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# Venous Thromboembolism in Liver Cirrhosis: An Emerging Issue

Xingshun Qi and Andrea Mancuso

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## Abstract

Venous thromboembolism (VTE) carries a high morbidity and mortality and leads to a substantial economic burden. From the traditional perspectives, liver cirrhosis tends to bleeding but not VTE. However, modern concepts suggest that liver cirrhosis is also at a risk of VTE. The pooled incidence and prevalence of VTE in liver cirrhosis are 1% (95% confidence interval: 0.7–1.3%) and 1% (95% confidence interval: 0.7–1.2%), respectively. Evidence indicates that a higher international normalized ratio and a lower albumin should be associated with a higher probability of VTE in liver cirrhosis. Additionally, the presence of VTE significantly worsens the outcomes of liver cirrhosis.

**Keywords:** venous thromboembolism, liver cirrhosis, risk factor, prognosis, epidemiology

## 1. Introduction: venous thromboembolism

Venous thromboembolism (VTE) consists of deep vein thrombosis (DVT) and pulmonary embolism (PE). VTE is a major public health condition.

First, VTE represents a substantial economic burden in this world. A systematic review of 10 cost-of-illness studies explored the costs in the different regions [1]. The initial VTE costs 3000–9500$ in the United States. The additional inpatient costs are significantly increased with the duration of VTE. In the United States, the VTE over 3, 6, and 12 months costs 5000$, 10,000$, and 33,000$, respectively; by comparison, in the EU, the VTE over 3 and 12 months costs 1800$ and $32,000$, respectively. The additional costs of VTE-related complications are

also expensive. The post-thrombotic syndrome costs 426–11,700$, and the heparin-induced thrombocytopenia costs 3118–41,133$.

Second, VTE carries a relatively high incidence. In the United States, the annual incidence of VTE is 1/1000 and is gradually increased with the age [2]. A 25-year population-based study, which was conducted in Olmsted County, Minnesota, United States, found that the annual incidence of VTE was 1.17/1000 and that the annual incidences of DVT and PE were 0.48/1000 and 0.69/1000, respectively [3]. A community-based study, in which 342,000 inhabitants were enrolled between April 1, 1998, and March 31, 1999, in Western France, demonstrated that the annual incidence of VTE was 1.83/1000 (95% confidence interval: 1.69–1.98) and that the annual incidences of DVT and PE were 1.24/1000 (95% confidence interval: 1.12–1.36) and 0.60/1000 (95% confidence interval: 0.52–0.69), respectively [4]. Recently, a new community-based study, in which 367,911 inhabitants were enrolled between March 1, 2013, and February 28, 2014, in Western France, demonstrated that the annual incidence of VTE was significantly decreased to 1.57/1000 (95% confidence interval: 1.44–1.69) [5]. A prospective community-based study, in which 151,923 permanent residents of northeastern metropolitan Perth in Western Australia were followed from October 1, 2003, to October 31, 2004, found that the annual incidence of VTE was 0.83/1000 (95% confidence interval: 0.69–0.97) and that the annual incidences of DVT and PE were 0.52 (95% confidence interval: 0.41–0.63) and 0.31 (95% confidence interval: 0.22–0.40), respectively [6]. Indeed, necropsy examinations demonstrated a higher incidence of VTE. Based on a review of necropsy reports from a Swedish Malmo general hospital, 34.7% (347/994) of necropsy cases had VTE, and 9.4% (93/994) of them had fatal PE [7].

Third, VTE produces a high mortality and is a major cause of death in the general population. A population-based cohort study of 2218 patients with DVT or PE from Olmsted County, Minnesota, demonstrated that the 7-day, 30-day, and 1-year survival rates were 96.2, 94.5, and 85.4% in patients with DVT alone and 59.1, 55.6, and 47.7% in patients with PE with or without DVT [8]. A retrospective review of necropsy data from inpatients at King's College Hospital between January 1991 and December 2000 demonstrated that 5.2% (265/6833) of death cases were attributed to fatal PE [9]. The VTE Impact Assessment Group in Europe (VITAE) estimated that the total number of symptomatic VTE events per annum within the six EU countries, including France, Germany, Italy, Spain, Sweden, and the United Kingdom, were 465,715 (404,664–538,189) DVT cases, 295,982 (242,450–360,363) PE cases, and 370,012 (300,193–483,108) VTE-related deaths [10].

## 2. Risk factors for the development of VTE

Virchow's triad, which includes vessel injury, blood flow stasis, and hypercoagulopathy, is a classical explanation for the development of VTE [11]. According to the 7th American College of Chest Physicians Conference on Antithrombotic and Thrombolytic Therapy, the major risk factors for VTE included surgery, trauma (major or lower extremity), immobility, paresis, malignancy, cancer therapy (hormonal, chemotherapy, or radiotherapy), previous

VTE, increasing age, pregnancy and the postpartum period, estrogen-containing oral contraception or hormone replacement therapy, selective estrogen receptor modulators, acute medical illness, heart or respiratory failure, inflammatory bowel disease, nephrotic syndrome, myeloproliferative disorders, paroxysmal nocturnal hemoglobinuria, obesity, smoking, varicose veins, central venous catheterization, and inherited or acquired thrombophilia [12]. Currently, accumulated evidence has identified more and more risk factors for the development of VTE. A meta-analysis of 14 studies demonstrated a dose-response relationship between duration of travel and development of VTE [13]. Hippisley-Cox et al. developed and validated the QThrombosis web calculator (www.qthrombosis.org) for predicting the risk of VTE between 1 and 5 years [14]. In the calculator, the information should be provided regarding age, sex, ethnicity, smoking status, varicose vein surgery, chronic kidney disease (stage 4 or 5), cancer, heart failure, chronic obstructive airways disease, Crohn's or ulcerative colitis, previous admission in last 6 months, antipsychotics, and body mass index. For women, some additional information regarding hormone replacement therapy, an oral contraceptive, and tamoxifen is needed. Rogers et al. also conducted a case-crossover study to evaluate the triggers of hospitalization for VTE [15]. A total of 399 subjects with VTE hospitalizations were enrolled from the Health and Retirement Study in the United States. The investigators found that infection was the most frequent trigger of VTE (52.4%) and the use of erythropoiesis stimulating agents was the most strong trigger of VTE (adjusted incidence rate ratio = 9.33, 95% confidence interval: 1.19–73.42). More recently, Tsai et al. [16] also assessed the hospital-level determinants of VTE diagnosis. An interesting finding was that patients treated in urban hospitals had a higher risk of VTE diagnosis than those treated in rural hospitals. Except for the above-mentioned findings in the general population, lots of studies focused on the prediction of VTE in patients with cancer, patients undergoing surgery, and other specific population, which were beyond the scope of the present work.

## 3. Liver cirrhosis

According to the Global Burden of Disease Study 2010, liver cirrhosis is the 11th leading cause of death and accounts for 50,000 deaths in the United States, 2010 [17]. It is also the 8th leading cause of years of life lost from premature death. According to the Global Burden of Disease Study 2013, liver cirrhosis is the 13th leading cause of global years of life lost [18]. The major complications of liver cirrhosis should be esophageal variceal bleeding and ascites [19–21]. Liver cirrhosis is divided into four major stages according to the two complications. They include stage 1 (neither varices nor ascites), stage 2 (varices without ascites), stage 3 (ascites), and stage 4 (variceal bleeding) [22]. Considering the potential risk of lethal variceal bleeding, a patient with liver cirrhosis is considered to have a bleeding diathesis and is often contraindicated for antithrombotic drugs [23]. At present, emerging evidence suggests that a cirrhotic patient is also at a risk of thrombosis due to the loss of anticoagulant proteins [23]. A nationwide Danish case-control study of 99,444 patients with VTE and 496,872 population controls found a significantly higher risk of VTE in patients with liver cirrhosis (all VTE: risk ratio = 1.74, 95% confidence interval: 1.54–1.95; DVT: risk

ratio = 2.02, 95% confidence interval: 1.78–2.31; PE: risk ratio = 1.41, 95% confidence interval: 1.20–1.65) [24]. Additionally, a nationwide US population-based study of 408,253 admissions with compensated cirrhosis, 241,626 admissions with decompensated cirrhosis, and 575,057 admissions without liver diseases demonstrated a significantly higher risk of VTE in cirrhotic patients younger than 45 years (compensated cirrhosis: adjusted odds ratio = 1.23, 95% confidence interval: 1.04–1.46; decompensated cirrhosis: adjusted odds ratio = 1.39, 95% confidence interval: 1.15–1.69) [25].

## 4. Epidemiology of VTE in liver cirrhosis

The prevalence and incidence of VTE in liver cirrhosis are greatly heterogeneous among studies. Thus, our team systematically reviewed and synthesized the data regarding the epidemiology of VTE in liver cirrhosis [26]. Among the 20 included studies, the pooled incidence and prevalence of VTE in liver cirrhosis were 1% (95% confidence interval: 0.7–1.3%) and 1% (95% confidence interval: 0.7–1.2%), respectively; the pooled incidence and prevalence of DVT in liver cirrhosis were 0.6% (95% confidence interval: 0.4–0.8%) and 0.7% (95% confidence interval: 0.6–0.9%), respectively; the pooled incidence and prevalence of PE in liver cirrhosis were 0.28% (95% confidence interval: 0.13–0.49%) and 0.36% (95% confidence interval: 0.13–0.7%), respectively. Such epidemiological data should be important for physicians and patients to recognize the potential risk of VTE.

## 5. Risk factors for VTE in liver cirrhosis

Due to the relative rarity of VTE in liver cirrhosis, it is necessary to obtain the knowledge regarding risk factors for VTE and to further screen high-risk patients who will receive medical prophylaxis for VTE. Except for traditional risk factors in the general population (i.e., older age, comorbidity, surgery), which were reported in the second paragraph of this article, two risk factors related to liver diseases have been more widely recognized, such as international normalized ratio (INR) and albumin. First, cirrhotic patients often have an elevated INR, which reflects an auto-anticoagulation status. Thus, it appeared to be reasonable that the risk of VTE would be lower if INR was higher. However, this was not the case. Northup et al. for the first time found that the risk of VTE was not associated with INR [27]. Dabbagh et al. also confirmed that an elevated INR did not protect against the development of VTE during hospitalization [28]. Smith et al. showed that the risk of in-hospital VTE was similar between patients with INR <2.0 and INR ≥2.0 [29]. Indeed, our team observed a positive relationship between INR and risk of VTE [30]. This phenomenon should be explained by the fact that INR is a component of Child-Pugh score and reflects the severity of liver dysfunction, rather than the absolute hemostasis disturbance. Second, several studies coherently found a lower albumin in cirrhotic patients with VTE than those

without [27, 31–33]. But a statistical significance was achieved in only two of them [27, 33]. Taken together, a prediction algorithm of VTE in liver cirrhosis should be warranted.

# 6. Prognosis of liver cirrhosis and VTE

## 6.1. Effect of VTE on the survival in cirrhotic patients

By analyzing the data from the Nationwide Inpatient Sample (1998–2006), Wu et al. found that the in-hospital mortality of compensated cirrhosis was 16.8 and 7.6% in patients with and without VTE, respectively (odds ratio = 2.16, 95% confidence interval: 1.96–2.38); the in-hospital mortality of decompensated cirrhosis was 18.6 and 11.1% in patients with and without VTE, respectively (odds ratio = 1.66, 95% confidence interval: 1.47–1.87) [25]. More recently, a single-center retrospective study of 2006 admissions with cirrhosis by our team also demonstrated an approximately 10-fold higher in-hospital mortality in patients with VTE than those without VTE (33.3 vs. 3.4%, $P < 0.001$) [30].

## 6.2. Effect of liver cirrhosis on the survival in VTE patients

A nationwide Danish cohort study of 4392 VTE patients, which included 745 and 3647patients with and without cirrhosis, respectively, explored the effect of cirrhosis on the 30-day death [34]. According to the sites of VTE, the 30-day mortality was 7% (95% confidence interval: 5–10%) and 3% (95% confidence interval: 2–3%) in DVT patients with cirrhosis and without liver cirrhosis, respectively; the 30-day mortality was 35% (95% confidence interval: 29–42%) and 16% (95% confidence interval: 14–19%) in PE patients with cirrhosis and without liver cirrhosis, respectively.

## 6.3. Effect of liver cirrhosis on the development of cancer in VTE patients

A population-based Danish cohort study of 2755 VTE patients with liver diseases, which included 1867 VTE patients with non-cirrhotic liver diseases and 888 VTE patients with liver cirrhosis, explored the effect of cirrhosis of the development of cancer [35]. VTE patients with liver cirrhosis had a significantly higher 1-year risk of cancer than VTE patients with non-cirrhotic liver diseases (4.3 vs. 2.7%).

# 7. Conclusions

Physicians should recognize that cirrhotic patients are at a risk of VTE. Once VTE is diagnosed, the outcomes of cirrhotic patients would be worse. INR and albumin should be potential risk factors of VTE in cirrhosis. However, until now, no prediction model for VTE in such patients was well established.

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