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Impact of Anticoagulation on Upper-Gastrointestinal Bleeding in Cirrhosis. A Retrospective Multicenter Study

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Recent studies have shown that liver cirrhosis (LC) behaves as an acquired hypercoagulable state with increased thrombotic risk. This is why anticoagulation therapy (AT) is now frequently used in these patients. Variceal bleeding is a severe complication of LC. It is unknown whether AT may impact the outcome of bleeding in these patients. Fifty-two patients on AT with upper gastrointestinal bleeding (UGIB) were evaluated. Portal vein thrombosis (PVT) and different cardiovascular disorders (CVDs) were the indication for AT in 14 and 38 patients, respectively. Overall, 104 patients with LC and UGIB not under AT matched for severity of LC, age, sex, source of bleeding, and Sequential Organ Failure Assessment (SOFA) score served as controls. UGIB was attributed to portal hypertension (PH) in 99 (63%) patients and peptic/vascular lesions in 57 (37%). Twenty-six (17%) patients experienced 5-day failure; SOFA, source of UGIB, and PVT, but not AT, were independent predictors of 5-day failure. In addition, independent predictors of 6-week mortality, which was observed in 26 (11%) patients, were SOFA, Charlson Comorbidity index, and use of AT for a CVD. There were no differences between patients with/without AT in needs for rescue therapies, intensive care unit admission, transfusions, and hospital stay. *Conclusions:* Factors that impact the outcome of UGIB in patients under AT are degree of multiorgan failure and comorbidity, but not AT itself. (HEPATOLOGY 2015;62:575-583)

The use of anticoagulant therapy (AT) for prevention and management of thrombotic events may complicate the management of upper gastrointestinal bleeding (UGIB), increasing the morbidity/mortality associated to it.[1-4]

Until recently, liver cirrhosis (LC) has been considered a hypocoagulant and prohemorrhagic condition owing reduction in platelet count and increase in prothrombin time. Currently, this paradigm has been challenged by the observation that patients with

Abbreviations: AT, anticoagulant therapy; CCI, Charlson Comorbidity Index; CI, confidence interval; EV, esophageal varices; GI, gastrointestinal; GV, gastric varices; HCC, hepatocellular carcinoma; ICU, intensive care unit; INR, international normalized ratio; LC, liver cirrhosis; LMWH, low molecular weight heparin; MELD, Model for End-Stage Liver Disease; NS, nonsignificant; PH, portal hypertension; PT, prothrombin time; PVT, portal vein thrombosis; SOFA, Sequential Organ Failure Assessment; UGIB, upper gastrointestinal bleeding; VB, variceal bleeding; VKAs, vitamin K antagonists; VKS, vitamin K supplementation.

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cirrhosis also exhibit a reduction in anticoagulant proteins, such as antithrombin III, protein S, or C, together with an increase in procoagulant factors, such as Factor VIII or von Willebrand factor.[5-8] This new rebalanced hemostatic scenario is extremely fragile with a lower threshold for tipping toward thrombosis or bleeding in different clinical circumstances.[9-12] Indeed, recent data have established that the risk of developing thrombotic events of patients with chronic liver disease when hospitalized is significantly higher than in the general population, ranging between 0.5% and 6.3%. Moreover, the presence of severe portal hypertension (PH) and reduction in portal blood flow velocity,[15] among other factors, facilitates the development of splanchnic venous thrombosis. The median reported annual incidence of portal vein thrombosis (PVT) is approximately 16%.[16,17] In addition, the use of anticoagulation (either low-molecular-weight heparin [LMWH] or oral vitamin K antagonists) has been shown to be effective in achieving recanalization of the involved vessels.[18,19] As a consequence of all these facts, the use of anticoagulants in patients with cirrhosis has dramatically increased in recent years.

Variceal bleeding (VB) is a frequent, potentially lethal complication in patients with LC and PH.[20] However, it is unknown whether previous use of anticoagulation could impact the outcome of UGIB in these patients.

The aim of the present study was to evaluate this issue in a cohort of patients with cirrhosis admitted for an episode of UGIB while being treated with anticoagulation for different clinical indications in a retrospective, multicenter, matched study.

Patients and Methods

Cohort Recruitment and Data Collection. We retrospectively analyzed data of patients with cirrhosis admitted for UGIB at the Bleeding Units of nine Spanish tertiary Universitary Hospitals (Barcelona: Hospital Clinic, Hospital Vall d'Hebron, Hospital de la Santa Creu i Sant Pau Parc Taulí Sabadell; Madrid: Hospital Universitario Ramon y Cajal, Hospital General Gregorio Marañon, Hospital Puerta de Hierro Majadahonda; Valencia: Hospital La Fe; Santander: Hospital Marqués de Valdecilla) from May 2005 to July 2012. Only centers with a prospective register of all patients with cirrhosis admitted to the hospital with this hemorrhagic complication were eligible for the current study. All patients with cirrhosis of any etiology, diagnosed by liver biopsy and/or unequivocal clinical, laboratory, and U.S. data, admitted to these nine units with a bleeding from the upper gastrointestinal tract during this period of time that were registered were eligible for the study. UGIB source was diagnosed by upper digestive endoscopy.

Clinical records of patients were retrospectively reviewed to identify whether they were taking anticoagulant treatment or not. From the same register, for each identified patient having UGIB while taking AT, 2 patients with cirrhosis and bleeding not receiving AT were matched for severity of liver failure (Child-Pugh[21] score $\pm$ 1 point), age ($\pm$ 5 years), sex, source of UGIB, and degree of multiorgan dysfunction assessed by Sequential Organ Failure Assessment (SOFA) score.[22] Exclusion criteria were pregnancy and previous liver transplantation.

In all patients fulfilling the selection criteria, clinical, biochemical, radiological, and endoscopic data as well clinical outcome were collected in a predesigned case report form.

The ethics committees of all the included centers approved the study protocol. The study was conducted according to the guidelines of the Declaration of Helsinki and the applicable provisions of Good Clinical Practice in clinical trials.

Definitions and Study Endpoints. The primary endpoint of the study was 5-day treatment failure defined as a combined endpoint of: failure to control bleeding, early rebleeding, or death within 5 days.[23] Secondary outcomes were: 6-week mortality[23] and severity of bleeding.

Patients were managed according to Baveno V recommendations. Briefly, after admission, early vasoactive

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agents were initiated (somatostatin or terlipressin) and an initial endoscopy was performed within the first 12 hours. During endoscopy, appropriate endoscopic therapy was applied according with the diagnosed source of bleeding (preferentially endoscopic band ligation if esophageal varices (EV), glue if fundal gastric varices (GV), and clips or sclerosant injection if peptic lesions). In patients with PH-related bleeding, vasoactive drugs were maintained for up to 5 days whereas they were stopped in the other causes of bleeding. Antibiotic prophylaxis was administered to all patients from admission until day 7.

In patients on AT, treatment was stopped and patients resumed taking AT as soon as possible according to the clinical indication and the hospital accepted guidelines. Owing to the retrospective nature of the study, we do not have data if anticoagulation was reversed on admission in all patients. However, as shown in Table 4, the percentage of patients receiving vitamin K was significantly higher in anticoagulated patients.

In all patients, liver function was assessed by Child-Pugh[21] and the Model for End-Stage Liver Disease (MELD)[24] scores, which constitute the most frequent tools to predict mortality in patients with cirrhosis. Considering that MELD can overestimate risk when international normalized ratio (INR) is artificially elevated by anticoagulation, we also used an alternative score, MELD-XI,[25] that, despite omission of INR, is nearly as accurate as MELD in predicting short-term survival in cirrhosis.

Comorbidity was defined using the Charlson Comorbidity Index (CCI).[26] This is a well-validated weighted comorbidity score derived from unselected hospital admissions that predicts 1-year mortality after hospital discharge. It has been used in many contexts and has repeatedly measured the burden of comorbidity reliably. The different comorbidities were assigned weights of 1, 2, 3, and 6, depending on their association with mortality. The conditions included in the original score (in order of weighting) were myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, connective tissue disease, peptic ulcer disease, mild liver disease, diabetes, hemiplegia, moderate or severe renal disease, diabetes with end organ damage, leukemia, lymphoma, moderate or severe liver disease, metastatic solid tumor, and acquired immunodeficiency syndrome.

Statistical Analysis. Patient characteristics were compared using *t* tests and chi-square tests, as appropriate. Data are presented as percentages and summary statistics of mean ± standard deviation (SD), as appropriate.

Conditional and unrestricted standard logistic regression models were used to examine the association to the 5-day treatment failure and 6-week mortality outcomes. Variables selected to enter into step-wise regression were those with $P < 0.1$. A set of sensitivity analyses was conducted to assess the role of anticoagulation by considering portal vein thrombosis (PVT) and the matching variables. Adjusted models were built adjusting for the covariates as well as using the propensity scores (i.e., the predicted probability of anticoagulation or the reason for anticoagulation, given the mentioned set of covariates).[27,28]

All analyses were performed using SAS software (9.2; SAS Institute Inc., Cary, NC) or Statistical Package for Social Sciences (version 19.0; SPSS, Chicago, IL), and a level of significance was established at the two-sided 5% level.

Results

Patient Characteristics. Fifty-two patients with cirrhosis admitted for UGIB while they were taking AT were admitted in the nine participating centers during the period of the study. One hundred four (1:2) matched patients with cirrhosis who were not receiving anticoagulants and experienced a UGIB were selected from the overall population of patients with UGIB admitted to the same nine centers during the same period of time. Overall, 156 patients were enrolled in the study.

Main characteristics of all included patients, as well as the reasons for anticoagulation for the 52 patients receiving this treatment, are summarized in Table 1. Ninety-nine patients had a PH-related UGIB. Supporting Table 1 shows the characteristics of the subgroup of 99 patients with PH UGIB. Median duration of follow-up was 13.9 months (mean, 20.2 ± 21.5; range, 0-96) after the bleeding episode. Median Child-Pugh score was 9 (range, 5-14; scores can range from 5 to 15, with higher scores indicating more severe liver disease). Only 9 patients of the 34 with PVT also had an associated hepatocellular carcinoma (HCC). In none of them were there suggestive signs of malignancy at imaging studies.

In the subgroup of 14 patients that were receiving anticoagulation for splanchnic vein thrombosis, repermeabilization had already occurred in 2, as observed by imaging studies performed during admission for the bleeding episode. In the remaining 12 patients, the thrombus was still present and located in the portal

Table 1. Baseline Characteristics of Patients According to the Use of Anticoagulation or Not

Variable	Nonanticoagulated Patients n = 104	Anticoagulated Patients n = 52	*P* Value
Age, years	63 ± 11	63 ± 11	0.8
Sex, male, %	73	73	1.0
Etiology of cirrhosis: viral/alcoholic/other, %	53/40/7	46/33/21	0.07
Reasons for anticoagulation (%)			
Atrial fibrillation	–	24 (46)	
Prosthetic heart valves	–	6 (12)	
Systemic thrombotic episodes	–	22 (42)	
Splanchnic veins thrombosis	–	14/22 (65)	
Source of bleeding			
PH (%)	66 (63)	33 (63)	0.9
EV (n)	53	26	
GV (n)	5	3	
Portal hypertensive gastropathy (n)	8	4	
Peptic lesions (%)	32 (31)	15 (29)	
Gastroduodenal ulcers (n)	18	9	
Erosions (n)	12	5	
Gastric polyps (n)	2	1	
Vascular lesions (%)	6 (6)	4 (8)	
Gastric antral vascular ectasia (n)	1	1	
Angiodysplasias (n)	1	1	
Dieulafoy lesion (n)	4	2	
Child class: A/B/C, %	6/64/30	8/65/27	0.8
Child score	9 ± 2	9 ± 2	0.8
SOFA score	3.6 ± 1.7	3.2 ± 2.3	0.3
CCI	6.1 ± 1.7	7.0 ± 1.7	0.002
MELD score	15 ± 4	20 ± 7	<0.001
MELD XI	15.0 ± 4.3	14.2 ± 5.5	0.3
Laboratory data			
Bilirubin, mg/dL	2.7 ± 2.8	2.0 ± 2.4	0.1
Albumin, g/L	28.2 ± 6.0	29 ± 8	0.6
Creatinine, mg/dL	1.1 ± 0.4	1.3 ± 1.1	0.2
Platelets, $10^3/mm^3$	125 ± 76	153 ± 110	0.1
PT, %	59 ± 15	35.9 ± 19.7	<0.001
INR	1.5 ± 0.3	2.8 ± 1.7	<0.001
ALT, U/L	136.5 ± 442.4	59.6 ± 64.8	0.2
AST, U/L	62.5 ± 102.4	50.2 ± 83.3	0.4
Previous decompensation			
Previous ascites	45 (43)	24 (46)	0.7
Previous hepatic encephalopathy	18 (17)	13 (25)	0.2
Prophylaxis with B-blockers, %	17	23	0.4
Previous VB, %	21	25	0.6
PVT, %	14	37	0.002
HCC, %	10	15	0.3

Values are expressed as mean ± SD.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.

vein and/or its branches in 11 patients and extended to the superior mesenteric vein in the remaining 1. Degree of vein obstruction was partial in 8 and complete in 4 patients.

Thirty-eight of the fifty-two patients received oral vitamin K antagonists whereas the remaining 14 were receiving LMWH.

As expected, variables influenced by vitamin K antagonists (VKAs), such as MELD score, INR, and prothrombin time (PT), differ significantly between patients receiving or not anticoagulation (Table 1 and Supporting Table 1). In addition, there were also differences in prevalence of comorbidities, as assessed by the CCI. No other major differences were observed between both groups either in the overall cohort (Table 1) or in the subgroup of 99 patients experiencing a PH-related UGIB (Supporting Table 1).

Five-Day Treatment Failure. A total of 26 of 156 patients (17%) experienced 5-day treatment failure. Age, presence of nontumoral PVT, degree of multiorgan dysfunction assessed by SOFA, and source of UGIB were significantly associated with 5-day treatment failure in univariate analysis (Table 2). When these variables, together with the use of anticoagulation, were included

Table 2. Uni- and Multivariate Logistic Regression Analyses* of 5-Day Treatment Failure in Whole Cohort of Patients (n = 156)

	Univariate Analysis		Multivariate Analysis	
Variable	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Age, years	0.95 (0.91-.99)	0.018		
Anticoagulation	1.59 (0.7-3.8)	0.290		
Reason for anticoagulation		0.571		
Nonanticoagulation	1 (Reference)			
Anticoagulation for PVT	1.6 (0.4-6.48)			
Anticoagulation for CVD	1.58 (0.6-4.1)			
Source of bleeding		0.078		0.040
Peptic lesions	1 (Reference)		1 (Reference)	
PH	3.7 (1.04-13.2)		5.1 (1.01-23.4)	
Vascular lesions	6.3 (1.05-37.6)		13.8 (1.71-110.3)	
SOFA score	1.17 (0.8-1.6)	0.031	1.3 (1.0-1.6)	0.047
Child score	1.03 (0.8-1.3)	0.836		
MELD XI	1.02 (0.9-1.11)	0.640		
CCI	.8 (0.6-1.09)	0.171		
PVT (%)	3.3 (1.2-9.5)	0.018	3.6 (1.3-9.7)	0.013
Shock	2.6 (0.9-7.2)	0.062		

*The conditional logistic regression accounting for the matching design variables lead to nonsignificant results for anticoagulation (OR [95%CI]: 1.7 [0.7-4.2]; *P* = 0.272. Goven that the assessment of the matched groups (i.e., anticoagulation) was not significant, standard logistic regression has been conducted to identify any predictors for 6-weeksmortality irrespectively of their inclusion in the matching scheme.

Abbreviation: OR, odds ratio.

in a multivariate analysis, only the SOFA score, presence of PVT, and source of UGIB were shown to be independent risk factors predicting 5-day treatment failure. Because PVT was unbalanced in patients receiving AT or not, we also have estimated the potential impact of receiving anticoagulation, for any reason or more specifically differentiating those patients receiving AT for a CVD or for PVT, on the risks of 5-day treatment failure in a range of scenarios designed to rule out bias. Indeed, we have conducted six analyses: (1) unadjusted; (2) adjusted by matching variables; (3) adjusted using propensity scores considering the matching variables; (4) adjusted using propensity scores considering the matching variables+PVT; and (5) conditional logistic regression using the matching variables. The results shown in Table 3 confirm the lack of a significant impact of the use of anticoagulation on 5-day treatment failure in any of these scenarios.

Table 3. Risks of 5-Day Treatment Failure and of 6-Week Mortality in a Range of Different Scenarios Designed to Rule Out a Potential Bias of the Baseline Characteristics of Patients, Mainly the Presence of Nonmalignant PVT

			Risk for Reason of AT*		
	Anticoagulation for Any Reason*			PVT	Other Reason of AT Than PVT
	P Value	OR (95% CI)	*P* Value	OR (95% CI)	OR (95% CI)
Five-day treatment failure					
(1) Unadjusted	0.290	1.59 (0.67-3.77)	0.571	1.62 (0.40-6.49)	1.58 (0.61-4.10)
(2) Adjusted by matching variables	0.185	1.88 (0.74-4.81)	0.250	1.06 (0.22-5.07)	2.47 (0.85-7.22)
(3) Adjusted by PS using matching variables	0.197	1.78 (0.74-4.24)	0.387	1.46 (0.35-6.00)	1.97 (0.74-5.26)
(4) Adjusted by PS using matching variables+PVT	0.462	1.42 (0.56-3.63)	0.532	1.22 (0.28-5.36)	1.77 (0.65-4.79)
(5) Conditional LR	0.272	1.67 (0.67-4.20)	0.545	1.82 (0.28-11.95)	1.63 (0.57-4.69)
Six-week mortality					
(1) Unadjusted	0.076	2.51 (0.91-6.95)	0.085	0.92 (0.11-7.99)	3.20 (1.11-9.26)
(2) Adjusted by matching variables	0.058	2.97 (0.96-9.18)	0.077	1.08 (0.11-10.53)	3.97 (1.19-13.28)
(3) Adjusted by PS using matching variables	0.047	2.89 (1.02-8.23)	0.029	0.75 (0.08-6.89)	4.22 (1.40-12.75)
(4) Adjusted by PS using matching variables+PVT	0.058	2.83 (0.97-8.25)	0.050	0.91 (0.10-8.58)	3.68 (1.24-10.96)
(5) Conditional LR	0.069	2.83 (0.92-8.71)	0.188	2.00 (0.13-31.98)	3.03 (0.88-10.43)

Analyses: (1) unadjusted; (2) adjusted by matching variables (Child-Pugh score, age, gender, source of UGIB, and SOFA score); (3) adjusted using propensity scores considering the matching variables; (4) adjusted using propensity scores considering the matching variables+PVT; and (5) conditional logistic regression using the matching.

*Reference = no AT.

Abbreviations: OR, odds ratio; PS, propensity scores; LR, logistic regression.

Table 4. Uni- and Multivariate Logistic Regression Analyses* of 6-Week Mortality in Whole Cohort of Patients (n = 156)

	Univariate Analysis		Multivariate Analysis	
Variable	**OR (95% CI)**	***P* Value**	**OR (95% CI)**	***P* Value**
Anticoagulation	2.5 (0.9-6.95)	0.076		
Reason for anticoagulation:		0.085		0.07
Non-anticoagulation	1 (Reference)		1 (Reference)	
Anticoagulation for PVT	0.92 (0.1-7.98)		1.08 (0.1- 10.5)	
Anticoagulation for CVD	3.2 (1.1-9.25)		3.9 (1.1-13.2)	
Bilirubin	1.2 (1.06-1.4)	<0.01		
Child score	1.48 (1.02-2.1)	0.009		
MELD XI	1.17 (1.06-1.3)	0.002		
MELD	1.17 (1.07-1.3)	0.001		
SOFA score	1.5 (1.2-1.98)	<0.001	1.7 (1.3- 2.2)	<0.001
CCI	1.3 (1.03-1.75)	0.026	1.5 (1.1-3.0)	0.012

*The conditional logistic regression accounting for the matching design variables lead to nonsignificant results for anticoagulation (OR (95% CI): 2.8 (0.9-8.7); $P = 0.069$. Given that the assessment of the matched groups (i.e., anticoagulation) was not significant, standard logistic regression has been conducted to identify any predictors for 6-week mortality irrespectively of their inclusion in the matching scheme.

Abbreviation: OR, odds ratio.

Similar results were obtained analyzing only patients having a PH-related UGIB.

Of the 38 patients receiving vitamin K supplementation (VKS), 9 had 5-day treatment failure and 29 not, whereas this happens in 2 and 12 of those receiving LMWH (nonsignificant; NS), showing that the type of anticoagulation used did not influence the results.

Six-Week Mortality. Seventeen patients died within 6 weeks. Causes of death were: multiorgan failure secondary to infections in 5 patients; hepatic failure in 10; hypovolemic shock in 1; and sudden death in 1. Univariate analysis identified the degree of liver dysfunction as assessed by Child-Pugh, MELD, MELD XI score, and bilirubin, as well as the SOFA score and the CCI, as significant factors associated with 6-week mortality. There was also a trend for anticoagulants when they were used to treat CVD (Table 4). When MELD, SOFA, CCI, and the reason for anticoagulation were included in a multivariate analysis, the SOFA score and the CCI, but not the use of anticoagulants, were identified as independent risk factors predicting 6-week mortality (Table 4). However, a trend for increased mortality was observed in patients receiving AT for a CVD. To further analyze the potential impact of AT on survival, again the different scenarios previously tested for 5-day treatment failure were analyzed (Table 3).

The risk of death at 6 weeks is consistently higher in patients with UGIB receiving AT for other reasons than PVT, ranging between a 3.03- and 4.2-fold increase versus patients not receiving AT (Table 3).

Indeed, 6-week mortality was 21% in patients receiving anticoagulation to treat a CVD, but 8% in the remaining two groups: patients receiving anticoagulants to treat PVT or in those not receiving anticoagulants.

Six of the thirty-eight patients receiving VKA and 3 of the 14 LMWH died (NS), showing no influence of the type of anticoagulation on mortality. Among patients with PH-related UGIB, 13 died. Similar results were observed when only patients with PH-related UGIB were analyzed (data not shown).

UGIB Characteristics. In 62% of patients, hematemesis was the main manifestation of UGIB and 15% experienced hypovolemic shock. Patients who bled while they were on anticoagulation had lower hemoglobin and hematocrit, required more blood units transfused, had more hypotension, and presented more frequently hypovolemic shock (Table 5). In 35% (18 of 38) of patients receiving oral anticoagulation, the INR value was recorded as being above the therapeutic range [>3]). Fifteen of them needed VKS depending

Table 5. Severity of Bleeding in Whole Cohort and in Patients With or Without AT

Variable	**Whole Cohort (156)**	**Patients Without AT (104)**	**Patients on AT (52)**	***P* Value**
MAP, mmHg	82.5 ± 15.1	84 ± 15	80 ± 15	0.2
Hemoglobin, g/dL	9.9 ± 5.2	10.4 ± 6.2	8.9 ± 2.1	0.08
Hematocrit, %	29.2 ± 6.6	30 ± 7	27.8 ± 5.4	0.06
Hematemesis, %	62	67	52	0.07
Shock, %	15	10	25	0.01
Blood requirement, n	4.3 ± 2.8	4.0 ± 2.5	4.8 ± 3.2	0.1
Plasma requirement, %	16	14	21	0.2
VKS, %	14	7	29	<0.001
ICU admission, %	21	20	23	0.7
Length of stay, days	14.2 ± 12.7	13.6 ± 11.5	15.6 ± 15	0.4
Active bleeding, %	32	33	28	0.6
Five-day failure, %	17	14	21	0.3
Six-week mortality, %	11	8	17	0.08
Rescue therapy, %	15	13	17	0.5

on the severity of the situation. Fresh frozen plasma requirements were more frequent in AT patients, although the difference did not reach statistical significance (Table 5).

Despite these aspects reflecting an initial more severe bleeding, there were no significant differences in the need of rescue therapy (surgery, new endoscopic treatments, or transjugular intrahepatic portosystemic shunt), hospital length of stay, intensive care unit (ICU) admission, 5-day treatment failure, or 6-week mortality among groups (Table 5).

Discussion

The change in the paradigm that patients with cirrhosis were naturally anticoagulated, together with the more frequent recognition of thrombotic events during follow-up, has favored the use of anticoagulation in these patients. Although there is not a rationale to think that anticoagulation "per se" may increase the risk of portal hypertensive bleeding, once these patients experience a bleeding episode, the severity and mortality risk is a major concern. However, until now these facts have not been evaluated in patients with cirrhosis. Thus far, only two small studies performed in patients with noncirrhotic PVT evaluated the effect of anticoagulation on UGIB,[24,25] suggesting that anticoagulation does not increase severity or mortality. Moreover, VB has a better prognosis in patients with noncirrhotic PH than in those with cirrhosis, probably because of the lower liver reserve of the latter. Indeed, 6-week mortality ranges between 15% and 20% in patients with cirrhosis and is less than 2% in patients with noncirrhotic PH.[20,23,29,30] Therefore, we aimed to assess the influence of anticoagulation on treatment failure, mortality, and severity of UGIB in patients with cirrhosis.

The results of our study show that AT has no influence on 5-day treatment failure. The rate of 5-day treatment failure was 17%, a value within the reported range in recent studies of VB not including anticoagulated patients. In the current cohort, PVT, severity of multiorgan failure assessed by the SOFA score, as well as the vascular nonvariceal origin of the UGIB were the only independent factors predicting 5-day treatment failure. The first two factors remained predictive when analyzing the subgroup of patients with PH-related bleeding. Liver function evaluated as either Child or MELD did not predict 5-day treatment failure. This may be owing to the fact that the studied population had a relatively good liver function (71% of patients were Child A or B and the mean MELD score, excluding patients who were on oral anticoagulation, was 15).

Lack of a significant impact of anticoagulation in 5-day treatment failure was observed, despite the fact that patients who bled under AT were more likely to present with hypotension and/or shock and showed a trend toward a lower hemoglobin and hematocrit value, when compared to controls. These data suggest that implementation of adequate treatment strategies, based on drugs, endoscopic treatment, and hemostatic support, if needed, are able to effectively control these more severe bleeding episodes. This finding is further supported by the fact that there was no difference in need of rescue therapy in patients receiving or not AT.

Six-week mortality was observed in 11% of the entire cohort. This figure is in the low range of the 6-week mortality reported in most recent studies.[31,32] The SOFA score and the CCI, variables evaluating the overall performance of the patients and of the degree of comorbidities, together with the use of anticoagulation for a CVD, were the factors significantly associated with risk of death.[22,33]

The reported mortality rate in several studies of UGIB in patients with CVD using AT ranged between 8% and 11%.[34-37] Although the studies cannot be directly compared, this reported mortality rate is clearly below the 21% observed in our cohort of patients with cirrhosis. The deleterious impact of the presence of a comorbidity on mortality has further been evidenced by a recent meta-analysis[38] that demonstrated an increase in mortality of UGIB in patients with CVD (13.3% vs. 6.9% in patients without CVD disease; relative risk: 2.39; 95% confidence interval [CI]: 1.51-3.78). Thus, presence of comorbidity is a major factor influencing mortality in patients with UGIB either with or without cirrhosis.

Many potential mechanisms for the observed association between comorbidities and outcome after UGIB have been proposed, including reduced organ perfusion in cardiac failure, decreased oxygen levels in respiratory diseases, poor nutritional status in advanced liver disease, or reduced platelet and clotting function as observed in end-stage renal and hepatic disease. Interestingly, although anticoagulation does not significantly affect survival, there was a trend for higher 6-week mortality in patients receiving this treatment because of cardiovascular comorbidity (in most cases, prosthetic valves or atrial fibrillation). These data, if confirmed, suggest that anticoagulation may further increase the risk of death in patients with more severe disease and with comorbidities. The only observed adverse effect of being on anticoagulation at the time of admission for bleeding

was the need of more blood transfusion (on average, 4.0 ± 2.5 vs. 4.8 ± 3.2 units in anticoagulated patients; $P = 0.1$), but without any negative impact in treatment failure and mortality. Such a benign course may have been influenced by the prompt withdrawal of anticoagulation and to the administration of vitamin K when appropriate (although we cannot rule out that there could be more fatal bleeding episodes not reaching the hospital in these patients).

In conclusion, the degree of multiorgan dysfunction and comorbidities, but not AT per se, are factors associated with an increased morbidity/mortality in patients with cirrhosis and UGIB.

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