen may complicate liver disease: approximately 50% of patients with severe liver disease exhibit bleeding secondary to abnormal fibrinogen molecules. Noor et al[16] reported 40% patients had acquired dysfibrinogenemia. Another study conducted by Rai et al[20] reported that patients with chronic liver disease had significantly low fibrinogen level.

We found that acquired dysfibrinogenemia had a significant association with the severity of disease graded by Child-Pugh score. Patients with Child-Pugh score C had high prevalence of acquired dysfibrinogenemia 83.33%. Many of previous studies demonstrated that prolonged thrombin time increases with increases severity of disease[21,22].

CONCLUSION

The prevalence of acquired dysfibrinogenemia was quite high in patients with chronic liver disease. Also we observed that acquired dysfibrinogen tends to increase with increases the severity of disease by Child-Pugh score.

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