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TOPIC HIGHLIGHT

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Deep vein thrombosis and pulmonary embolism in cirrhotic patients: Systematic review

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Abstract

Patients with liver cirrhosis were traditionally believed to be protected against development of blood clots. Lately, studies have shown that these patients may probably be at an increased risk of venous thrombotic complications. Although the hemostatic changes in the chronic liver disease patients and the factors that may predict bleeding *vs* thrombotic complications remains an area of active research, it is believed that the coagulation cascade is delicately balanced in these patients because of parallel reduced hepatic synthesis of pro and anticoagulant factors. Thrombotic state in cirrhotic patients is responsible for not only portal or non-portal thrombosis [deep vein thrombosis (DVT) and pulmonary embolism (PE)]; it has also been associated with progression of liver fibrosis. The use of anticoagulants in cirrhosis patients is a challenging, and often a scary situation. This review summarizes the current literature on the prevalence of venous thrombosis (DVT and PE), risk factors and safety of prophylactic and therapeutic anticoagulation in patients with chronic liver disease.

Key words: Deep venous thrombosis; Chronic liver disease; Cirrhosis; Thrombosis; Anticoagulation; Pathogenesis; Portal vein thrombosis

Core tip: In this review, the current literature on the risk of venous thromboembolism (VTE) in cirrhosis patients is updated. There is no doubt that these patients are at risk for both venous thrombosis and bleeding, often presenting a challenge to the providers. VTE prophylaxis should be considered in all hospitalized cirrhotic patients, unless absolutely contraindicated. While the risk of bleeding from therapeutic anticoagulation cannot be excluded, a case of careful anticoagulation for treatment of VTE event should be made in the hands of experts.

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INTRODUCTION

Liver cirrhosis is associated with an increased risk of bleeding complications. For decades, it was believed that the increased INR and thrombocytopenia seen in these patients was enough to protect these patients from developing thrombotic complications, and hence the concept of "autoanticoagulation". Over the last few years, grow-

ing body of evidence indicates that liver disease may be associated with an increased risk of thrombotic complications as well[1]. Portal vein thrombosis is common in patients with liver cirrhosis, seen in 10%-25% of the patients, with increased prevalence seen in patients with more severe disease[2-4]. Data is also emerging regarding occurrence of non-splanchnic venous thromboembolic events (VTE) in these patients, mostly lower extremity deep vein thrombosis (DVT) and pulmonary embolism (PE)[5,6].

The economic and health care burden attributable to liver disease is huge, with approximately 1% of the total national health care expenditure spent on care of these patients[7]. Development of VTE is associated with increased length of hospital stay[8-10], hospitalization cost[11] and possibly mortality as well[8]. It has also been proposed that hypercoagulation state may lead to progression of fibrosis, possibly through activation of hepatic stellate cells or as a result of local ischemic changes secondary to hepatic microthrombi[12-15]. A recent study showing decreased risk of decompensation of cirrhosis with prophylactic enoxaparin therapy provides additional support to this burgeoning concept[16]. Understanding of hemostatic pathways in cirrhotics is important not only to predict the bleeding or thrombotic complications in these patients, it also provide us with a therapeutic opportunity to possibly change the natural course of disease[13].

We hereby aim to briefly review the current literature on the changes in the coagulation/hemostatic cascade, prevalence of thrombotic complications and the role of prophylactic and therapeutic anticoagulation in this "high risk" patient population. For the purpose of this review, we will mostly restrict ourselves to the non-portal VTE in cirrhotic patients. The etiology and pathophysiology of hepatic vein thrombosis (Budd-Chiari syndrome) and portal vein thrombosis has recently been reviewed and elucidated and is out of scope of this review[17-19].

MECHANISMS

Over the years, there has been a paradigm shift in our understanding of coagulation abnormalities in cirrhosis. It is now well known that the reduced production of procoagulant factors and platelets is balanced by concomitant decreased levels of anticoagulants (such as protein C and antithrombin), thereby maintaining a delicate hemostatic balance between the two[20]. What tips this balance is not entirely known. It has been proposed that an added insult in the form of sepsis or bacterial infection (possibly through impaired platelet aggregation in the presence of increased endotoxins), renal failure (impaired platelet function) and Vitamin K deficiency (decreased activity of Vitamin K dependent procoagulant factors) may lead to disturbances of the hemostatic balance in favor of bleeding[21].

On the other hand, there are many compensatory hemostatic mechanisms that are seen in cirrhotic patients. It has been shown that these patients have elevated von Willebrand factor (vWF) levels which may contribute to greater platelet adhesion and compensate for defects in platelet number and function[22]. Increased vWF levels may also contribute to increased Factor Ⅷ levels by binding to Factor Ⅷ and thereby preventing its cleavage and clearance[23]. Another possible explanation for increased factor Ⅷ levels seen in cirrhotics is decreased expression of lipoprotein receptor-related protein, responsible for clearance of Factor Ⅷ[20,23]. Low protein C levels and antithrombin levels are secondary to decreased synthetic protein function of diseased cirrhotic liver parenchymal cells[20].

Despite the reduced coagulation factors, *in vitro* studies have shown that the thrombin generation remains preserved in cirrhosis as compared to healthy controls, in the presence of protein C activator like thrombomodulin or snake venom extract[24-27]. At baseline, cirrhosis patients seem to have a procoagulant imbalance which is likely secondary to increased factor Ⅷ levels and decreased protein C levels seen in cirrhotics[28]. The study by Tripodi *et al*[28] showed that in cirrhotic patients the *in vitro* activated protein C (APC) resistance test is impaired. This impaired APC resistance test worsened with progressive deterioration of liver disease from Child Pugh Class A to C. In fact, the hypercoagulability seen in plasma of patients with Child Pugh C cirrhosis has been shown to be similar to that conferred by congenital protein C deficiency or Factor V Leiden mutation[27,28]. A recent *in vitro* study showed that the procoagulant imbalance decreased with addition of exogenous purified protein C to restore the normal levels[29]. Major factors impacting hemostasis in these patients are summarized in Table 1.

PREVALENCE AND RISK FACTORS

A population based nested case control study involving 625 patients with VTE matched with 625 non VTE patients from Olmsted County, Minnesota found that patients with "serious liver disease" had 90% decreased risk of developing VTE. However, out of 1250 patients in the study only 11 patients had severe liver disease (5 with VTE, 6 without VTE)[30]. Patients with acute hepatitis, chronic hepatitis and cirrhosis were all grouped together into the same "serious liver disease" category. As such, this study did not reflect the true magnitude of risk of VTE seen in patients with chronic liver disease, more importantly cirrhotic patients. Since then, evidence has been accumulating with respect to risk of VTE in cirrhotic patients. Till date, there are no prospective randomized trials evaluating the incidence of DVT or PE in this patient population and with the overall low event rate, prospective trials are perhaps impractical.

The incidence of VTE has varied from 0.5% to 8.1% in different series[6,8] (Table 2). In one of the earliest studies, Northup *et al*[6] found that 113 cirrhotic patients out of more than 21000 cirrhotic admissions over an 8 year period developed VTE, giving the incidence of about 0.5%. A retrospective review of 2074 hospitalized cir-

Table 1 Hemostasis changes in chronic liver disease patients

Factors favoring anticoagulant state	Factors favoring prothrombotic state
Thrombocytopenia (decreased thrombopoietin, splenic sequestration)	Decreased liver synthesis of antithrombin III, protein C, protein S
Thrombocytopathy (impaired platelet function)	Elevated von Willebrand factor levels
Vitamin K deficiency	Increased factor Ⅷ levels
Decreased synthesis of coagulation factors including Factor Ⅱ, Ⅶ, Ⅸ, Ⅹ, Ⅴ, fibrinogen	Genetic predispositions like Factor Ⅴ Leiden
Reduced clearance of tissue plasminogen activator	

rhotic patients in Spain showed an incidence of 0.8% (17) for non-portal VTE[31]. Of note, five of the 17 patients who underwent further laboratory testing, all had evidence of antiphospholipid antibodies as well as decreased protein C, protein S and antithrombin Ⅲ.

We had previously shown that hospitalized cirrhotic patients did not have a lower risk of DVT/PE than the matched non-cirrhotic controls without selected co-morbidities including chronic kidney disease, congestive heart failure and solid organ cancers[5]. The incidence of VTE in 963 cirrhotic patients and 12405 non-cirrhotic patients without selected comorbidities including CKD, CHF or cancers who were admitted during the same period was 1.87% and 0.98%, respectively (OR = 1.78, 95%CI: 1.1-2.2, P = 0.007). On multivariable analysis, when adjusted for comorbidities using Charlson Index, presence of cirrhosis was not associated with a higher risk of VTE (OR = 0.87, 95%CI: 0.2-2.6, P = 0.06). The incidence of VTE was significantly lower in cirrhotics (1.87%) as compared to patients with selected comorbidities, including CKD (7%; OR = 0.25, 95%CI: 0.15-0.41), CHF (7.75%; OR = 0.23, 95%CI: 0.14-0.37), and cancer (6.1%; OR = 0.29, 95%CI: 0.17-0.52).

A retrospective cohort study by Dabbagh *et al*[32] showed that a higher INR does not translate to a decreased risk of VTE in cirrhotic patients. The study included 190 patients with chronic liver disease, separated into quartiles using INR values of 1.4, 1.7, and 2.2. Over a 7 year period, 12 patients developed VTE with an incidence of 6.3%. There was no difference in the VTE rates in patients in different INR quartiles. Also, study showed a higher incidence of VTE in patients with Child-Pugh stage C cirrhosis as compared to Child-Pugh stage A cirrhosis (8% *vs* 4.2%, P = 0.6), though not statistically significant. This study again showed that the risk of VTE does not decrease with worsening INR or more decompensated disease (more than 50% of the included patients were Child-Pugh stage C cirrhotics). The risk was still present even with INR > 2.2. Similar results have been seen in other retrospective studies from Indonesia and Saudi Arabia as well[9,33]. In the study by Aldawood *et al*[9], the median length of hospital stay of the patients who developed VTE was significantly longer as compared to the patients without VTE (43 *vs* 8 d, P = 0.004). There was a trend towards higher mean Child Pugh score in patients who developed VTE (10.3 ± 1.97 *vs* 8.25 ± 2.57, P = 0.052). The incidence of VTE was 0.73% (including PVT) and 0.65% in two other case control studies[11,34]. In a study by Walsh *et al*[11] including 27 chronic liver disease patient with VTE and 81 matched CLD patients without VTE (controls), cases had a longer (9 d *vs* 5 d, P = 0.02) and a significantly more expensive ($20137 *vs* $8450, P = 0.03) hospital stay as compared to the controls. One of the reasons for lower incidence of VTE in this study (0.65%) may be greater use of VTE prophylaxis as more than 90% of the patients included in the study received either mechanical or pharmacological prophylaxis.

In a large Danish population based study using data from National Registry of Patients containing records of all hospital discharges, 99444 patients with hospitalization between 1980 and 2005 for index episode of VTE and 496872 population controls (matched by age, gender, and county but not by hospitalization) were included[35]. The study showed that the risk of VTE was higher in patients with liver cirrhosis (OR = 1.74, 95%CI: 1.54-1.95). When the analysis was restricted to unprovoked VTE, risk of VTE was seen to be twice in patients with cirrhosis 2.06 (95%CI: 1.79-2.38) as compared to non-cirrhotic patients. Sub-analysis by stratifying the data into 5 year intervals, authors found that the risk of VTE was decreasing over time, with the highest risk seen in period between 1990 and 1994, perhaps from use of thromboprophylaxis. This study did not have the data regarding severity of liver disease, such as Child Pugh score and could not assess the risk factors in cirrhotics that predict the development of VTE. Also, the cases were compared to population based controls that likely had fewer hospitalizations. The results were similar to another cohort study with nested case-control analysis using General Practitioner Research Database which showed a relative risk of 1.65 (OR = 1.65, 95%CI: 0.97-2.82) for VTE in patients with chronic liver disease[36].

In another population based study by Wu *et al*[8] using US Nationwide Inpatient Sample (1998-2006), prevalence of VTE was assessed in patients with compensated (n = 408253) and decompensated cirrhosis (n = 241626), defined by Baveno Status Classification. Patients with stage I (no ascites or varices) and Ⅱ Baveno (presence of varices without bleeding) were classified as compensated while stage Ⅲ (presence of ascites with or without varices) and Ⅳ (variceal bleeding with or without ascites) as decompensated cirrhosis. The patients were further stratified according to age. The increased risk of VTE was restricted to cirrhotic patients below the age of 45 years, for both compensated (OR = 1.23; 95%CI: 1.04-1.46) and decompensated cirrhosis (1.39; 95%CI: 1.15-1.69). Beyond the age of 45, the risk was modestly lower in compensated cirrhotic patients (OR = 0.90; 95%CI: 0.85-0.95) as compared to controls and similar in decompensated cirrhotics (OR = 0.97; 95%CI: 0.91-1.04).

Table 2 Risk of venous thromboembolism in chronic liver disease patients: major studies

Ref.	Type	*n*	Control	VTE% (*n*) DVT/PE	RR/OR (95%CI)	Comments
Northup *et al*[6], 2006	Case control	21000 cirrhotics	113 (cirrhotic patients without VTE)	0.5 (113) (74 DVT, 22 PE, 17 both)	Risk factor for VTE: low albumin 0.25 (0.10-0.56)	INR, MELD: no correlation
García-Fuster *et al*[31], 2008	Retrospective	2074 cirrhotic patients		0.8 (17) (11 DVT, 7 PE, 1 both)		5 patients had antiphospholipid antibodies
Gulley *et al*[5], 2008	Case control	963 cirrhotics	Control 1:12405 non cirrhotic patients without selected co-morbidities Control 2: non cirrhotic patients with CKD (1692), HF (4489), or solid organ cancer-673	1.87 (18)	Risk factor for VTE: Albumin 0.47 (0.23-0.93) PTT: 0.88 (0.84-0.94)	Cirrhosis not a risk factor on multivariate analysis OR 0.87 (0.2-2.6)
Dabbagh *et al*[32], 2010	Retrospective cohort	190 chronic liver disease patients stratified by INR quartiles		6.3 (12)		Higher INR or higher Child-Pugh stage does not prevent VTE
Lesmana *et al*[33], 2010	Case control	256 cirrhotic patients		4.7 (12)	Risk factor for VTE: Diabetes 4.26 (1.21-15.0)	
Anthony Lizarraga *et al*[34], 2010	Case control	108 CLD patients with VTE (includes 22 patients with PVT)	108 CLD patients without VTE	0.73 (108 out of 14,790 admissions) Includes PVT as well		Cases had lower albumin and hematocrit, higher platelet count, bilirubin and aPTT
Aldawood *et al*[9], 2011	Retrospective cohort	226 cirrhotic patients		2.7 (6)		Significantly longer median LOS in patients with VTE (43 *vs* 8 d, P = 0.004)
Walsh *et al*[11], 2013	Case control	27 CLD patients with VTE	81 CLD patients without VTE	0.65 (17 out of 2606 admissions) (14 DVT, 3 PE)	Risk factor for VTE: low albumin 5.14 (1.05-25.2)	VTE patients had lower transaminases, albumin and hematocrit
Søgaard *et al*[35], 2009	Population based, case control	VTE = 99444	Population controls without VTE 496872		Cirrhosis: RR 1.74 (1.54-1.95)	RR 2.06 (1.79–2.38) for unprovoked VTE
Wu *et al*[8], 2010	Population based, case control	Compensated cirrhotics = 408253 Decompensated = 241626	Non cirrhotic controls = 575057	0.8% for cirrhotics,	Age < 45 yr compensated: 1.23 (1.04-1.46) decompensated: 1.39 (1.15-1.69) Age > 45 yr compensated: 0.90 (0.85-0.95) decompensated: 0.97 (0.91-1.04)	VTE associated with increased mortality and LOS in both compensated and decompensated cirrhotics
Saleh *et al*[37], 2011	Population based	Alcoholic CLD: 4927000 Non-alcoholic CLD: 4565000		0.6% for alcoholicCLD 0.9% for non-alcoholic CLD		
Ali *et al*[10], 2011	Population based cross-sectional	449798 cirrhotic patients		1.80% (1% DVT, 0.9% PE)	Greater morbidity, malnutrition, black race, central venous line associated with higher risk of VTE	DVT associated with longer LOS

DVT: Deep vein thrombosis; PE: Pulmonary embolism; INR: International normalized ratio; MELD: Model for end stage liver disease; CLD: Chronic liver disease; VTE: Venous thromboembolism; CKD: Chronic kidney disease; PVT: Paroxysmalventriculartachycardia; LOS: Length of stay.

VTE was also associated with increased mortality (compensated cirrhotics OR = 2.16; 95%CI: 1.96-2.38, decompensated cirrhosis OR = 1.66, 95%CI: 1.47-1.87) as well as increased length of stay (compensated cirrhotics 1.03 increase, 95%CI: 0.95-1.11, decompensated cirrhotics 86% increase, 95%CI: 78%-94%) in all cirrhotics. The authors concluded that the younger cirrhotic patients may have a higher risk of VTE because of risk conferred by cirrhosis, while in older patients, age related factors may balance or take precedence over cirrhosis related risk factors. This is the largest and the only study to our knowledge that has looked at the differential risk of VTE with respect to the age of the cirrhotics compared to the non cirrhotic patients. In addition, this study also showed an almost two fold increase in mortality and length of hospitalization related to VTE, though the study did not adjust for other possible comorbid conditions like renal failure or respiratory failure. Another population based study included patients with diagnostic codes for chronic alcoholic liver disease and chronic non-alcoholic liver disease who were discharged from short-stay hospitals from 1979 through 2006 using National Hospital Discharge Survey[37]. Study found an overall low rate of VTE, with the prevalence lower in patients with alcoholic as compared to non-alcoholic chronic liver disease (0.6% *vs* 0.9%, $P < 0.0001$). The study did not include data on the severity of the liver disease, reason for hospitalization, proportion of patients hospitalized more than once, and the basis for the diagnosis of liver disease.

Ali *et al*[10] used Nationwide Inpatient Sample Database and included 449798 hospitalizations for cirrhosis in 2005. VTE comprised 1.8% of these hospitalizations though this rate was lower than VTE in overall all hospitalized patients (3.7%, $P < 0.05$). While VTE was not associated with increase in mortality, it was associated with increased LOS by 52% (95%CI: 45%-61% increase LOS) in cirrhotic patients with DVT. In this study, as compared to the study by Wu *et al*[8], cirrhotics with VTE were older as compared to cirrhotics without VTE [36.7% of cirrhotics with VTE were age 65 years and older compared to 29.5% of cirrhotics without VTE ($P < 0.001$)].

The population database based studies have an advantage of large sample size, however, they suffer from limitations including miscoding, missed information as well as lack of laboratory data (thereby MELD score or Child Pugh Score) and clinical details including use of DVT prophylaxis or accurate stratification by severity of liver cirrhosis[8,10,35]. It is obvious that most of the studies above have different study designs, inclusion criteria, period of study, availability of clinical and laboratory data and outcomes. One thing that stands out is that cirrhotic patients have a significant risk of VTE, if not higher than non-cirrhotic patients and this risk cannot be trivialized or ignored.

RISK FACTORS

Studies have attempted to define the risk factors associated with VTE complications in cirrhotics (Table 2). In a case control study by Northup *et al*[6] involving 113 cirrhotic patients with VTE, low serum albumin was an independent risk factor development of VTE (OR = 0.25, 95%CI: 0.10-0.56, $P < 0.001$). Also, INR or platelet counts were not associated with VTE risk. Low albumin was also found to be an independent risk factor in another case control study[5]. This study found that low serum albumin (OR = 0.47, 95%CI: 0.23-0.93, $P = 0.03$) and partial thromboplastin time (PTT) (OR = 0.88: 95%CI: 0.84-0.94, $P = 0.04$) were risk factors of developing DVT/PE in cirrhotics. Diabetes was an independent risk factor for VTE (OR = 4.26; 95%CI: 1.206-15.034; $P = 0.024$) in a retrospective study from Indonesia[33]. Two other retrospective case control series comparing chronic liver disease patients with and without VTE found that VTE cases had significantly lower albumin and hematocrit as compared to non VTE controls, with albumin lower than 1.9 g/dL increasing the risk of VTE more than 5 times compared to patients with albumin greater than 2.7 g/dL (OR = 5.14, 95%CI: 1.05-25.2)[11,34]. It is important to note that both these studies involved patients with portal and nonportal thrombosis. In addition, Anthony Lizarraga *et al*[34] found that chronic liver disease patients with VTE had higher bilirubin (1.71 *vs* 1.11; $P < 0.01$), higher platelet counts (143 *vs* 109; $P = 0.03$), and activated PTT (87 *vs* 60.3 s; $P < 0.01$) as compared with controls. Factors that were associated with higher risk of VTE in cirrhotics included greater comorbidity (as reflected by the Charlson index), black race (OR = 1.25, 95%CI: 1.02-1.55), malnutrition (OR = 1.29, 95%CI: 1.05-1.59) and central venous line placement (OR = 1.7, 95%CI: 1.54-2.04)[10].

Of all the risk factors above, hypoalbuminemia appears to be the most consistent risk factor amongst these studies, with one study finding a five times higher risk in patients with albumin less than 1.9 g/dL. Low albumin may be a reflection of overall decreased liver synthetic function, including a balanced decreased synthesis of the anticoagulant factors like antithrombin Ⅲ, protein C and protein S and the vitamin K dependent coagulant factors Ⅱ, Ⅶ, Ⅸ and Ⅹ. It is interesting to note that elevated INR does not decrease the risk of bleeding and/or thrombosis[6,32].

MANAGEMENT

The current consensus guidelines for VTE prevention do not specifically address the hospitalized cirrhotic patients[38]. Despite the increasing recognition of thrombotic complications in the cirrhotic patients, prophylaxis against VTE in this patient population is frequently avoided. Pharmacological prophylaxis is often not given because of the perceived increased risk of bleeding. Also, mechanical prophylaxis with graduated compression stockings or intermittent pneumatic devices can often be challenging as these can lead to skin breakdown, a condition not so uncommon in cirrhotics with pre-existing

lower extremity swelling and frequently lower extremity cellulitis[39]. In a retrospective study from Saudi Arabia, more than 75% of the hospitalized patients did not receive any mechanical or pharmacological prophylaxis against DVT[9]. Similar low prevalence of DVT prophylaxis was seen in other studies as well[6,32]. In the study by Northup *et al*[6], 21% of the hospitalized cirrhotic patients received prophylaxis, and only 33% of these patients received pharmacological prophylaxis. A greater percentage of chronic liver disease patients (44%) received pharmacological prophylaxis while another 52% received mechanical prophylaxis in a recent study, which may reflect growing awareness about the VTE risk in this patient population[11].

EFFICACY AND SAFETY

To date, there are no randomized studies to evaluate the efficacy and safety of the pharmacological prophylaxis of VTE in hospitalized patients with cirrhosis. A recent meta-analysis of three small retrospective cohort studies with 531 cirrhotic patients (208 with heparin prophylaxis) showed no reduction in the risk of VTE with prophylactic heparin (pooled OR = 1.65 95%CI: 0.36-7.54)[40]. As the authors pointed, the included studies were small in size and had marked clinical heterogeneity with very different inclusion and exclusion criteria[9,41]. Also, the incidence of VTE in the pooled sample was very low (3 events in prophylaxis group and 6 events in no pharmacological group), therefore the sample size was probably insufficient to estimate the real protective effect of the intervention.

The same meta-analysis also found that use of heparin was not associated with higher risk of bleeding in cirrhosis (pooled OR = 0.87 95%CI: 0.34-2.18)[40]. Again, the five studies included in the meta-analysis had very different inclusion criteria (*e.g.*, HCC was an exclusion criteria in one[16] while another study was done in cirrhotic patients with HCC[41]) and involved very different doses of the anticoagulant [prophylactic UFH (unfractionated heparin) or LMWH (low molecular weight heparin)[16,41,42] *vs* therapeutic anticoagulation[43]]. Most of the included studies did not have bleeding risk as the major outcome, therefore the possibility of under reporting or missed bleeding events cannot be excluded. Other than one randomized study, all were retrospective studies and it is possible that patients with perceived higher risk of bleeding did not receive anticoagulation. The largest study evaluating the safety of prophylactic anticoagulation in hospitalized cirrhotic patients found that the prophylaxis was not associated with increased risk of bleeding or death[42]. This retrospective study evaluated 235 patients accounting for 355 discrete hospitalizations to the non ICU bed between 2007 and 2010 who received prophylactic UFH or LMWH. Despite thromboprophylaxis, five patients (1.4%) were diagnosed with VTE (three non-splanchnic DVT, two PE). Nine of 355 (2.5%) had an episode of GI bleeding during hospitalization, five of whom required blood transfusion. Only 3 out of these 9 patients had major bleeding according to standard definition. Heparin induced thrombocytopenia was diagnosed in two patients (0.5%). That no patients died from VTE related complications is of great importance. Prophylactic enoxaparin was also found to be safe in an interesting prospective Italian study[16]. In this randomized study, 34 outpatients with cirrhosis between Child Pugh classes B7-C10 received prophylactic subcutaneous enoxaparin at the dose of 4000 IU/d for 48 wk. Enoxaparin was well tolerated with discontinuation of therapy in only 1 patient at week 36 because of marked thrombocytopenia. Two patients had episodes of bleeding from esophageal varices controlled with conservative endoscopic therapy. Epistaxis was seen in 2 patients. Occurrence of bleeding episodes did not differ between the prophylactic enoxaparin group and control group (P = 0.521). Interestingly, this study showed that prophylactic anticoagulation was associated with significant reduction in risk of development of PVT (HR = 0.098; 95%CI: 0.014-0.697; P = 0.020) occurrence of decompensation (HR = 0.331; 95%CI: 0.148-0.741; P = 0.007), and was associated with survival benefit (HR = 0.366; 95%CI: 0.082-0.795; P = 0.018).

More data is available for safety of anticoagulation in cirrhotic patients with portal vein thrombosis[44-46]. In a study by Delgado *et al*[45] involving 55 cirrhotic patients with portal vein thrombosis, 47 patients received anticoagulation therapy with LMWH with 21 subsequently shifted to vitamin K antagonists (VKA). Remaining 8 patients were initiated and continued on VKA therapy. During the median follow up period of 19 mo, five patients had bleeding that was attributed to the anticoagulation therapy. Platelet count less than 50×10^9/L (P = 0.02) and use of VKA (P = 0.53) were the only factors that were observed more frequently in patients with bleeding secondary to anticoagulation treatment. The anticoagulation treatment with LMWH was also well tolerated in 28 cirrhotic patients with non-neoplastic PVT with no patient requiring interruption of anticoagulation during the treatment duration of more than 6 mo[44].

Although the studies had different designs and used different anticoagulation treatment, the anticoagulation therapy was safely tolerated in all these studies. It is important to realize that in all these studies, patients received primary or secondary prophylaxis for esophageal varices with either endoscopic variceal ligation or use of non-selective beta blockers prior to initiation of anticoagulation. However, anticoagulation treatment was associated with high risk of bleeding complications in a retrospective Spanish study including 17 cirrhotic patients with non-splanchnic VTEs (11 patients with DVT, 7 with PE and 1 with both)[31]. Eleven patients were treated with LMWH while remaining were switched to VKA within a week after initiating LMWH treatment. Majority (83%) of these patients suffered from bleeding complications with six (35%) of them requiring blood transfusions. Only three patients (21%) could continue the anticoagulation treatment beyond six months.

The use of oral VKA has to be considered against the fact that INR is often already elevated in many cirrhotic patients. The target INR is not established as it cannot differentiate between the elevation in INR from underlying cirrhosis *vs* that from VKA[47]. The inter-laboratory variation in the INR in cirrhotic patients is unacceptably high, thereby further complicating the monitoring[48]. It has long been established that INR does not does not predict the bleeding risk in these patients as it fails to capture changes in anticoagulants going on in cirrhotic patients while it measures only the activity of procoagulants[49]. Newer monitoring tests including using a modified INR $_{liver}$[50] rather than INR (using plasma from patients with liver disease rather than plasma from noncirrhotic patients on oral anticoagulants to generate International Sensitivity Index used to calculate INR), thrombin generation assays[27], viscoelastic tests of hemostasis including thromboelastography and thromboelastometry[51] have been proposed but very likely will not offset some of the limitations seen with traditional INR as a marker of coagulation abnormalities seen in these patients.

As discussed above, more data is available with use of LMWH in cirrhotics. While the use of LMWH appears to be safe, its use has its own limitations. In addition to the subcutaneous injection as well as relative contraindication with renal insufficiency, the monitoring of anticoagulant effect in cirrhotics with anti Xa levels is not completely reliable. In a study involving 84 cirrhotic patients requiring prophylactic or therapeutic enoxaparin, Bechmann *et al*[52] found that treatment with standard doses of enoxaparin failed to achieve target anti Xa levels recommended for prophylactic or therapeutic use. Authors also noted negative correlation between the anti Xa levels and the severity of liver disease as assessed by Child Pugh score and the MELD score and concluded that it was likely secondary to decreased synthesis of antithrombin in cirrhotic patients. However, *in vitro* studies evaluating the effect of LMWH on thrombin generation has shown that cirrhotic patients show an increased response to LMWH, in spite of reduced antithrombin and anti-Xa activity levels. The low anti-Xa levels may actually be a laboratory artifact while the efficacy of LMWH is preserved[53,54]. These studies show that increasing the dose of LMWH as a reflex to low anti Xa levels is not necessary and potentially can lead to hemorrhagic complications.

The newer direct thrombin inhibitors like dabigatran and direct factor Xa inhibitors like rivaroxaban and apixaban have advantage of oral intake and are usually given in a fixed dose without requiring any laboratory monitoring in non-cirrhotic patients[55]. However, the data on the use of these agents in cirrhotic patients is limited and the unavailability of any reversible agents in case of active bleeding has limited the clinical applicability of these agents for now.

In summary, we believe that there is enough evidence to make a case for careful anticoagulation in individual cirrhotics-both for prophylaxis as well as treatment for VTE after due consideration for variceal prophylaxis with either endoscopic treatment or non-selective beta blockers or both. In patients with decompensated cirrhosis, use of LMWH may be preferred over oral VKA agents. For reasons stated above, close monitoring of anticoagulation management in the hands of coagulation experts cannot be overemphasized.

CONCLUSION

Chronic liver disease and cirrhosis represent a state of overall decreased liver synthetic function, including a balanced decreased synthesis of the anticoagulant thrombotic factors like antithrombin Ⅲ, protein C and protein S and the vitamin K dependent procoagulant factors Ⅱ, Ⅶ, Ⅸ and Ⅹ on top of thrombocytopenia and/or thrombocytopathia. Though the bleeding risk in advanced liver disease remains the most feared complication of the precariously balanced procoagulant and anticoagulant cascade, VTE complications can certainly not be ignored. These complications are associated with increased hospital length of stay and cost, leading to increased health care burden, in addition to worse patient outcomes. Thromboprophylaxis against VTE should be considered very cautiously in a cross talk between experts in coagulation and hepatology in all these patients. In the absence of absolute contraindications, anticoagulation therapy should be offered of course to all the cirrhotic patients with confirmed VTE.

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