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Management of haemostatic alterations and associated disorders in cirrhosis in Spain: A national survey

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ABSTRACT

Background: Knowledge of haematological abnormalities in cirrhosis has greatly improved in recent years.
Aims: To evaluate how Spanish Digestive Disease specialists manage haemostatic alterations and associated disorders in patients with cirrhosis.
Methods: All members of the Spanish Association for the Study of the Liver and Spanish Society of Digestive Pathology were invited to fill in a web-based questionnaire.
Results: 135 professionals, 93 hepatologists and 42 non-hepatologists responded to the survey. The concept of rebalanced haemostasis was known by 74.8% of them. Most specialists corrected the INR and thrombocytopenia before invasive procedures with moderate risk of bleeding or major surgery and in severe gastrointestinal bleeding. The threshold of platelets and, especially, INR used to administer blood products varied greatly. Pharmacological prophylaxis of venous thromboembolism prevailed, but it was highly dependent on the INR and platelet figures. Most participants initiated anticoagulation regardless of the degree of portal vein thrombosis, even in patients ineligible for transplantation. In potential candidates, only 56% maintained it indefinitely or until liver transplantation. No major differences between hepatologists and non-hepatologists were found.
Conclusions: A significant variability and certain deviation from current guidelines was observed among Spanish Digestive Disease specialists regarding management of haemostatic alterations and associated disorders in cirrhosis.

1. Introduction

Cirrhosis has long been perceived as an acquired bleeding disorder. In the last two decades, however, it has been noted that haemostasis in patients with cirrhosis is in a precarious equilibrium that can easily be tipped towards either a prohaemorrhagic or a prothrombotic phenotype [1]. Furthermore, it has been suggested that this potential prothrombotic state is intimately involved in the progression of liver disease by generating thrombi in the hepatic microcirculation that lead to parenchymal extinction and activating hepatic stellate cells via protease-activated receptors [2].

This conceptual change is based on the following observations: (1) Platelet function in cirrhosis is not defective and might actually be overactivated, as recent studies show elevated circulating markers of *in vivo* platelet activation and an enhanced response to common agonists related to systemic inflammation [3]. This platelet hyperactivity coupled with increased levels of von Willebrand factor preserve primary haemostasis despite the cirrhosis-associated thrombocytopenia [4]; (2) Cirrhosis, unlike hereditary coagulopathies, affects the whole spectrum of the coagulation cascade (i.e. both procoagulant and anticoagulant factors), which results in a "rebalanced haemostasis" [5,6]; (3) Traditional coagulation tests (e.g. prothrombin time or partial thromboplastin time) do not adequately reflect this new haemostatic balance, since they do not take into account the inhibition of thrombin by anticoagulant factors [1]; (4) These traditional tests and platelet count do not adequately assess the risk of unprovoked bleeding or

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bleeding secondary to invasive procedures [7–9], nor is there evidence that their correction improves their evolution or reduces this risk [9,10]; (5) The use of global haemostasis assays that take into account the full interplay of all coagulation factors has revealed a normal and even increased generation of thrombin in cirrhotic patients with alteration of traditional coagulation tests [11,12]; (6) The increasing recognition of the existence of thrombotic complications in cirrhotic patients both in the splanchnic [13] and peripheral territory [14]; (7) Evidence that anticoagulant therapy in cirrhotic patients does not seem to increase either the frequency of bleeding episodes or their mortality when such episodes occur [15,16]; and (8) Experimental studies showing that anticoagulant therapy improves liver fibrosis and reduces portal hypertension [17], and evidence from a clinical trial that anticoagulation led to a reduction in portal thrombosis and other complications of liver disease, and to increased survival [16].

Despite these significant advances in the field there is still no high-quality evidence to recommend thresholds for the correction of thrombocytopenia and coagulopathy before invasive procedures or in episodes of variceal and non-variceal bleeding. Current guidelines on non-variceal upper gastrointestinal bleeding do not include recommendations in this regard [18,19], and those on variceal bleeding differ from each other [20,21] or acknowledge that no guidance can be provided on the basis of currently available data [22]. Similarly, recommendations for venous thromboembolism (VTE) prophylaxis in hospitalized patients with cirrhosis are absent in current guidelines [23] and there is an urgent need to establish the benefit/risk ratio of anticoagulant therapy for treating portal vein thrombosis (PVT) in cirrhotic patients [24]. As a reflection of the above, the strength of recommendations from the only two consensus statements on these topics was usually low, and with certain differences between them [25,26]. Moreover, there is no data describing the actual management of these alterations by the professionals involved in the healthcare of cirrhotic patients.

We therefore designed a questionnaire aimed at exploring the real-life clinical management of haemostatic alterations and associated disorders in cirrhosis by Spanish specialists in Digestive Diseases.

2. Material and methods

2.1. Questionnaire

The design of the survey aimed to cover all major clinical problems related to haemostatic alterations and associated disorders in cirrhosis. Questions were selected based on current guidelines and expert reviews on each topic. Explanatory notes were added before the survey and, if needed, before each section to clarify the questions posed. The first draft was sent to the staff members of our Department of Digestive Diseases to ascertain whether the questions were well understood. After their feedback and an internal discussion process, the definitive survey included 46 questions divided into six sections: (1) Demographic and professional profile of participants (7/46 questions); (2) Concept of "rebalanced haemostasis" and whether knowledge of it had changed their management of haemostatic alterations associated with cirrhosis (2/46 questions); (3) Correction of the INR prolongation and thrombocytopenia before invasive procedures with different risks of bleeding (10/46 questions): low (<3%, e.g. paracentesis, thoracentesis, central venous cannulation, or biopsies taken during gastrointestinal or respiratory endoscopy), moderate (3–10%, e.g. endoscopic variceal ligation, endoscopic polypectomy, percutaneous liver biopsy, ERCP with sphincterotomy, or minor surgery), and major surgery (e.g. hepatic resection or surgical oncology) [25,27]; (4) Prevention strategies for venous thromboembolism in hospitalized patients with cirrhosis (5/46 questions); (5) Correction of the INR prolongation and thrombocytopenia in cirrhotic patients with variceal and non-variceal gastrointestinal bleeding (9/46 questions); (6) Management of non-malignant PVT in patients with cirrhosis (13/46 questions). The extension of PVT was graded by the Yerdel classification [28]. The questionnaire was created as an online survey with SurveyMonkey (SurveyMonkey Inc.; San Mateo, California, USA; https://www.surveymonkey.com). A full copy of the questionnaire is available as Supplementary material (Annex 1).

2.2. Survey distribution

The Spanish Association for the Study of the Liver and the Spanish Society of Digestive Pathology sent a survey invitation to a total of 1726 practising clinical members. The survey could also be accessed through the research website of the Spanish Society of Digestive Pathology. The questionnaire did not contain any identifying information and data was collected anonymously. Participants could respond from October 22 to December 22, 2017.

A flow chart of the design and distribution of the study is shown in Supplementary Fig. S1.

2.3. Categorization of INR figure and platelets

The INR figure was categorized into three groups using the cut-offs values from the Child–Pugh score [29]. Platelets were categorized into four groups according to the severity of thrombocytopenia: mild (>75,000/μl–150,000/μl), moderate (51,000/μl–75,000/μl), severe (25,000/μl–50,000/μl) and very severe (<25,000/μl).

2.4. Statistical analysis

Quantitative variables were expressed as mean (standard deviation), and qualitative variables as absolute value and proportions. Comparisons between groups were performed with unpaired Student's t-test, or Fisher's exact test. Statistical analysis was performed with IBM SPSS Statistics v22.0 for Mac (IBM Corp, Armonk, NY) and GraphPad Prism v6.00 for Mac OS X (GraphPad Software, San Diego, CAP).

3. Results

3.1. Demographic and professional profile of participants

One hundred and thirty-five professionals (7.8%) from 33 of the 50 provinces of Spain (Supplementary Fig. S2) completed the survey in an average time of 22 min. Of the 135 participants, 93 were hepatologists and 42 non-hepatologists. The demographic and professional profile of the overall population surveyed and of each of these two groups is summarized in Table 1. Most professionals had more than five years of experience and treated more than ten cirrhotic patients per month. The most prominent differences between groups were that hepatologists worked more frequently in tertiary-level hospitals and treated more cirrhotic patients per month.

3.2. Concept of "rebalanced haemostasis"

The concept of rebalanced haemostasis associated with cirrhosis was known by 74.8% of the participants. Awareness of this was more frequent in hepatologists, although 17.2% of them were not familiar with this concept (70.6% of whom worked in a tertiary-level hospital). Its knowledge led most professionals to use a

Table 1
Baseline characteristics of the proffesionals surveyed.

Question[a]	All professionals (n = 135)	Hepatology (n = 93)	Non-hepatology (n = 42)	p[b]
Age (years) (Q 1.1)	43.9 (10.5)	45.0 (10.4)	41.6 (10.6)	0.091
Sex (%female) (Q 1.2)	69 (51.1)	48 (51.6)	21 (50.0)	1
Years of experience (Q 1.4)				0.072
<5 years	29 (21.4)	15 (16.1)	14 (33.3)	
5–15 years	53 (39.3)	40 (43.0)	13 (31.0)	
>15 years	53 (39.3)	38 (40.9)	15 (35.7)	
Type of hospital (Q 1.5)				<0.001
Tertiary-level	95 (70.4)	77 (82.8)	18 (42.9)	
Secondary-level	23 (17.0)	11 (11.8)	12 (28.6)	
Primary-level	14 (10.4)	5 (5.4)	9 (21.4)	
Outpatient clinic	3 (2.2)	0 (0)	3 (7.1)	
N of cirrhotic patients treated per month (Q 1.7)				<0.001
<10	13 (9.6)	0 (0)	13 (31.0)	
10–30	46 (34.1)	25 (26.9)	21 (50.0)	
>30	76 (56.3)	68 (73.1)	8 (19.0)	
Concept of rebalanced hemostasis (Q 2.1)				0.002
Known	101 (74.8)	77 (82.8)	24 (57.1)	
Not known	34 (25.2)	16 (17.2)	18 (42.9)	
Change of management (Q 2.2)				0.372
No	14 (13.9)	8 (10.4)	6 (25.0)	
More restrictive in transfusing	83 (82.2)	65 (84.4)	18 (75.0)	
More liberal in transfusing	2 (2.0)	2 (2.6)	0 (0)	
Other	2 (2.0)	2 (2.6)	0 (0)	

Abbreviation: Q, question.
[a] Cuantitative variables are expressed as means and standard deviations, whereas qualitative variables as absolute values and proportions.
[b] Comparisons between groups of hepatology and non-hepatology were performed with unpaired Student's t-test, or Fisher's exact test.

more restrictive transfusion strategy irrespective of their speciality (Table 1).

3.3. Correction of the prolongation of INR/thrombocytopenia before invasive procedures

In procedures with low risk of bleeding, most professionals did not correct the prolongation of INR or thrombocytopenia, whereas their reversal predominated in procedures of moderate risk of bleeding and major surgery. Only a minority of professionals used global coagulation tests (i.e. thromboelastography or thromboelastometry) to guide transfusion of blood products (Table 2). Thrombocytopenia was reversed more frequently than INR in low risk procedures (35.1% vs 17%; p = 0.0009), but not in those of moderate risk (84.3% vs 88.8%, p = 0.559) or major surgery (88.6% vs 94.7, p = 0.058). Severe thrombocytopenia was the most frequent threshold to trigger transfusion in all procedures, while the INR threshold varied greatly in low-risk procedures and was similar in procedures with higher risk (i.e. INR <1.7) (Table 2). In both scheduled and urgent invasive procedures, fresh frozen plasma was the most frequent type of blood product used to reverse the INR prolongation, although its use decreased from 83% in scheduled procedures (Fig. 1A) to 53% in urgent procedures (Fig. 1B). The verification of INR reversal with a post-transfusion analysis varied greatly between professionals (Fig. 1D), and was usually not performed after platelet transfusion (Fig. 1E).

This transfusion policy was similar between hepatologists and non-hepatologists, although post-transfusion analysis to verify the platelet increase was more frequently performed by the latter group (Fig. 1E).

3.4. Prevention of venous thromboembolism

Table 3 summarizes the answers to the five questions from this section. In patients with risk factors for VTE and without contraindication to anticoagulant therapy, most professionals used pharmacological prophylaxis (76%) with low-molecular-weight heparins (LMWH) (99.1%). Its indication was highly dependent on the INR (50%) and platelets (69%) figures. The threshold of INR and platelets beyond which its prescription was withdrawn varied greatly. Mechanical prophylaxis (i.e. compression stockings or intermittent pneumatic compression systems) was usually not used (only in 33.9%) in patients with contraindication to anticoagulant therapy. After a VTE, a third of specialists did not test for thrombophilia.

Regarding differences between hepatologists and non-hepatologists, in the former group the indication of pharmacological prophylaxis relied more on the platelet count and thrombophilia testing was performed more frequently in patients who developed a VTE.

3.5. Correction of INR/thrombocytopenia in cirrhotic patients with variceal and non-variceal gastrointestinal bleeding

Table 4 summarizes the main results in this section. The decision to administer blood products depended on the severity of the bleeding and not on its origin. In mild bleeding, most professionals did not correct the INR or platelet count, whereas in severe bleeding their reversal prevailed. Thrombocytopenia was corrected more frequently than INR in mild variceal (36.1% vs 18.5%; p = 0.003) and non-variceal bleeding (32.8% vs 18.3%; p = 0.012), but both were similarly managed if the bleeding was severe (70.3 vs 58.3; p = 0.0571, and 72.3% vs 62.5%; p = 0.166, respectively). Severe thrombocytopenia was the most frequent threshold used to trigger transfusion irrespective of the origin and severity of the bleeding, whereas that of INR varied greatly. Fresh frozen plasma was the most common type of blood product used to reverse the INR prolongation (75.9%) (Fig. 1C).

No major differences were found between hepatologists and non-hepatologists in this section.

Table 2
Correction of the prolongation of INR and thrombocytopenia before invasive procedures.

Question[a]	INR				Platelets			
	All professionals (n = 135)	Hepatology (n = 93)	Non-hepatology (n = 42)	p	All professionals (n = 135)	Hepatology (n = 93)	Non-hepatology (n = 42)	p[c]
Low risk of bleeding (Q 3.1/3.7) (*N* = 135/134)[b]				0.307				0.326
I do not correct it	111 (82.2)	79 (84.9)	32 (76.2)		86 (64.2)	59 (64.1)	27 (64.3)	
Global coagulation tests	1 (0.7)	1 (1.1)	0 (0)		1 (0.7)	0 (0)	1 (2.4)	
Based on figure of INR/platelets	23 (17.0)	13 (14.0)	10 (23.8)	0.292	47 (35.1)	33 (35.9)	14 (33.3)	0.077
1.2–1.6/≤25	10 (43.5)	5 (38.5)	5 (50.0)		16 (34.0)	8 (24.2)	8 (57.1)	
1.7–2.3/26–50	7 (30.4)	3 (23.0)	4 (40.0)		39 (61.7)	23 (69.7)	6 (42.9)	
>2.3/51–75	6 (26.1)	5 (38.5)	1 (10.0)		2 (4.3)	2 (6.1)	0 (0)	
/76–100					0 (0)	0 (0)	0 (0)	
Moderate risk of bleeding (Q 3.2/3.8) (*N* = 134/134)[b]				0.727				0.396
I do not correct it	16 (11.9)	10 (10.8)	6 (14.6)		13 (9.7)	7 (7.6)	6 (14.3)	
Global coagulation tests	5 (3.7)	4 (4.3)	1 (2.4)		2 (1.5)	1 (1.1)	1 (2.4)	
Based on figure of INR/platelets	113 (84.3)	79 (84.9)	34 (82.9)	0.658	119 (88.8)	84 (91.3)	35 (83.3)	0.753
1.2–1.6/≤25	87 (77)	61 (77.2)	26 (76.5)		9 (7.6)	6 (7.1)	3 (8.6)	
1.7–2.3/26–50	22 (19.5)	16 (20.3)	6 (17.6)		92 (77.3)	67 (79.8)	25 (71.4)	
>2.3/51–75	4 (3.5)	2 (2.5)	2 (5.9)		16 (13.4)	10 (11.9)	6 (17.1)	
/76–100					2 (1.7)	1 (1.2)	1 (2.9)	
Major surgery (Q 3.3/3.9) (*N* = 132/131)[b]				0.211				1
I do not correct it	4 (3.0)	4 (4.4)	0 (0)		0 (0)	0 (0)	0 (0)	
Global coagulation tests	11 (8.3)	9 (10.0)	2 (4.8)		7 (5.3)	5 (5.6)	2 (4.8)	
Based on figure of INR/platelets	117 (88.6)	77 (85.6)	40 (95.2)	0.686	124 (94.7)	84 (94.4)	40 (95.2)	0.481
1.2–1.6/≤25	92 (78.7)	60 (77.9)	32 (80.0)		5 (4.0)	3 (3.6)	2 (5.0)	
1.7–2.3/26–50	21 (17.9)	15 (19.5)	6 (15.0)		86 (69.4)	62 (73.8)	24 (60.0)	
>2.3/51–75	4 (3.4)	2 (2.6)	2 (5.0)		24 (19.3)	14 (16.7)	10 (25.0)	
/76–100					9 (7.3)	5 (6.0)	4 (10.0)[d]	

Abbreviations: Q, question; INR, international normalized ratio.

[a] Qualitative variables are expressed as absolute values and proportions.

[b] The total number of answers to each question in relation to the prolongation of INR and thrombocytopenia, respectively.

[c] Comparisons between groups of hepatology and non-hepatology were performed with unpaired Student's t-test, or Fisher's exact test.

[d] The threshold of platelets of one professional in this group was actually 150,000/μl, but was included in this subgroup for homogenization issues.

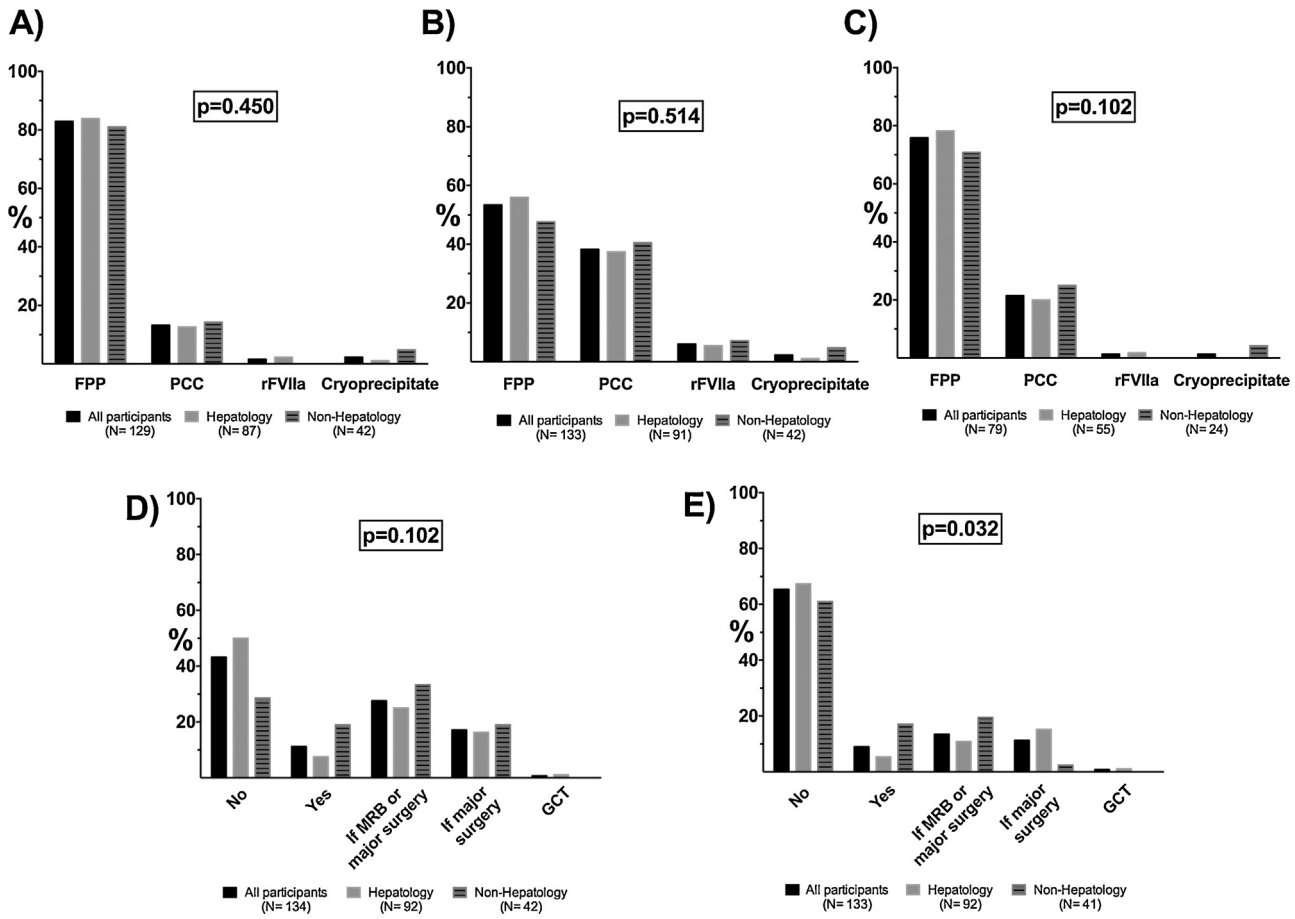

Fig. 1. Type of blood products used to correct the prolongation of INR before scheduled (A) or urgent (B) invasive procedures and in gastrointestinal bleeding (C) and performance of a post-transfusion analysis to verify the reversal of INR (D) and increase of platelets (E) before invasive procedures. Post-transfusion analysis to verify the platelet increase was more frequently performed by hepatologists, with no other significant difference between groups regarding the remaining questions.
Abbreviations: FFP: Fresh frozen plasma; PCC: Prothrombin complex concentrate; rFVIIa: Recombinant factor VIIa; MRB: Moderate risk of bleeding; GCT: Global coagulation tests.

3.6. Management of non-malignant portal vein thrombosis (PVT) in cirrhosis

The prescription of anticoagulant therapy regardless of the degree of PVT prevailed whether or not the patient was a candidate for liver transplantation (LT), although this prescription was more frequent in potential candidates (85.2% vs 60.4%, $p < 0.0001$). After the recanalization of PVT, the duration of anticoagulant therapy varied greatly in both groups: half of the participants maintained anticoagulation indefinitely or until LT in potential candidates, while in non-LT candidates, 60% stopped anticoagulant therapy after 6 months. Thrombophilia testing after PVT was performed by most professionals, for which the majority followed the indications of the haematologists. Table 5 summarizes all these results.

Other aspects of PVT management such as type of anticoagulant therapy with different levels of INR and platelet count, type of thrombophilia testing, transjugular intrahepatic portosystemic shunt insertion for acute PVT, anticoagulant therapy in chronic PVT, and use of anti-factor Xa to monitor therapy with LMWH are shown in Supplementary Table S1.

Again, the management of PVT was similar for hepatologists and non-hepatologists.

4. Discussion

To the best of our knowledge, this is the first study describing Digestive Disease specialists' real-life clinical management of haemostatic alterations and associated disorders in cirrhotic patients. We found a high variability in management of both hepatologists and non-hepatologists with no major differences between the two groups in any of the areas surveyed. Transfusion of blood products to improve or normalize coagulation parameters prevailed in invasive procedures with higher risk of bleeding and severe gastrointestinal haemorrhages. Moreover, 25% of participants were not familiar with the concept of rebalanced haemostasis, a majority performed thrombophilia testing after VTE, and 44% did not continue anticoagulant therapy indefinitely or until liver transplantation in potential candidates after recanalization of acute PVT.

The INR threshold used to administer blood products before invasive procedures or in gastrointestinal bleedings was responsible for most of this variability, as the management of thrombocytopenia was more homogeneous. Indeed, most specialists transfused platelets if they were below 50×10^9/l. This threshold is currently recommended by several guidelines and experts in the field to trigger platelet transfusion before invasive procedures, as it seems to ensure normal primary haemostasis [1,2,25,26]. However, this recommendation is supported only by biological plausibility, and it has recently been challenged by a study in which bleeding after invasive procedures was unpredicted by platelet count [9]. Cost and safety issues have also been raised and have led a group of experts to recommend a wait-and-see policy until more studies become available [30]. The heterogeneous management of INR prolongation further shows the discrepancies

Table 3
Prevention of venous thromboembolism.

Question[a]	All professionals (n = 135)	Hepatology (n = 93)	Non-hepatology (n = 42)	p[c]
Risk factors for VTE, no contraindicaction to anticoagulant therapy and figure of INR (Q 4.1) (*N* = 102)[b]				0.510
No pharmacocological PF	15 (14.7)	12 (16.2)	3 (10.7)	
Mechanical PF	9 (8.8)	7 (9.5)	2 (7.1)	
PhPF regardless of INR value	39 (38.2)	25 (33.8)	14 (50.0)	
Dependent on figure of INR	39 (38.2)	30 (40.5)	9 (32.1)	0.284
1.2–1.6	21 (53.8)	16 (53.3)	5 (55.6)	
1.7–2.3	12 (30.8)	8 (26.7)	4 (44.4)	
>2.3	6 (15.4)	6 (20.0)	0 (0)	
Risk factors for VTE, no contraindicaction to anticoagulant therapy and figure of platelets (Q 4.2) (*N* = 93)[b]				0.020
No pharmacocological PF	16 (17.2)	12 (18.2)	4 (14.8)	
Mechanical PF	6 (6.5)	4 (6.1)	2 (7.4)	
PhPF regardless of platelet count	22 (23.7)	10 (15.2)	12 (44.4)	
Dependent on figure of platelets ($10 \times 3/\mu l$)	49 (52.7)	40 (60.6)	9 (33.3)	0.807
≤25	11 (22.4)	8 (20.0)	3 (33.3)	
26–50	32 (65.3)	27 (67.5)	5 (55.6)	
51–75	5 (10.2)	4 (10.0)	1 (11.1)	
76–100	1 (2.0)	1 (2.5)	0 (0)	
Type of anticoagulant therapy (Q 4.3) (*N* = 116)[b]				0.310
LMWH	115 (99.1)	80 (100)	35 (97.2)	
Unfractionated heparins	1 (0.9)	0 (0)	1 (2.8)	
Fondaparinux	0 (0)	0 (0)	0 (0)	
Direct oral anticoagulants	0 (0)	0 (0)	0 (0)	
Risk factors for VTE, contraindicaction to anticoagulant therapy and mechanical PF (Q 4.4) (*N* = 112)[b]				0.275
No	74 (66.1)	55 (69.6)	19 (57.6)	
Yes	38 (33.9)	24 (30.4)	14 (42.4)	
Thrombophilia testing (Q 4.5) (*N* = 119)[b]				0.013
No	38 (31.9)	20 (23.8)	18 (51.4)	
Yes, regardless of age	66 (55.6)	52 (61.9)	14 (40.0)	
Yes, if <50 years	15 (12.6)	12 (14.3)	3 (8.6)	

Abbreviations: VTE, venous thromboembolism; INR, international normalized ratio; Q, question; PF, prophylaxis; PhPF, pharmacological prophylaxis; LMWH, low-molecular-weight heparins.

[a] Qualitative variables are expressed as absolute values and proportions.

[b] The total number of answers to each question, excluding those whose answer was "I do not know/no opinion".

[c] Comparisons between groups of hepatology and non-hepatology were performed with unpaired Student's t-test, or Fisher's exact test.

among current guidelines [20–22,25] and highlights the need for high quality data to determine whether or not to transfuse blood products and which thresholds to use. The current presumption that global coagulation tests will greatly assist in this regard faces the difficulties in their implementation in daily clinical practice, since few specialists had access to them (<9%). Regardless of the threshold of platelets and INR used, most specialists transfused blood products to correct them both before invasive procedures with moderate or high risk of bleeding and in severe gastrointestinal haemorrhage, thereby suggesting that the view of cirrhosis as an acquired bleeding disorder still dominates in clinical practice. Likewise, a United Kingdom nationwide study of transfusion practice for patients with cirrhosis showed that one-third of patients with cirrhosis were transfused at least one blood component during hospitalization. This figure is striking and comparable to cohorts admitted into intensive care. The thresholds of platelets and INR used also varied greatly [31]. In contrast to this study, participants in our survey corrected thrombocytopenia more frequently than coagulopathy in low-risk procedures and mild gastrointestinal bleedings. This finding is consistent with the current notion that platelets are the key element in ensuring haemostasis in cirrhosis [25,26]. Interestingly, and in line with present evidence indicating that non-variceal bleeding in patients with cirrhosis leads to substantial morbidity and mortality [32], specialists managed the haemostatic alterations in variceal and non-variceal bleedings similarly.

Regarding VTE and PVT, the use of pharmacological prophylaxis in the former prevailed among participants, but its prescription was highly dependent on the figure of INR and platelets and, once again, the threshold used varied greatly. It could therefore be inferred that patients with advanced liver disease (i.e. those with greater risk of VTE) would not receive any type of prophylaxis since they frequently have more severe thrombocytopenia and coagulopathy and mechanical prophylaxis was rarely used by participants. This is in keeping with the low reported use of prophylactic anticoagulation for VTE in this population [2]. As far as anticoagulation of acute PVT is concerned, most participants initiated anticoagulant therapy regardless of the degree of PVT, even in non-LT candidates. These results follow the unproven hypothesis that PVT negatively impacts the natural history of cirrhosis [1,2]. However, duration of anticoagulant therapy in potential candidates for LT frequently did not follow current guidelines, with only 56% of specialists maintaining anticoagulation indefinitely or until LT [22,24,25]. Testing for thrombophilia was frequently performed after VTE and PVT,

Table 4
Correction of INR/thrombocytopenia in cirrhotic patients with variceal and non-variceal gastrointestinal bleeding.

Question[a]	INR				Platelets			
	All professionals (n = 135)	Hepatology (n = 93)	Non-hepatology (n = 42)	p	All professionals (n = 135)	Hepatology (n = 93)	Non-hepatology (n = 42)	p[c]
Mild variceal bleeding (Q 5.1/5.6) (*N* = 119/119)[b]				0.786				0.273
I do not correct it	96 (80.7)	68 (81.0)	28 (80.0)		75 (63.0)	54 (65.1)	21 (58.3)	
Global coagulation tests	1 (0.8)	1 (1.2)	0 (0)		1 (0.8)	0 (0)	1 (2.8)	
Based on figure of INR/platelets	22 (18.5)	15 (17.9)	7 (20.0)	0.986	43 (36.1)	29 (34.9)	14 (38.9)	0.602
1.2–1.6/≤25	9 (40.9)	6 (40.0)	3 (42.9)		6 (14.0)	4 (13.8)	2 (14.3)	
1.7–2.3/26–50	10 (45.5)	7 (46.7)	3 (42.9)		35 (81.4)	23 (79.3)	12 (85.7)	
>2.3/51–75	3 (13.6)	2 (13.3)	1 (14.2)		2 (4.6)	2 (6.9)	0 (0)	
/76–100					0 (0)	0 (0)	0 (0)	
Severe variceal bleeding (Q 5.2/5.7) (*N* = 120/118)[b]				0.762				0.316
I do not correct it	49 (40.8)	35 (41.7)	14 (38.9)		34 (28.8)	24 (29.3)	10 (27.8)	
Global coagulation tests	1 (0.8)	1 (1.2)	0 (0)		1 (0.8)	0 (0)	1 (2.8)	
Based on figure of INR/platelets	70 (58.3)	48 (57.1)	22 (61.1)	0.257	83 (70.3)	58 (70.7)	25 (69.4)	0.477
1.2–1.6/≤25	33 (47.1)	22 (45.8)	11 (50.0)		12 (14.5)	8 (13.8)	4 (16.0)	
1.7–2.3/26–50	27 (38.6)	21 (43.8)	6 (27.3)		67 (80.7)	48 (82.8)	19 (76.0)	
>2.3/51–75	10 (14.3)	5 (10.4)	5 (22.7)		3 (3.6)	1 (1.7)	2 (8.0)	
/76–100					1 (1.2)	1 (1.7)	0 (0)	
Mild non-variceal bleeding (Q 5.3/5.8) (*N* = 120/119)[b]				0.302				0.833
I do not correct it	98 (81.7)	71 (84.5)	27 (75.0)		80 (67.2)	55 (66.3)	25 (69.4)	
Global coagulation tests	0 (0)	0 (0)	0 (0)		0 (0)	0 (0)	0 (0)	
Based on figure of INR/platelets	22 (18.3)	13 (15.5)	9 (25.0)	0.506	39 (32.8)	28 (33.7)	11 (30.6)	0.419
1.2–1.6/≤25	9 (40.9)	4 (30.8)	5 (55.6)		4 (10.3)	2 (7.1)	2 (18.2)	
1.7–2.3/26–50	10 (45.5)	7 (53.8)	3 (33.3)		33 (84.6)	24 (85.8)	9 (81.8)	
>2.3/51–75	3 (13.6)	2 (15.4)	1 (11.1)		2 (5.1)	2 (7.1)	0 (0)	
/76–100					0 (0)	0 (0)	0 (0)	
Severe non-variceal bleeding (Q 5.4/5.9) (*N* = 120/119)[b]				0.773				0.247
I do not correct it	44 (36.7)	30 (35.7)	14 (38.9)		33 (27.7)	21 (25.3)	12 (33.3)	
Global coagulation tests	1 (0.8)	1 (1.2)	0 (0)		0 (0)	0 (0)	0 (0)	
Based on figure of INR/platelets	75 (62.5)	53 (63.1)	22 (61.1)	0.214	86 (72.3)	62 (74.7)	24 (66.7)	0.706
1.2–1.6/≤25	37 (49.3)	25 (47.2)	12 (54.5)		14 (16.3)	10 (16.1)	4 (16.7)	
1.7–2.3/26–50	30 (40.0)	24 (45.3)	6 (27.3)		67 (77.9)	49 (79.0)	18 (75.0)	
>2.3/51–75	8 (10.7)	4 (7.5)	4 (18.2)		4 (4.7)	2 (3.2)	2 (8.3)	
/76–100					1 (1.2)	1 (1.6)	0 (0)	

Abbreviations: Q, question; INR, international normalized ratio; PCC, prothrombin complex concentrate; rFVIIa, recombinant factor VIIa.

[a] Qualitative variables are expressed as absolute values and proportions.

[b] The total number of answers to each question in relation to the prolongation of INR and thrombocytopenia, respectively.

[c] Comparisons between groups of hepatology and non-hepatology were performed with unpaired Student's t-test, or Fisher's exact test.

Table 5
Management of non-malignant portal vein thrombosis in cirrhosis.

Question[a]	All professionals (n = 135)	Hepatology (n = 93)	Non-hepatology (n = 42)	p[c]
Thrombophilia testing in acute or chronic PVT (Q 6.1) (N = 113)[b]				0.159
No	30 (26.5)	17 (24.6)	13 (38.2)	
Yes	83 (73.5)	62 (75.4)	21 (61.8)	
Anticoagulant therapy in potential candidates for LT and acute PVT (Q 6.3) (N = 108)[b]				0.368
I do not administer anticoagulant therapy	0 (0)	0 (0)	0 (0)	
Yerdel ≥II	14 (13.0)	12 (15.6)	2 (6.5)	
Yerdel III and IV	2 (1.9)	1 (1.3)	1 (3.2)	
Regardless of the degree of PVT	92 (85.2)	64 (83.1)	28 (90.3)	
Anticoagulant therapy in non-LT candidates and acute PVT (Q 6.4) (N = 111)[b]				0.650
I do not administer anticoagulant therapy	3 (2.7)	3 (3.8)	0 (0)	
Yerdel ≥II	29 (26.1)	22 (27.8)	7 (21.9)	
Yerdel III and IV	11 (9.9)	8 (10.1)	3 (9.4)	
Regardless of the degree of PVT	67 (60.4)	45 (57.0)	22 (68.8)	
Other: if symtomatic	1 (0.9)	1 (1.3)	0 (0)	
Duration of anticoagulant therapy in potential candidates for LT after recanalization of PVT (Q 6.5) (N = 109)[b]				0.195
6 months	29 (26.6)	17 (22.1)	12 (37.5)	
12 months	19 (17.4)	13 (16.9)	6 (18.8)	
Indefinitely or until LT	61 (56.0)	47 (61.0)	14 (43.8)	
Duration of anticoagulant therapy in non-LT candidates after recanalization of PVT (Q 6.6) (N = 109)[b]				0.861
6 months	65 (59.6)	46 (59.7)	19 (59.4)	
12 months	39 (35.8)	28 (36.4)	11 (34.4)	
Indefinitely or until LT	5 (4.6)	3 (3.9)	2 (6.3)	

Abbreviations: Q, question; LT, liver transplantation; PVT, portal vein thrombosis.
[a] Qualitative variables are expressed as absolute values and proportions.
[b] The total number of answers to each question, excluding those whose answer was "I do not know/no opinion".
[c] Comparisons between groups of hepatology and non-hepatology were performed with unpaired Student's t-test, or Fisher's exact test.

although current guidelines do not recommend its performance after VTE, whether provoked or unprovoked [33,34], and only recommend "considering" their screening after PVT in patients with cirrhosis [24]. Whether this implies that participants question cirrhosis as a hypercoagulable state cannot be ascertained.

The main limitation of the present study was the low rate of response to the questionnaire, which was similar to that achieved in several previous surveys on other topics [35,36]. Nevertheless, the demographic and professional profile of participants is fairly illustrative of the Spanish Digestive Disease specialists dealing with cirrhotic patients. The absence of major differences in management between hepatologists and non-hepatologists probably responds both to the absence of homogeneous recommendations in current guidelines and gaps in knowledge in the field. The non-inclusion of questions regarding management of haemostatic alterations during liver transplantation constitutes another limitation. They might have shown a distinct management from that of other major surgeries as an increasingly number of transplant centres use a restrictive transfusion policy or use a tromboelastography-guided transfusion algorithm. However, as the survey was directed at all specialists in Digestive Diseases, we presumed that few specialists not related to a transplant programme would know their local transfusion strategy. Moreover, their inclusion could have increased the response burden and led to a decrease in participation. Similarly, the inclusion of other specialties involved in the management of cirrhotic patients, such as anesthesiologists, surgeons, and interventional radiologists, might have derived in very different results. The decision not to include them was based on the fact that, apart from the Invasive Procedures section, they do not directly manage the other sections surveyed. All in all, the questionnaire thoroughly evaluated how Spanish Digestive Disease specialists manage haemostatic alterations and associated disorders in patients with liver cirrhosis. Our results highlight the need for further haemostasis research in cirrhotic patients. Studies using global coagulation tests to identify those patients who really need the administration of blood products are eagerly awaited and should validate and expand the results from a recent clinical trial in which a tromboelastography-based algorithm reduced blood product transfusions before invasive procedures compared to the standard of care [27]. Until these studies take place, the implementation of educational interventions such as training programmes, development of guidelines or awareness campaigns might facilitate and homogenize the management of these matters.

In conclusion, our survey has revealed a significant variability among Spanish Digestive Disease specialists regarding management of haemostatic alterations and associated disorders in cirrhosis. A fixed duration of anticoagulation in potential candidates for liver transplantation after recanalization of acute portal vein thrombosis and thrombophilia testing after venous thromboembolism represent the most remarkable deviations from current guidelines.

Conflict of interest

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.dld.2018.06.003.

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