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A M E R I C A N C O L L E G E O F



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## Coagulopathy Does Not Protect Against Venous Thromboembolism in Hospitalized Patients With Chronic Liver Disease

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**Background:** It is uncertain whether pathologically prolonged international normalized ratio (INR) seen in chronic liver disease (CLD) protects against venous thromboembolism (VTE). Previous studies reported VTE incidence of 0.5% to 1.9% in patients with CLD. We sought to evaluate VTE incidence among hospitalized patients with CLD according to INR levels.

**Methods:** This was a retrospective cohort study performed at a tertiary university hospital. We included all adult patients admitted with a primary diagnosis of CLD over a 7-year period. The primary outcome was the development of VTE during hospital stay. Patients were divided into quartiles according to their highest admission INR. VTE events and prophylaxis rates were compared among INR quartiles.

**Results:** During the allotted 7-year period, we included 190 patients. Of these, 12 developed VTE events, yielding a VTE incidence of 6.3%. There was no significant difference in the incidence of VTE between INR quartiles. Hospital mortality rates were higher in the higher INR quartiles than in the lower ones ( $P < .001$ ), but hospital length of stay was not significantly different. Of the patients with documented VTE, one (4.2%) was Child-Pugh stage A, three (4.6%) were stage B, and eight (8.0%) were stage C ( $P = .602$ ). VTE prophylaxis was not used in 75% of patients.

**Conclusions:** An elevated INR in the setting of CLD does not appear to protect against the development of hospital-acquired VTE. The notion that “auto-anticoagulation” protects against VTE is unfounded. Use of DVT prophylaxis was extremely low in this population.

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**Abbreviations:** CLD = chronic liver disease; INR = international normalized ratio; IQR = interquartile range; VD-US = venous Doppler ultrasound; VQ = ventilation-perfusion; VTE = venous thromboembolism

Chronic liver disease (CLD) and cirrhosis are prevalent in the United States, accounting for >400,000 hospitalizations and 27,000 deaths in 2002.<sup>1,2</sup> Many patients with CLD have an elevated international normalized ratio (INR) because of coagul-

opathy caused by the disease. Clinicians often have a sense of security that these patients are at a reduced risk for venous thromboembolism (VTE) due to “auto-anticoagulation.” However, defective synthesis of anticoagulant factors, including protein C, protein S, and antithrombin III, occurs in CLD and may increase the risk of VTE.<sup>3,4</sup> In addition, elevated levels of antiphospholipid antibodies have been found in some patients with cirrhosis and may be a risk factor for thrombosis.<sup>5,6</sup>

Studies investigating the incidence of VTE in patients with cirrhosis have reported a risk equal to<sup>7</sup> or less than<sup>8</sup> that of other medically ill hospitalized patients. To our knowledge, no study has evaluated the relationship between the level of pathologic INR elevation and VTE. We sought to evaluate this relationship in hospitalized patients. It is our hope that the results

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of this and future studies will lead to recommendations regarding VTE prophylaxis and treatment in patients with CLD. We feel this is an issue that has not been adequately addressed, even in the most recent American College of Chest Physicians guidelines for prevention of VTE.<sup>9</sup>

## MATERIALS AND METHODS

### Patients

We retrospectively reviewed the charts of patients with discharge *International Classification of Diseases, 9th edition* diagnosis codes corresponding to CLD and cirrhosis (571, 571.5, 571.8, and 571.9) who were admitted to a tertiary care University Hospital between January 1, 2000, and January 31, 2007. Patients were eligible for inclusion in the study if they were 18 years or older and were admitted primarily for CLD. CLD was defined based on clinical and pathologic criteria. Histologic diagnosis was not required. Only patients with documented CLD in the medical records were included. CLD was classified as alcoholic, chronic active viral hepatitis (hepatitis B and C), cryptogenic, and other types, such as nonalcoholic steatohepatitis and autoimmune. Patients were excluded if, at the time of admission, they were being treated with chronic anticoagulation therapy, had known active VTE, or were under palliative care. If a patient had multiple admissions during the study period, we only included the most recent admission during which a spiral CT scan of the chest and/or lower extremity venous Doppler ultrasound (VD-US) was performed. If neither of these studies was performed during any of the admissions during the study period, the most recent admission was included. The study was approved by the University of Missouri–Columbia Health Sciences Institutional Review Board. The approval allowed for retrospective chart review and anonymous results reporting without informed consent.

### Data Collection

For each patient, gender, height, and weight were documented, and BMI was calculated. Obesity was defined as a BMI > 29 kg/m<sup>2</sup>. History of alcohol, tobacco, and illicit drug use was documented for each patient, although no distinction was made between alcohol use and abuse. Known risk factors for VTE were documented, including surgery or trauma within the preceding 30 days, active malignancy, prior history of VTE, use of oral contraceptive pills or hormone-replacement therapy, and inherited hypercoagulable conditions.

The cause of CLD was recorded as documented in the electronic medical record or based on histopathologic diagnosis whenever available. Admission platelet count, lowest serum albumin, highest total bilirubin, and highest INR of the pertinent hospital admission were recorded. The control of ascites and grade of hepatic encephalopathy were documented, and Child-Pugh score and stage were determined. Furthermore, any type of mechanical or pharmacologic DVT prophylaxis that was administered during hospitalization was recorded, including sequential compression device, low-molecular-weight heparin, unfractionated heparin, or fondaparinux.

### VTE Risk Factor Score

A risk factor score was calculated for each subject, based on the study by Kucher and colleagues.<sup>10</sup> The major risk factors of active malignancy, prior VTE, and hypercoagulability (defined as the

presence of any of the following: factor V Leiden mutation, prothrombin gene mutation, lupus anticoagulant, anticardiolipin antibodies, and deficiencies of protein C, protein S, or antithrombin III) were each assigned a score of 3. The intermediate risk factor of major surgery within the previous 30 days was assigned a score of 2. The minor risk factors of age > 70 years, obesity, bed rest, and the use of oral contraceptives or hormone-replacement therapy were each assigned a score of 1. High-risk patients were defined as those with a score  $\geq 4$ .

### Outcome Measures

The primary outcome was defined as the development of symptomatic DVT or pulmonary embolism, as confirmed by extremity VD-US, spiral CT scan of the chest, high probability ventilation-perfusion (VQ) scan, or pulmonary angiography. The secondary outcome measures were hospital length of stay and in-hospital mortality.

### Statistical Analysis

Patients were divided into four quartiles according to the highest INR. Baseline characteristics were compared among the four groups. Variables were expressed as means or medians with SD or interquartile range (IQR) according to normality testing using Kolmogorov-Smirnov tests. Categorical values were expressed as units and percentages. Comparisons were performed using analysis of variance, Kruskal-Wallis test for continuous variables, and  $\chi^2$  or Fisher exact tests for categorical variables. Significance was defined as  $P < .05$ , and all tests were two-sided.

## RESULTS

We identified 193 patients who met the inclusion criteria and excluded three because of a lack of INR data. Data on 190 patients were included in the final analysis. The subjects were divided into quartiles separated by INR values of 1.4, 1.7, and 2.2 (Table 1). The baseline demographics were similar among the quartiles. The calculated VTE risk score was also similar, as was the number of patients with a history of VTE. In all four quartiles, the most common cause of CLD was alcohol related, followed by hepatitis B or C, and then other rare causes such as autoimmune, nonalcoholic steatohepatitis, or unknown cause (Table 2). The median total bilirubin, albumin, and admission platelet counts were significantly different between quartiles, and there was a significant trend of increasing Child-Pugh score and stage in the higher quartiles.

Of the three diagnostic tests for VTE (spiral CT scan of the chest, VQ scan, and VD-US), 55 (29%) patients underwent one test for VTE, 25 (13%) underwent two tests, and two patients (1.1%) underwent three tests. The majority of patients, 108 (57%), were not tested for VTE. VD-US was the most commonly used test, followed by spiral CT scan and VQ scan (Table 3). There was no significant difference among the quartiles in DVT prophylaxis, whether mechanical or pharmacologic (Table 3). Approximately 75% of all

**Table 1—Baseline Characteristics and Venous Thromboembolism Risks of the Study Patients by International Normalized Ratio Quartile**

Characteristic	INR Quartiles				P Value
	First Quartile INR < 1.4 (n = 47)	Second Quartile 1.4 ≤ INR < 1.7 (n = 61)	Third Quartile 1.7 ≤ INR < 2.2 (n = 38)	Fourth Quartile INR ≥ 2.2 (n = 44)	
Median age (IQR)	52 (16)	49 (18)	51 (20)	51 (14)	.967
Male sex	34 (72)	34 (56)	22 (58)	31 (71)	.203
Median BMI (IQR)	27.5 (7.22)	26.0 (9.91)	26.5 (9.72)	27.5 (9.40)	.942
Smoking	28 (60)	40 (66)	26 (68)	30 (68)	.8
Alcohol use	34 (72)	42 (69)	28 (74)	35 (80)	.68
VTE risk factors					
Malignancy	13 (28)	18 (30)	5 (13)	8 (18)	.198
History of VTE	1 (2.1)	3 (4.9)	0 (0)	1 (2.3)	.5
Age > 70 y	3 (6.4)	7 (11.5)	4 (10.5)	4 (9.1)	.834
Obesity (BMI > 29)	16 (24.6)	21 (36.8)	14 (40)	17 (42.5)	.942
Surgery	10 (21.3)	7 (11.5)	7 (18.4)	9 (20.5)	.513
Estrogen products	1 (2.1)	0 (0)	0 (0)	0 (0)	.38
Hypercoagulable state	0 (0)	0 (0)	0 (0)	0 (0)	NS
Median VTE risk score (range)	2 (0-6)	1 (0-7)	1 (0-5)	1 (0-6)	.593

Data are presented as No. (%) unless otherwise indicated. INR = international normalized ratio; IQR = interquartile range; VTE = venous thromboembolism.

patients received no prophylaxis. There was no significant difference in VTE incidence between the cohort receiving prophylaxis, whether mechanical or pharmacologic, and the group that did not receive prophylaxis. In-hospital VTE occurred in 12 patients (6.3%) over the study period, but there was no significant difference in the incidence of VTE between INR quartiles. More patients died in the higher INR quartiles than in the lower ones ( $P < .001$ ), but hospital length of stay was not significantly different. Of the patients with documented VTE, one (4.2%) was

Child-Pugh stage A, three (4.6%) were stage B, and eight (8.0%) were stage C ( $P = .602$ ) (Fig 1).

## DISCUSSION

The incidence of new VTE in our study was 6.3%. This is higher than the previously reported incidences of 1.9% and 0.5%, according to Gulley et al<sup>7</sup> and Northup et al,<sup>8</sup> respectively. Our study shows that elevated INR in CLD should not give clinicians a

**Table 2—Cause and Severity of Chronic Liver Disease by INR Quartile**

Characteristic	INR Quartiles				P Value
	First Quartile INR < 1.4 (n = 47)	Second Quartile 1.4 ≤ INR < 1.7 (n = 61)	Third Quartile 1.7 ≤ INR < 2.2 (n = 38)	Fourth Quartile INR ≥ 2.2 (n = 44)	
Cause of CLD					.952
Alcohol	21 (45)	26 (43)	17 (45)	20 (45)	...
Hepatitis B or C	13 (28)	22 (36)	12 (32)	17 (39)	...
Cryptogenic	11 (23)	11 (18)	8 (21)	5 (11)	...
Other	2 (4)	2 (3)	1 (3)	2 (5)	...
Severity of CLD					
INR median (IQR)	1.2 (0.2)	1.6 (0.2)	1.95 (0.3)	2.85 (1.4)	< .0001
Ascites	18 (38.3)	37 (60.7)	28 (73.7)	32 (72.7)	.002
Encephalopathy	7 (14.9)	13 (21.3)	14 (36.8)	16 (36.4)	.038
Median total bilirubin, mg/dL (IQR)	1.4 (2.4)	2.2 (3.0)	3.8 (7.7)	5.8 (12.1)	< .001
Median albumin, mg/dL (IQR)	2.6 (1.3)	2.3 (0.9)	1.9 (0.8)	2.1 (0.8)	.001
Median admission platelet count (IQR)	172 (138)	119 (98)	103 (119)	117 (117)	.001
Median Child-Pugh Score (IQR)	7 (3)	9 (3)	10 (2)	12 (2)	< .01
Child-Pugh Stage					
Stage A	15 (32)	9 (15)	0 (0)	0 (0)	< .01
Stage B	24 (51)	31 (51)	8 (21)	3 (6.8)	< .01
Stage C	8 (17)	21 (34)	30 (79)	41 (93)	< .01

Data are presented as No. (%) unless otherwise indicated. CLD = chronic liver disease. See Table 1 for expansion of other abbreviations.

**Table 3—Primary and Secondary Outcomes**

Characteristic	First Quartile INR < 1.4 (n = 47)	Second Quartile 1.4 ≤ INR < 1.7 (n = 61)	Third Quartile 1.7 ≤ INR < 2.2 (n = 38)	Fourth Quartile INR ≥ 2.2 (n = 44)	All (N = 190)	P Value
In-hospital VTE	3 (6)	3 (5)	4 (11)	2 (5)	12 (6.3)	.665
Hospital mortality	2 (4)	2 (3)	5 (13)	14 (32)	23 (12.1)	< .001
Hospital LOS, d (IQR)	3 (5)	4 (6)	4 (10)	5 (8)	4 (6)	.221
Diagnostic testing						
VD-US	10 (21.3)	19 (31.1)	12 (31.6)	19 (43.2)	60 (31.6)	.168
Spiral CT scan	10 (21.3)	16 (26.3)	11 (28.9)	9 (20.5)	46 (24.2)	.763
VQ scan	2 (4.3)	1 (1.6)	1 (2.6)	1 (2.3)	5 (2.6)	.864
DVT prophylaxis						
None	33 (70)	46 (75)	29 (76)	34 (77)	142 (74.7)	.603
Pharmacologic	7 (15)	5 (8)	1 (3)	4 (9)	17 (9)	.603
Mechanical	7 (15)	10 (16)	8 (21)	6 (14)	31 (16.3)	.603

Data are presented as No. (%) unless otherwise indicated. VD-US = venous Doppler ultrasound. VQ = ventilation-perfusion. See Table 1 for expansion of other abbreviations.

sense of security. In this study, half of cases of VTE occurred in patients with INR > 1.6, and there was still a risk of VTE with INR > 2.2. Most of our study subjects were Child-Pugh stage C, which is unique from other published reports, in which most patients had less-advanced stages of disease. As expected, use of DVT prophylaxis in our study population was low, around 25%. Interestingly, there was not a significant association between prophylaxis and VTE incidence. It is possible that prophylaxis failed in this group of patients, as has been shown in some medical patients.<sup>11</sup> However, these results should be considered with caution, as the low incidence of VTE and low use of prophylaxis cause our study to lack adequate power to make these conclusions.

Our study population had a baseline malignancy rate of 23.5%, which is higher than the 15% malignancy rate reported by Northup. Although this risk factor could have increased the incidence of VTE, a  $\chi^2$  analysis of subjects with and without malignancy yielded a VTE incidence of 4.5% and 6.8%, respectively, with a P value of .58, indicating that higher rates of malignancy did not explain the higher incidence of VTE in our study.

Our study has several limitations. First, it was a retrospective review with the inherent limitations of such studies. Second, this study was based on *International Classification of Diseases, 9th edition* coding, which could have been omitted or incorrect. Third, we relied on clinical and pathologic assessment to diagnose CLD rather than a histologic diagnosis, and only 10% of our cohort had biopsy-proven cirrhosis. However, all patients had clinical documentation of CLD as reflected by clinical notes of treating physicians and patients with questionable diagnoses were not considered. Fourth, there was no systematic assessment for VTE, and only 43% of patients underwent testing. Because of the low rate of testing, we expect the actual incidence of VTE to be higher than what we found. Nonetheless, most

current studies advocate the outcome of symptomatic VTE as a valid end point, which we adopted in our study as well. Last, we used the Kucher-Goldhaber scoring, which was used for general medical or surgical patients. The risk score did not take into account factors such as congestive heart failure, infection, chronic lung disease, or blood product transfusion. All these factors and especially blood product transfusion may carry additional risk and should be investigated in this specific group.

On the other hand, our study has much strength. This is the first study that focused on the relationship between the level of pathologic INR elevation and incidence of VTE, thus making the results more clinically relevant. We also collected data on DVT prophylaxis, which was not evaluated in previous reports. We had higher rates of Child-Pugh C advanced disease with higher INR values, which further validate our results.

In conclusion, our findings suggest that an elevated INR in the setting of CLD does not appear to protect against the development of hospital-acquired VTE. Furthermore, the notion that auto-anticoagulation protects against VTE is unfounded, as patients in higher INR quartiles had equal incidence of VTE to

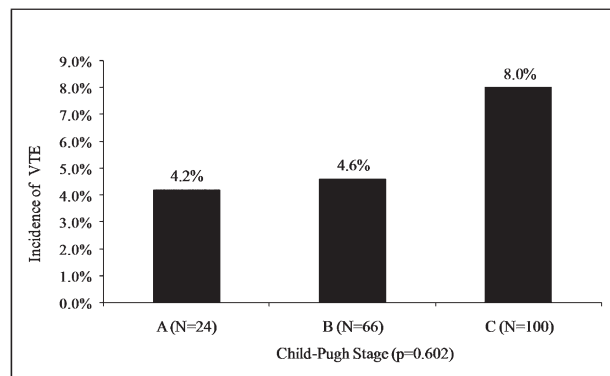


FIGURE 1. Incidence of venous thromboembolism based on Child-Pugh Stage.



those in lower quartiles. In fact, patients with Child-Pugh stage C had the highest incidence of VTE. We also found that use of DVT prophylaxis was extremely low in this population. Further prospective studies are necessary to evaluate the role of prophylaxis in this particular group of patients.

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**Author contributions:** *Dr Dabbagh*: contributed to concept, design, analysis, interpretation, manuscript draft, and overall supervision.

*Ms Oza*: contributed to design, data collection, and review of the manuscript.

*Dr Prakash*: contributed to data collection and review of the manuscript.

*Dr Sunna*: contributed to data collection, review of the manuscript, and supervision.

*Dr Saettele*: contributed to analysis, interpretation, and manuscript draft and review.

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