Venous Thromboembolism in Patients with Liver Cirrhosis:

Findings from the RIETE Registry

Running Head: VTE in Patients with Cirrhosis

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ABSTRACT

Background: Patients with liver cirrhosis are not only at increased risk of bleeding, but also may suffer from complications such as venous thromboembolism (VTE). Data are limited about the relative frequency, clinical course, management, and outcomes of VTE in these patients.

Methods: We used the data from RIETE, a prospective multicenter international registry of consecutive patients with objectively-confirmed VTE (deep vein thrombosis [DVT], pulmonary embolism [PE], or both) and focused on those with biopsy-confirmed cirrhosis. We compared the outcomes in VTE patients with and without cirrhosis. Main outcome measures included 90-day PE-related mortality, all-cause mortality, recurrent VTE, and major bleeding.

Results: Among 43,611 eligible patients with acute VTE, 187 (0.43%) had cirrhosis. Of these, 184 (98.4%) received anticoagulation (median duration: 109 [IQR: 43-201] days; most common agent and daily dose: enoxaparin 177 [IQR: 138-200] IU/Kg/day). During the course of anticoagulation, patients with cirrhosis had a higher-rate of 30-day fatal bleeding (2.1% versus 0.16%; P<0.001), and all-cause mortality (11% versus 3.4%; P<0.001), but similar rates of fatal PE (0.53% versus 0.46%, P=0.57), compared with VTE patients without cirrhosis. Ninety-day and 1-year outcomes were consistently worse in VTE patients with cirrhosis. The 1-year cumulative incidence of VTE recurrence was 8.5% in patients with cirrhosis and 2.9% in those without cirrhosis.

Conclusions: Coexisting cirrhosis is an infrequent but challenging co-morbidity in patients with VTE. Most patients were treated with anticoagulation, with low rates of fatal PE, elevated risk of recurrent VTE, and very high risk of bleeding, including fatal bleeds.

INTRODUCTION

Patients with liver cirrhosis are at an increased risk for hemorrhagic complications due to: 1) the reduced synthesis of coagulation factors, 2) thrombocytopenia secondary to hypersplenism and reduced synthesis of thrombopoietin and 3) conditions such as esophageal varices and portal gastropathy.(1) However, it is now known that cirrhosis could also lead into a hypercoagulable state due to an increase in procoagulants (factor VIII) and reduction of natural anticoagulants (protein C, protein S, antithrombin).(2) Therefore, some patients with cirrhosis, particularly those with additional risk factors for thrombosis (surgery, immobilization, malignancy) may also be at increased risk for venous thromboembolism (VTE) including deep venous thrombosis (DVT) and pulmonary embolism (PE).(1,3)

Data about the clinical course and management of limb DVT and PE in patients with liver cirrhosis are limited,(4) and the natural history of these patients has not been clearly elucidated. There are no clear guidelines for treatment or monitoring the response to anticoagulant therapy in patients with cirrhosis, in part because it is a common exclusion criterion in randomized trials of antithrombotic therapy for VTE.(5) Real-world treatment patterns for these patients –in whom anticoagulant therapy decisions are complicated by the coexistence of coagulopathy and increased risk of bleeding–remain unknown. Further, although a recent study suggested higher 30-day mortality rates in VTE patients with coexisting cirrhosis compared with those without cirrhosis,(6) the study was based on discharge codes, with limited granular clinical information. Clinically important outcomes including bleeding events, VTE recurrences, and VTE-related mortality remain unknown in this population, as are longer-term outcomes. The absence of such information impacts future research and routine decision-making for cirrhotic patients with VTE.

The Registro Informatizado de la Enfermedad TromboEmbolica (RIETE) registry is a large multinational registry of patients with VTE. Using the data from RIETE, we report the clinical presentation, treatment pattern and outcomes of patients with cirrhosis who

developed VTE. We compared the clinical presentation and outcomes in patients with and in those without cirrhosis.

METHODS

Data Source and Study Protocol

RIETE is a prospective multicenter international registry of consecutive patients with objectively-confirmed VTE. The methodology of the registry has been described elsewhere (ClinicalTrials.gov identifier: NCT02832245).(7) Briefly, RIETE includes 283 collaborating centers from 28 countries. The protocol for patient enrollment in RIETE has been approved by ethics committees at each of the participating enrolling centers. The study protocol for the current manuscript was drafted by two of the authors (BB and MM) and reviewed by all coauthors.

Patients

We included patients with biopsy-confirmed cirrhosis who developed a VTE event (limb DVT, PE, or both). Although RIETE has been initiated since March 2001, presence or absence of cirrhosis has been captured in the registry since February 2009. Therefore, in the current study, we considered eligible patients from 02/25/2009 to 08/06/2018. Patients with thrombosis at unusual sites (including isolated portal vein thrombosis) were excluded from the current study. The minimum duration of follow-up in RIETE is 3 months, although many patients may have 6-month, 1-year, or even more prolonged follow-up available. We compared the clinical presentation (including inpatient or outpatient status and presenting signs and symptoms), baseline co-morbidities and the laboratory data in those with VTE and cirrhosis versus those without cirrhosis. Cirrhosis in all patients was confirmed by liver biopsy.

Therapies

Patients were managed according to the clinical practice of each participating hospital (i.e., there was no standardization of treatment). We reported the type of VTE therapies used for patients, including whether not anticoagulation was used. In those receiving anticoagulants, we determined the type and duration of anticoagulation. We also assessed the use of thrombolytic therapy and inferior vena caval (IVC) filters.

Outcomes

The primary outcome was 30-day all-cause mortality. Other outcome measures included 30-day fatal bleeding, 30-day PE-related mortality, and similar outcomes at 90-day and 1-year follow-up. Bleeding was considered as major, according to RIETE definition, if it was overt and required a transfusion ≥2 units of blood, involved a critical site (retroperitoneal, spinal or intracranial), or was fatal.(7) We also explored non-major bleeding events. We compared the index VTE presentation, patterns of therapy, and outcomes in patients with VTE and cirrhosis, compared with VTE patients who did not have cirrhosis.

Statistical Analysis

Continuous data were reported as mean and standard error of the mean (or median and interquartile range [IQR], where appropriate) and compared using t-test (or its non-parametric counterpart, where needed). Categorical variables were reported as frequencies and percentages and compared using a Chi squared test. We used multivariable adjustment using a Cox proportional hazard model for assessment of outcomes in VTE patients with versus those without cirrhosis. For all a priori defined analyses, we considered a two-sided P-value of <0.05 as significant. Analyses were performed by the IBM SPSS software (version 25).

RESULTS

Between February 25 2009 and August 6, 2018, there were 43,611 patients with VTE in RIETE, of whom 187 (0.43%) had biopsy-confirmed diagnosis of cirrhosis. Of those 187 patients, 99 presented with DVT, 69 had PE and 19 had both DVT and PE. In patients with cirrhosis and VTE, compared with the rest of patients in RIETE, there was a greater proportion of men (66% versus 49%, P<0.001), diabetes (29% versus 15%, P<0.001), chronic heart failure (12% versus 7.2%, P<0.001) or active cancer (40% versus 23%, P<0.001) (Table 1). As expected, they had a higher relative frequency of gastroduodenal ulcer (11% versus 1.6%, P<0.001) and esophageal varices (17% versus 0.0.4%, P<0.001) and had lower mean hemoglobin values and platelet counts (12±2.4 versus 13±3.2; and 170.4±109.1 versus 235.2±96.9; P<0.001 respectively for both comparisons).

Treatment

Overall, 3 of the 187 (1.6%) patients with cirrhosis and VTE were never started on anticoagulation, compared with 198 (0.46%) of VTE patients without cirrhosis (P=0.056). In the remaining 184 (98.4%) who received anticoagulation, the median duration of treatment was 109 days (IQR: 43-201 days). Enoxaparin was the most commonly used agent (median dose: 177 IU/Kg/day [IQR: 138-200 IU/Kg/day]). No patient with cirrhosis underwent thrombolytic therapy, while 10 (5.3%) patients received an inferior vena caval filter (Table 2). In the rest of the RIETE cohort (i.e. those without cirrhosis), the median total duration of anticoagulation in those who received anticoagulants was 181 days (IQR: 101-323 days). Enoxaparin was the most commonly used agent for initial therapy (median dose: 188 IU/Kg/day [IQR: 160-200 IU/Kg/day).

Outcomes

By the end of 30 days of follow-up, 20 (11%) patients with cirrhosis and VTE died, including 4 (2.1%) with fatal bleeding events and 1 (0.53%) with PE-related death. Respective

numbers were 1,472 (3.4%) total deaths (P<0.001), 68 (0.16%) fatal bleeds, and 198 (0.46%) PE-related deaths (P=0.57), in the rest of the cohort. All-cause mortality and fatal bleeding were similarly more frequent in patients with cirrhosis at 90-day follow-up (Table 3).

The 1-year cumulative incidence of all-cause mortality and fatal bleeding were higher in those with cirrhosis, compared with patients without cirrhosis (32.4% versus 11.3%, P=xx for Log-rank test; and 3.2% versus 0.5%, P=xx for Log-rank test, respectively). The 1-year cumulative incidence of PE-related mortality was 0.6% in those with cirrhosis and 0.5% in those without cirrhosis.

The 1-year cumulative incidence of VTE recurrence was 8.5% in patients with cirrhosis and 2.9% in those without cirrhosis (P=xx for Log-rank test; Figure 2A). In addition, the 1-year cumulative incidence of major or clinically-relevant non-major bleeding was 16.4% in patients with cirrhosis, compared with 7.6% in those without cirrhosis (P=xx for Log-rank test; Figure 2B).

Subgroup Analysis

Discussion

In a large multinational registry of patients with VTE, we noted that a minority (0.43%) had cirrhosis. Most of these patients with cirrhosis and VTE were treated with anticoagulation. However, they faced with increased recurrent thrombotic event rates and hemorrhagic events (including fatal bleeds), compared with the rest of RIETE enrollees. Nearly a third of these patients died by the end of 1-year follow up.

The net clinical benefit of conventional antithrombotic treatment for VTE in patients with cirrhosis is uncertain. Although fatal PE occurred in only 1 patient with VTE and cirrhosis, non-fatal recurrent VTE was not uncommon (1-year cumulative incidence: 8.5%). Simultaneously, 1-year cumulative incidence of clinically relevant bleeding was as high as

16.4%, including 5 fatal bleeding events (4 of which occurred early in the course of anticoagulation). These findings are concerning and deserve further attention by hepatologists and thrombosis specialists.

There are many challenges to management of VTE in patients with cirrhosis. Patients with cirrhosis have been historically excluded from randomized trials of antithrombotic therapy randomized trials. Monitoring of international normalized ratio (INR) is also problematic in these patients because of underlying hepatic synthetic dysfunction. In our study, most of the participants received low-molecular weight heparins (at relatively similar daily doses compared with patients without cirrhosis) for the initial and the continued treatment of VTE. Although such therapy was associated with low rate of fatal PE, bleeding events were common, and indicate an unmet need for improvement. As such, alternative antithrombotic agents may need to be considered for patients with VTE and cirrhosis, such as the non–vitamin K antagonist oral anticoagulants (NOACs).

It should be considered that advanced liver disease may reduce plasma albumin concentration, thereby affecting the protein-bound moiety of medications such as apixaban and rivaroxaban [ref]. Appropriate doses would still need to be defined.

Few other studies have explored the presentation and outcomes of patients with cirrhosis who developed VTE. In a recent investigation based on administrative codes, Søgaard et al reported markedly lower rates of use of anticoagulation, but remarkably higher rates of all-cause 30-day mortality, compared with our study (including 35% mortality rate in PE patients with cirrhosis, and 16% in those without cirrhosis).(6)

Limitations

Our study has several limitations. First, we included patients with biopsy-confirmed cirrhosis. In this sense, caution should be exercised in generalizing the findings to cirrhotic patients who are diagnosed with other modalities. RIETE does not include detailed information about liver cirrhosis (including the etiology), or non-thrombotic complications.

As such, we were unable to report on factors such as bilirubin level, ascites, the markers of disease severity such as the MELD score, the Child Pugh score, or other cirrhosis-related non-hemorrhagic complications. However, the mortality rates that we observed were fairly similar to that of large groups of patients with cirrhosis studied in other investigations.(8) Further, RIETE includes accurate information about major therapies and outcomes, including the type of antithrombotic therapies, as well as thrombotic and hemorrhagic outcomes. Second, portal vein thrombosis is a distinct complication in patients with liver cirrhosis. Since RIETE does not specifically focus on detailed information related to patients with cirrhosis, we focused on cases of DVT and PE in this manuscript but did not investigate patients with portal vein thrombosis. Third, as a prospective registry, there are limitations in ascertaining the treatment effects, compared with randomized trials. Conducing a randomized trial in this patient population faces ethical and practical challenges. We hope our results, based on extensive patient-level data with multivariable adjustment for several potential confounders, provide helpful information for clinicians and investigators, until a randomized trial could be planned in future.

In conclusion, in our study of patients with cirrhosis and VTE, most patients were treated with low-molecular weight heparins, had a low rate of fatal PE, but notable cumulative incidence of non-fatal recurrent VTE. However, bleeding events, including fatal bleeds, were common and many occurred during the first month of therapy. Future studies are required to determine if a modified treatment strategy may help manage the thrombotic risk while not dramatically heightening the hemorrhagic risks, thereby improving the outcomes of patients with cirrhosis who develop VTE.

Disclosures:

We express our gratitude to **Sanofi Spain** for supporting this Registry with an unrestricted educational grant. We also express our gratitude to **Bayer Pharma AG** for supporting this Registry. **Bayer Pharma AG's** support was limited to the part of RIETE outside Spain, which accounts for a xxx% of the total patients included in the RIETE Registry. We also thank the RIETE Registry Coordinating Center, S&H Medical Science Service, for their quality control data, logistic and administrative support. Dr. Bikdeli reports that he serves as an expert (on behalf of the plaintiff) for litigation related to inferior vena caval filters. The content of the current manuscript is not directly related to that litigation. Dr. Bikdeli was supported by the National Heart, Lung, and Blood Institute, National Institutes of Health, through grant number T32 HL007854. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

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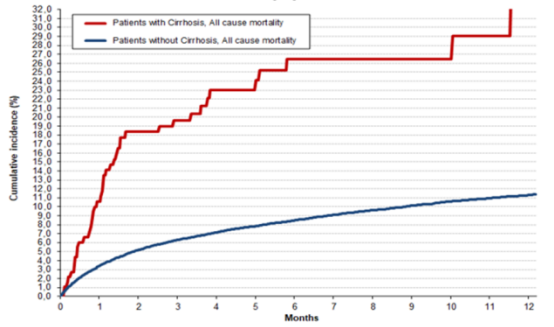
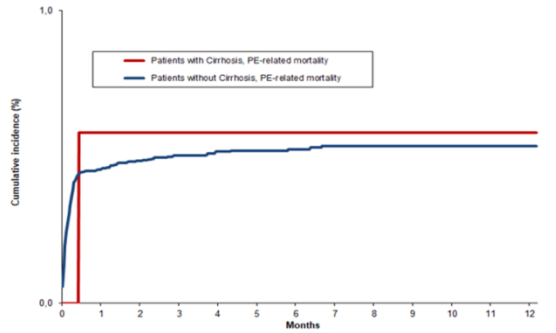
Figures:

Figure 1. One Year Cumulative Rate of All-cause Mortality (A), PE-related Mortality (B), and Fatal Bleeding (C)

(A)



		30 days	90 days	180 days	240 days	360 days
Cirrhosis	At Risk	180	145	94	50	30
	All-cause Mortality	19	34	41	41	43 (32.4%)
No Cirrhosis	At Risk	42,868	39,773	29,936	18,381	12,189
	All-cause Mortality	308	1,470	2,676	3,327	3,545 (11.3%)



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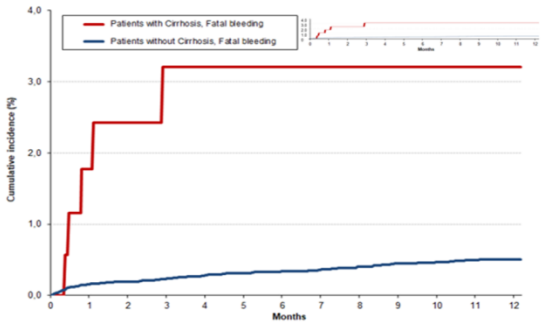
	PE-related Mortality	308	1,470	2,676	3,327	3,545 (11.3%)

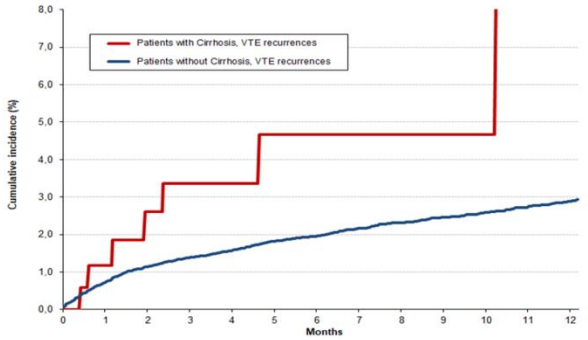
(C)



		30 days	90 days	180 days	240 days	360 days
Cirrhosis	At Risk	172	138	90	50	29
	Fatal Bleeding	3	5	5	5	5 (3.2%)
No Cirrhosis	At Risk	42,181	39,176	29,823	18,275	12,083
	Fatal Bleeding	66	97	126	137	150 (0.5%)

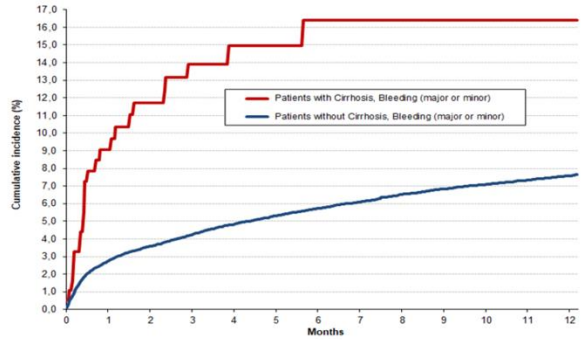
Figure 2. One Year Cumulative Rate of VTE recurrences (A) and Major or Clinically-relevant Non-major Bleeding

(A)



		30 days		90 days		180 days		240 days		360 days
Cirrhosis	At Risk	171		137		88		47		27
	VTE Recurrence	2		5		6		6		7 (8.5%)
No Cirrhosis	At Risk	42,172		38,966		29,314		17,977		11,824
	VTE Recurrence	308		570		728		792		859 (2.9%)

(B)



		30 days		90 days		180 days		240 days		360 days
Cirrhosis	At Risk	174		133		86		46		26
	Bleeding	16		23		25)		25		25 (16.4%)
No Cirrhosis	At Risk	42,322		38,524		28,906		17,661		11,633
	Bleeding	1,178		1,768		2,191		2,334		2,463 (7.59%)

Table1. Demographics, Co-morbidities, and Basic Laboratory Findings			
	Patients with VTE and Cirrhosis N (%) N=187	**Patients with VTE but without Cirrhosis N (%) N=43,424**	**P-Value**
VTE Presentation			
DVT Only	99 (53%)	19,424 (45%)	0.027
PE Only	69 (37%)	16,588 (38%)	0.761
Both DVT and PE	19 (10%)	7,412 (17%)	0.013
Demographics			
Male (%)	124 (66%)	21,106 (49%)	<0.001
Age (years ± SD)	67.3±11.2	65.1±17.8	0.008
Body mass index (kg/m2)	27±5	28±5.6	0.035
Inpatient status	65 (35%)	12,351 (30%)	0.104
Co-morbidities			
Diabetes	55 (29%)	6,404 (15%)	<0.001
Heart Failure	22 (12%)	3,117 (7.2%)	0.022
Prior vascular disease (coronary or peripheral)	15 (8.0%)	3,021 (7.0%)	0.563
Prior stroke	10 (5.3%)	2,768 (6.4%)	0.654
Chronic Lung Disease	28 (15%)	5,223 (12%)	0.214
Active Cancer	75 (40%)	10,015 (23%)	<0.001
Major bleeding within the past 30 days	8 (4.3%)	987 (2.3%)	0.079
Recent Surgery	21 (11%)	4,742 (11%)	0.918
Prior VTE	29 (16%)	6,506 (15%)	0.847
Gastroduodenal ulcer	21 (11%)	699 (1.6%)	<0.001
Esophageal varices	31 (17%)	19 (0.04%)	<0.001
Laboratory Tests			
Hemoglobin (gr/dl)	12±2.4	13±3.2	0.000
Platelet count	170.4±109.1	235.2±96.9	0.000
Plasma creatinine (gr/dl)	1.1±1.1	1±0.6	0.314
Background Therapies			
Non-steroidal anti-inflammatory agents	7 (3.7%)	2,882 (6.6%)	0.138
Antiplatelet agents	28 (15%)	7,316 (17%)	0.552
Corticosteroids	18 (9.6%)	3,974 (9.2%)	0.813

DVT: deep vein thrombosis; INR: international normalizd ratio; PE: pulmonary embolism; RIETE: Registro Informatizado de la Enfermedad TromboEmbolica

Table 2. Initial Treatment			
	Patients with VTE and Cirrhosis N (%)	**Patients with VTE but without Cirrhosis N (%)**	**P-Value**
No anticoagulation at all	3 (1.6%)	198 (0.46%)	0.056
Anticoagulation Regimen in Those Who Received Anticoagulation			
Duration of anticoagulation	109 days (IQR: 43-201)	181 days (IQR: 101-323)	
Median daily enoxaparin dose per Kg of body weight (for initial therapy)	177 IU/Kg/day (138-200)	188 IU/Kg/day (160-200)	
Thrombolytic therapy	0	671 (1.5%)	0.125
Vena caval filter	10 (5.3%)	1,160 (2.7%)	0.036
Outcomes			
30-day Outcomes			
30-day fatal bleeding	4 (2.1%)	68 (0.16%)	<0.001
30-day fatal gastrointestinal bleeding	1 (0.53%)	21 (0.05%)	0.090
30-day major bleeding (fatal or non-fatal)	16 (8.6%)	1,178 (2.7%)	<0.001
30-day major gastrointestinal bleeding (fatal or non-fatal)	4 (2.1%)	306 (0.70%)	0.045
30-day RIETE non-fatal major bleeding	5 (2.7%)	445 (1.0%)	0.045
30-day clinically-relevant non-major bleeding	7 (3.7%)	643 (1.5%)*	0.023
30-day clinically-relevant non-major gastrointestinal bleeding	1 (0.53%)	143 (0.33%)	0.462
30-day non-fatal VTE	1 (0.53%)	272 (0.63%)	1.000
30-day PE-related mortality	1 (0.53%)	198 (0.46%)	0.576
30-day all-cause mortality	20 (11%)	1,472 (3.4%)	<0.001
90-day Outcomes			
90-day fatal bleeding	5 (2.7%)	98 (0.23%)	<0.001
90-day fatal gastrointestinal bleeding	1 (0.53%)	26 (0.06%)	0.110
90-day major bleeding (fatal or non-fatal)	23 (12%)	1,768 (4.1%)	<0.001
90-day gastrointestinal major bleeding (fatal or non-fatal)	8 (4.3%)	476 (1.1%)	0.001
90-day RIETE non-fatal major bleeding	10 (5.3%)	585 (1.3%)	<0.001
90-day clinically-relevant non-major bleeding	8 (4.3%)	1,037 (2.4%)	0.093
90-day clinically-relevant gastrointestinal non-major bleeding	2 (1.1%)	231 (0.53%)	0.264
90-day non-fatal VTE	4 (2.1%)	463 (1.1%)	0.142
90-day PE-related mortality	1 (0.53%)	216 (0.50%)	0.607
90-day all-cause mortality	34 (18%)	2,677 (6.2%)	<0.001

1-year Outcomes			
1-year fatal bleeding	5 (2.7%)	150 (0.35%)	<0.001
1-year fatal gastointestinal bleeding	1 (0.53%)	40 (0.09%)	0.162
1-year major bleeding (fatal or non-fatal)	25 (13%)	2,469 (5.7%)	<0.001
1-year major gastrointestinal bleeding (fatal or non-fatal)	9 (4.8%)	704 (1.6%)	0.004
1-year RIETE non-fatal major bleeding	12 (6.4%)	747 (1.7%)	<0.001
1-year clinically-relevant non-major bleeding	8 (4.3%)	1,505 (3.5%)	0.543
1-year clinically-relevant gastrointestinal non-major bleeding	2 (1.1%)	364 (0.84%)	0.672
1-year non-fatal VTE	5 (2.7%)	673 (1.5%)	0.221
1-year PE-related mortality	1 (0.53%)	224 (0.52%)	0.621
1-year all-cause mortality	43 (23%)	3,775 (8.7%)	<0.001

DVT: deep vein thrombosis, IU: international units, LMWH: low-molecular-weight heparin, NOACs: Non-vitamin K oral anticoagulants, PE: pulmonary embolism, SD: standard deviation, VTE: venous thromboembolism

Table 3. Outcomes in Patients with Cirrhosis Compared with Those without Cirrhosis			
	Patients with VTE and Cirrhosis N (%)	**Patients with VTE but without Cirrhosis N (%)**	**P-Value**
30-day Outcomes			
30-day fatal bleeding	4 (2.1%)	68 (0.16%)	<0.001
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1-year fatal gastrointestinal bleeding	1 (0.53%)	40 (0.09%)	0.162
1-year major bleeding (fatal or non-fatal)	25 (13%)	2,469 (5.7%)	<0.001
1-year major gastrointestinal bleeding (fatal or non-fatal)	9 (4.8%)	704 (1.6%)	0.004
1-year RIETE non-fatal major bleeding	12 (6.4%)	747 (1.7%)	<0.001
1-year clinically-relevant non-major bleeding	8 (4.3%)	1,505 (3.5%)	0.543

1-year clinically-relevant gastrointestinal non-major bleeding	2 (1.1%)	364 (0.84%)	0.672
1-year non-fatal VTE	5 (2.7%)	673 (1.5%)	0.221
1-year PE-related mortality	1 (0.53%)	224 (0.52%)	0.621
1-year all-cause mortality	43 (23%)	3,775 (8.7%)	<0.001
DVT: deep vein thrombosis, IU: international units, LMWH: low-molecular-weight heparin, NOACs: Non-vitamin K oral anticoagulants, PE: pulmonary embolism, SD: standard deviation, VTE: venous thromboembolism			

Appendix

To be prepared by Mayra after the 15-day period of revision by all the RIETE Members.

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