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Prevalence of venous thromboembolism in patients with chronic liver disease: A Turgut Özal Medical Center based study

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Abstract

Venous thromboembolism (VTE) is an important complication observed in patients with chronic liver diseases. This study aims to present demographics and some clinical characteristics of patients with chronic liver disease (CLD) with an emphasis on the development of venous thromboembolism. The study was conducted with the data of patients having chronic liver disease who were admitted to Inonu University Turgut Özal Medical Center Liver Transplant Institute. 63 patients diagnosed with chronic liver diseases were included in the study. Chronic liver disease patients were confirmed according to the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM). Positive Doppler ultrasonography, computed tomography, or angiographic study documentation were used to confirm the presence of thrombosis. In conclusion, although patients with CLD are traditionally prone to bleeding disorders, VTE is also a serious complication in these patients. Therefore, it should be considered that anticoagulation treatment should be provided to all CLD patients with verified VTE.

Keywords: Venous thromboembolism, chronic liver disease, liver transplant

Introduction

Millions of individuals throughout the world are affected by chronic liver disease, which is becoming more and more regarded to be a condition in which various hemostatic mechanisms are active. Hepatic dysfunction causes 27,000 fatalities yearly in the United States [1]. The risk of bleeding is thought to be increased in people with end-stage liver disease. Because of irregularities found in measurements of platelet count, prothrombin time (PT), international normalized ratio (INR), and activated partial thromboplastin time (APTT), it is considered by some clinicians that patients with cirrhosis are "auto-anticoagulated". Thrombocytopenia which is attributed to hypersplenism, reduced hepatic synthesis of thrombopoietin, and immune-mediated platelet destruction is a prevalent symptom in individuals with chronic liver illness [2-5]. There are various degrees of qualitative platelet function abnormalities, which are magnified in end-stage liver disease [6]. Most procoagulant components are often found in lower concentrations in chronic liver disorders, which is evident in increased prothrombin time and thrombocytopenia.

Venous thromboembolism (VTE) is a complication that could be seen as a result of multifactorial events. Venous stasis, increased coagulation, and endothelial damage play a role in the pathophysiology of VTE and are known as Virchow's triad [7]. The most important of the three factors is venous stasis. However, stasis alone is insufficient for thrombus formation [8]. Obesity, smoking, cancer, heart failure, older age and even immobility among the populations due to recent COVID-19 outbreak may be involved in the etiology [9]. The risk of VTE may be raised in individuals with liver illness. On the other hand, even if there is a reduced risk of VTE reported in some cases associated with moderate to severe liver illness, patients

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with liver disease had a higher death rate when VTE was present [10]. In a single-centered study performed in 2006 patients with cirrhosis, rate of VTE was 0.4% during the hospitalization and those with VTE had significantly greater death rates than patients without VTE [11]. Therefore, patients with chronic liver disease (CLD) may suffer from various outcomes due to complex nature of pathophysiology. Furthermore, there are conflicting results in the literature, and most of the studies performed as retrospective surveys have some limitations.

Our aim was to determine the incidence and predictors of VTE and examine the practice of deep venous thrombosis (DVT) prophylaxis among hospitalized cirrhotic patients.

Material and Methods

This study was conducted with the data of patients having chronic liver disease who were admitted to Inonu University Turgut Özal Medical Center Liver Transplant Institute. This study was approved by the Human Research Ethics Committee of the İnönü University, Malatya, Türkiye (Approval number: 2023/4062). Before starting the study, patients' consent was obtained to be used in the study. 63 patients who were diagnosed with CLD were included in the study. Of the total 63 patients, 37 (58.73%) patients were male and 26 (41.27%) were female. The mean age of the patients was 49.98±20.72 years (mean age of women 38.84±21.82 years, mean age of men 57.81±15.75 years). Chronic liver diseases in all patients included in this study were confirmed according to the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM). In patients with chronic liver disease, all were newly diagnosed with VTE during hospitalization. Positive Doppler ultrasonography, computed tomography, or angiographic study documentation were also used to confirm the presence of thrombosis. Studies reporting incidence and/or prevalence of VTE (DVT and PE), in adult patients with CLD including cirrhosis in hospital or community setting were included. CLD was diagnosed based on clinical presentation, laboratory tests, radiological imaging, or liver biopsy, and VTE was diagnosed on radiological imaging. Exclusion criteria post liver transplant, liver resection, and in patients with hepatocellular carcinoma (HCC), or after treatment for HCC.

Only patients with chronic liver disease and a recent thrombotic condition were included in the study. Patients diagnosed with CLD and VTE prior to the admission to our hospital were excluded from the study.

Results

Coagulopathy were observed in 12 patients. Of 12 patients (19.04%) with coagulopathy, 7 were male and 5 were female. The incidence of coagulopathy among women was 19.23%, and 18.91% in men. Of those with total coagulopathy, 41.66% were women and 58.34% were men. Pulmonary embolism was seen in 1 male (1.58%) out of 63 patients. The incidence of pulmonary embolism among male patients was 2.70%. Portal thrombosis was seen in 1 male out of 63 patients (1.58%). The incidence of portal thrombosis among male patients was 2.70%. Ascites developed in 23 of 63 patients (36.50%). Ten of the patients who developed ascites were male and 13 were female. The rate of development of ascites was 50% among women and 27.03% among men. In total, 56.52% of those who developed ascites were female and 43.48% were male. The mean MELD score of 63 patients was 11.26±6.64 (men 12.21±7.28, women 9.92±5.46). Seventeen of 63 patients (6 women, 11 men) were TX (26.98%). While the rate of women with TX was 23.07%, this rate was 29.72% among men. Among those with TX, women were 35.30% and men 64.70%. Nine of 63 patients had malignancy (14.28%). Of the patients with malignancy, 6 were male and 3 were female. Of the total malignancies, 33.34% were female and 66.64% were male. While the incidence of malignancy among men was 16.21%, it was 11.53% in women. Encephalopathy was observed in 7 of 63 patients (4 male, 3 female, 11.11%). While the rate of encephalopathy among women was 11.54%, this rate was 10.81% in men. In total, 42.85% of those who developed encephalopathy were female and 57.15% were male. Demographics and characteristics of case patients were presented in Table 1.

Table 1. Demographics and characteristics of case patients

	Female	Male	Total case
	26 (41.27%)	37 (58.73%)	63
Age (years, mean±SD)	38.84±21.82	57.81±15.75	49.98±20.72
End-stage liver disease (MELD) score (mean±SD)	9.92±5.46	12.21±7.28	11.26 ±6.64
Transplant (TX incidence)	6 (23.07%)	11 (29.72%)	17
Malignancy (incidence)	3 (11.53%)	6 (16.21%)	9
Pulmonary embolism (incidence)	0	1 (2.70%)	1
Portal vein thrombosis (incidence)	0	1 (2.70%)	1
Ascites (incidence)	13 (50%)	10 (27.03%)	23
Encephalopathy (incidence)	3 (11.54%)	4 (10.81%)	7
Coagulopathy (incidence)	5 (19.23%)	7 (18.91%)	12

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Discussion

In order to maintain a normal hemostatic balance, the liver synthesizes a number of proteins that are involved in the coagulation, anticoagulation and fibrinolysis pathways. Therefore, a wide range of hemostatic problems may be experienced by patients CLD. Historically, patients with liver disease are prone to bleeding disorders. However, cirrhosis or CLD may commonly be linked to hypercoagulability, and both conditions might result in a wide range of thrombotic events. In contrast to healthy people, CLD patients may have a higher propensity to develop venous thrombosis despite indications of aberrant clotting times [12].

Previous studies in general indicate that patients with CLD had increased risk of VTE including portal vein thrombosis, pulmonary embolism and coagulopathy. In the present study, we have observed coagulopathy in 12 patients. Of 12 patients (19.04%) with coagulopathy, 7 were male and 5 were female. The incidence of coagulopathy among women was 19.23%, and 18.91% in men. Of those with total coagulopathy, 41.66% were women and 58.34% were men. Pulmonary embolism was seen in 1 male (1.58%) out of 63 patients. The incidence of pulmonary embolism among male patients was 2.70%. Portal thrombosis was seen in 1 male out of 63 patients (1.58%). The incidence of portal thrombosis among male patients was 2.70%. In a systemic review, it is reported that the occurrence of VTE ranges from 0.5% to 8.1% in different hepatic disorders. Incidence of non-portal VTE was 0.8% according to research of 2074 hospitalized cirrhotic patients in Spain [13].

The likelihood of portal vein thrombosis (PVT), a common consequence of cirrhosis, rises with disease severity. Normal blood flow in the PV is interrupted by a blood clot, which is the hallmark of PVT. The occurrence of PVT increases in the advanced stages of cirrhosis [14].

PVT affects about 1% of people in the general population, and it affects 5- 20% of people with cirrhosis. There is a strong correlation between PVT and advanced liver disease, even if the exact cause of PVT in cirrhosis patients is still unknown [15]. Seventy percent of participants in a cohort with liver cirrhosis and PVT had a concomitant systemic risk factor. Additionally, people with PVT appear to be more vulnerable to additional venous thromboembolic events [16].

Ascites, is one of the important complications associated with advanced chronic liver disease [17] and it is a common complication of cirrhosis [18]. In our study, we observed that ascites developed in 23 of 63 patients (36.50%). Ten of the patients who developed ascites were male and 13 were female. The rate of development of ascites was 50% among women and 27.03% among men. In total, 56.52% of those who developed ascites were female and 43.48% were male. In the development of the cirrhotic process, ascites implies hepatic decompensation. The prognosis is significantly worsened when ascites develops [18]. Ascites development is a significant turning point in the course of cirrhosis since it indicates that liver transplantation should be considered as a treatment option and is linked to a 50% mortality rate over the course of two years. The majority (75%) of patients who have ascites have cirrhosis underneath [19]. Cirrhosis is the cause of ascites in about 80% of cases. 20% of cirrhotic patients are diagnosed with ascites, and 20% of those who have ascites die within a year of diagnosis [20].

We calculated the model for end-stage liver disease (MELD) scores for 63 patients involved in our study. The mean MELD score of 63 patients was 11.26±6.64 (men 12.21±7.28, women 9.92±5.46). The hepatic function reserve in cirrhotic individuals is assessed using MELD score. The MELD score is utilized to predict survival in individuals with cirrhosis who have a transjugular intrahepatic portosystemic shunt. It has also been used to predict the post-operative course of cirrhotic patients undergoing surgical treatments and to assign priority on waiting lists for liver transplants [21].

We additionally collected the number of malignity cases among the patients. Nine of 63 patients had malignancy (14.28%). Of the patients with malignancy, 6 were male and 3 were female. Of the total malignancies, 33.34% were female and 66.64% were male. While the incidence of malignancy among men was 16.21%, it was 11.53% in women. Sorensen et al. [22] reported patients with cirrhosis have a higher chance of developing liver cancer as well as a number of extrahepatic malignancies. A recognized risk factor for the occurrence of liver cancer is chronic liver illness, particularly chronic hepatitis. Other cancer forms, however, could potentially be connected to CLD. Loosen et al (2022) examined the relationship between chronic hepatitis and the future diagnosis of cancer. Regardless of the cause of the condition, as well as the age and sex of the patient, the presence of chronic liver disorders is linked to a higher chance of developing cancer [23].

Another common side effect of chronic liver illness is hepatic encephalopathy (HE) [24]. In our study, encephalopathy was observed in 7 of 63 patients (4 male, 3 female) (11.11%). While the rate of encephalopathy among women was 11.54%, this rate was 10.81% in men. In total, 42.85% of those who developed encephalopathy were female and 57.15% were male. Patients with HE have a damaged liver that is unable to eliminate blood levels of neurotoxic chemicals including ammonia and manganese. As a result, these molecules may enter the brain, where they may have a number of negative consequences, such as impairing motor capabilities, altering the structure of astrocytes, and interfering with proper neurotransmitter functioning [25]. Raphael et al. (2016) determined the prevalence of HE in patients admitted with liver diseases. Hepatic encephalopathy was present in 0.4% of all patients admitted to the medical ward. Males were much more prevalent than females, with a representation rate of 78.4% (69/88) and 21.6% (19/88) respectively. The mean age was 47 years with an SD of 17 years. Although younger and older patients were present, with 22.7% (20/88) being between the ages of 18 and 35 and 25% (22/88) being beyond the age of

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60, the majority of patients (52.3%) were between the ages of 36 and 60 [25].

Conclusion

Cirrhosis and chronic liver disease reflect a condition of generally diminished hepatic synthetic activity. Along with thrombocytopenia and/or thrombocytopathia, this impaired activity includes a balanced reduced production of the anticoagulant thrombotic factors such antithrombin III, protein C, and protein S and the vitamin K dependent procoagulant factors II, VII, IX, and X. Complications of VTE should not be disregarded, even if the bleeding risk associated with advanced liver disease continues to be the most important complication of the delicately balanced procoagulant and anticoagulant processes. Thromboprophylaxis for VTE should be taken into account with caution in these patients. Anticoagulation treatment should be provided to all CLD patients with verified VTE if no obvious contraindication is present.

Conflict of Interests
The authors declare that there is no conflict of interest in the study.

Financial Disclosure
The authors declare that they have received no financial support for the study.

Ethical Approval
This study was approved by the Human Research Ethics Committee of the İnönü University, Malatya, Türkiye (Approval number: 2023/4062).

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