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ORIGINAL ARTICLE

Acquired Thrombophilic Hypercoagulable States Seen in Patients with Liver Cirrhosis: A Single Center Study

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ABSTRACT

Among the common hemostatic issues of the patients of liver cirrhosis, deep venous thrombosis, pulmonary embolism, and intrahepatic thrombus development are more often ignored. With an estimated frequency ranging from 0.6 to 26 percent, portal venous thrombosis is another potentially dangerous consequence of liver cirrhosis.

Objectives: To determine the frequency of various acquired thrombophilic / hypercoagulable states seen in patients with liver cirrhosis.

Study design: Descriptive, cross sectional.

Settings: Department of Medicine, Allied Hospital, Faisalabad

Study duration: 30th June 2019 to 29th December 2019

Materials & Methods: Cirrhosis cases ranging in age from 25 to 75 years old and of both genders were included in the study. Patients with HCC, heritable thrombophilias such as the Factor V leiden mutation, congenital budd chiari, and cholestatic liver disorders such as primary biliary cirrhosis (PBC) and primary sclerosing cholangitis were also eliminated. To assess for hepatic decompensation, ultrasonography, LFTs, and other baseline procedures were performed. Doppler USG was performed in each case with the assistance of the Radiology Department of Allied Hospital Faisalabad to assess for DVT, Budd-Chiari syndrome, and Portal venous thrombosis.

Results: Mean age of the patients enrolled was 52.08 ± 10.47 years. Among these 840 patients, 461 (54.88%) were male and 379 (45.12%) were females (ratio 1.2 **:** 1). Mean AST levels were 77.49 ± 8.93 units/liter. Mean ALT levels were 88.51 ± 9.17 units/liter. Mean total bilirubin levels were 8.33 ± 1.65 mg/dl. Frequency of various acquired thrombophilic / hypercoagulable states seen in patients with liver cirrhosis were as follows; portal vein thrombosis in 136 (16.19%) patients, budd chiari syndrome in 102 (12.14%), deep vein thrombosis in 96 (11.43%) and pulmonary embolism in 108 (12.86%) patients.

Conclusion: This study concluded that frequency of various acquired thrombophilic / hypercoagulable states seen in patients with liver cirrhosis is quite high.

Keywords: liver cirrhosis, hypercoagulable states, portal vein thrombosis.

INTRODUCTION

Cirrhosis of the liver is the last stage of chronic liver injury, characterized by fibrosis that causes loss of liver architecture. Gradually, the healthy liver tissue after affected by the liver injury is replaced with scar tissue due to fibrosis, eventually disturbing the liver function.[1]

Initially, there are frequently no symptoms. The fluid buildup in the abdomen may develop infected on its own. Hepatic encephalopathy and liver cancer are both possible complications.[1] More than 29 million individuals in Europe are affected, and over 300 million people globally are affected.[2] Hypercoagulation, also known as thrombophilia, is a proclivity for abnormal clot formation. Although bleeding is the most generally recognized clinical problem in patients with chronic liver disease and cirrhosis.[3]

Reduced anticoagulant factors, rise in factor VIII, von-Willebrand factor, and the possibility of thrombophilia are the primary causes of prothrombosis. [4,5] It has previously been argued that the process of coagulation is balanced in patients of cirrhosis since both pro- and anticoagulant mechanisms are equally affected.[6]

Patients are subjected to laboratory screening so if they require plasma or procoagulant agents they can be advised and hemorrhage can be prevented. Little emphasis has been devoted to the fact that, like procoagulant factors, anticoagulant equivalents are diminished to the same level in this scenario. As a result, for many years, the notion of coagulation rebalancing in CLD was dismissed.[7]

Among the common hemostatic issues of the patients of liver cirrhosis, deep venous thrombosis, pulmonary embolism, and intrahepatic thrombus development are more often ignored.[8] With an estimated frequency ranging from 0.6 to 26 percent, portal venous thrombosis is another potentially dangerous consequence of liver cirrhosis. [7,9] However, procoagulant imbalance may not be related with the existence of portal vein thrombosis (PVT) in cirrhotic individuals.[10] Splanchnic vein thrombosis is becoming more prevalent among doctors, either as a consequence of chronic liver illness or as the initial indication of a primary type of vascular liver disease.[11]

A thorough literature review yielded not a single local study detailing the incidences of the various prothrombotic states as described above seen in liver cirrhosis yet liver cirrhosis continues to be quite common amongst our local population owing to high prevalence of hepatitis B and Hepatitis C. However, as discussed above many cirrhotic patients have hypercoagulability and needs to undergo rigorous investigation. Therefore, we decided to conduct this study.

MATERIALS AND METHODS

This descriptive, cross-sectional study was conducted in the Department of Medicine, Allied Hospital, Faisalabad, from June 30th to December 29th, 2019. The study's goal was to "evaluate the prevalence of various acquired thrombophilic / hypercoagulable conditions found in individuals with cirrhosis of the liver." After the summary was approved, 840 consecutive patients with liver cirrhosis presenting with problems in the medical ward were invited to participate in the study. All patients were fully told about the study's goal, and their informed permission was obtained in each case.

All patients of aged 25-70 years either males or females diagnosis of cirrhosis confirmed by clinical, biochemical, and ultrasonography findings were included in the study. A patient was labeled as having liver cirrhosis if he has sonological evidence of cirrhosis along with raised serum bilirubin (more than 2.5 times the upper limit of normal) and prolonged prothrombin time (prolonged by more than 3 s).

A diagnosis of portal vein thrombosis was confirmed upon doppler USG abdomen showing reduced flow and thrombosis in portal vein. If any of these patients is confirmed upon USG showing hepatic vein thrombosis, it was labeled as Budd Chiari syndrome. And any patient with doppler USG showing thrombosis in deep veins of legs, was labeled as having deep vein thrombosis. Patients of pulmonary embolism were diagnosed on computed tomographic pulmonary angiography (CTPA) and raised D dimers. Sampling was done using non-probability, consecutive sampling.

All those patients with hepatocellular carcinoma, heritable thrombophilias like Factor V leiden mutation, congenital budd chiari, and those with cholestatic liver diseases, namely primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC) were excluded. All the bed bound patients and those with recent major surgery were also excluded.

To assess for hepatic decompensation, ultrasonography, LFTs, and other baseline procedures were performed. Doppler USG was done in each case with the help of Radiology Department of Allied Hospital Faisalabad to evaluate for DVT, Budd-Chiari syndrome and Portal venous thrombosis. The required data was gathered in a standardized proforma that included background information such as age, gender, child class, and the existence of several hypercoagulable conditions, among other things.

SPSS version 21 was used to analyze the data. For quantitative data such as age and LFTs, the mean and standard deviation were determined. In the case of qualitative factors such as gender and the existence of various acquired thrombophilias (as specified in the operational definition), frequency and percentages were determined. Tables and graphs were used to display data. Stratification was used to regulate effect modifiers such as gender and age. The patient's child class was determined using the aforementioned table. Chi square tests were used after stratification, and a p value of 0.05 was considered significant.

RESULTS

The aim was to "assess the prevalence of acquired thrombophilic / hypercoagulable conditions found in individuals with cirrhosis of the liver." Data was collected after the approval of the research committee, 840 patients of cirrhosis of the liver were enrolled through consecutive sampling technique. All patients were fully informed about the study's objection, and their informed permission was obtained in each case.

Patients enrolled in this study ranged from age 25 - 75 years, (mean age of 52.08 ± 10.47 years). Among these patients, 461 (54.88%) were male and 379 (45.12%) were females with male to female ratio of 1.2:1.

Distribution of patients according to child pugh class is shown in Table I. Mean AST levels were 77.49 ± 8.93 units/liter. Mean ALT levels were 88.51 ± 9.17 units/liter. Mean total bilirubin levels were 8.33 ± 1.65 mg/dl (Table I).

Frequency of various acquired thrombophilic / hypercoagulable states seen in patients with liver cirrhosis were as follows: (Table II).

Table-1: Details of various variables documented in the study (n=840).

Age (in years)	No. of Patients	%age
25-50	325	38.69
51-75	515	61.31
Total	840	100.0
Child Pugh class	No. of Patients	%age
A	317	37.74
B	286	34.05
C	237	28.21

Table 2: Frequency of various acquired thrombophilic / hypercoagulable states seen in patients with liver cirrhosis

Acquired thrombophilic / hypercoagulable states	Frequency (%)	
	Yes	No
Portal vein thrombosis	136 (16.19%)	704 (83.81%)
Budd Chiari syndrome	102 (12.14%)	738 (87.86%)
Deep vein thrombosis	96 (11.43%)	744 (88.57%)
Pulmonary embolism	108 (12.86%)	732 (87.14%)

Table 3: Stratification of the various acquired thrombophilic / hypercoagulable states with respect to age and gender.

Thrombophilic / hypercoagulable states		25-50 (n=325)	51-75 (n=515)	P-value	Male (n=461)	Female (n=379)	P value
Portal vein thrombosis	Yes	28	108	0.0001	89	47	0.007
	No	297	407		372	332	
Budd Chiari syndrome	Yes	01	101	0.0001	49	53	0.138
	No	324	414		412	326	
Deep vein thrombosis	Yes	67	29	0.0001	31	65	0.0001
	No	258	486		430	314	
Pulmonary embolism	Yes	01	107	0.0001	62	46	0.572
	No	324	408		399	333	

DISCUSSION

Review of literature have shown that hypercoagulability in the patients of End-stage-liver-disease (ESLD) is linked with basic alterations in the coagulation profile.[12] ED changes the vascular tone and leads to disturbance of the local pro- and anti-coagulant balance because of the endothelial cell surface production of tissue factor.[13] The tissue factor pathway inhibitors are released by the endothelial cells and may be reduced in the end-stage liver disease ESLD.[14] Inflammation and oxidative stress are also factors in the development of ED.[15]

In cirrhotic patients, lipopolysaccharide is detected by Toll-like receptors and promotes the generation of tumour necrosis factor- by monocytes. [16] Under physiological circumstances, portal endotoxemia occurs.[17] Endotoxin leakage into the systemic circulation is caused by liver damage due to decreased reticulo-endothelial clearance and porto-systemic shunts.[13] Nitric oxide dysregulation, which is common in ESLD patients, is linked to ED.[18]

Previous review of literature have shown that the cirrhosis of the liver is less likely to end-up in the development of VTE.[19] The research explaining the risk of VTE has been contradictory. [20,21] A larger population should be considered for the establishment of this relationship.

Ali et al[22] reported an incidence of 1.8% for venous thromboembolism (VTE) amongst hospitalized cases of liver cirrhosis. One of the first substantial assessments, a case-control research at a tertiary hospital, was published in 2008. When compared to controls, cirrhotic patients did not have a lower risk of DVT or pulmonary embolism (PE).[23] The risk of VTE was lower in individuals with advanced liver illness than in those with congestive heart failure or malignancy. Sgaard et al found that chronic liver disease (CLD), whether present or absent of cirrhosis, was related with a greater relative risk of spontaneous VTE compared to controls, with ORs of 2.06 and 2.1, respectively, in a retrospective study of the Danish National Registry.[24]

VTE was linked to an increase in short-term mortality in cirrhotic individuals. In a second investigation, Sgaard's group discovered that the corrected 30-day mortality rate ratios for DVT and PE were 2.17 and 1.83, respectively.[25] Wu and Nguyen[26] found that the odds ratio for VTE was 1.2 in the patients of compensated cirrhosis and 1.39 among the patients of decompensated cirrhosis.

Following the publication of these studies, the link between CLD and thromboembolism became widely accepted. In hospitalized patients with CLD, the prevalence of VTE ranges from

0.5 to 8.2 percent. [26-28] Dabbagh et al[28] reported on 190 people who got VTE over a seven-year period. Notably, the INR of 51 of these individuals was equal to or more than 2.2.

Singhal et al[29] discovered a 12.8 percent PVT incidence in 47 consecutive ESLD patients. Several papers have found a link between PVT and higher morbidity and death. Stine JG, et al[30] reported that even the liver transplant recipients experienced early hepatic artery thrombosis. 13.8 percent of these patients already had pre-transplant portal vein thrombosis. PVT was reported to be between 24% to 28% among the patients of cirrhosis.[31,32]

The thrombotic occlusion of the portal vein is widespread in chronic liver disease, with a prevalence ranging from 1% to 16% of the population.[33] The presence of increasing chronic liver diseases, particularly liver cirrhosis, is the primary risk factor for portal vein thrombosis.[30] Other risk factors include acquired or hereditary thrombophilia, epigastric processes, and malignant liver or choledocus disorders. There are, however, idiopathic types of thrombosis. [34] Increased liver resistance in cirrhosis is the cause of the deterioration in portal vein outflow seen in portal vein thrombosis.[35] Portal vein thrombosis was discovered in 16.3 percent of the 380 consecutive patients who underwent initial orthotopic liver transplantation. Only obesity was discovered to be an independent risk factor for this pre-transplant condition, which had no effect on patients' overall survival.[36]

CONCLUSION

Frequency of various acquired thrombophilic / hypercoagulable states seen in patients with liver cirrhosis is quite high. So, we recommend that in every patient of cirrhosis, various acquired thrombophilic / hypercoagulable states should be taken into consideration and its early recognition and management should be done in order to avoid inappropriate therapeutic procedure and reduce the morbidity and mortality of the community.

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