The landscape of rare coagulation factor deficiency management in Italy: a national hemophilia center survey

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ABSTRACT

Background: Rare bleeding disorders (RBDs) are a group of inherited conditions caused by deficiencies in specific coagulation factors, excluding hemophilia A/B and von Willebrand disease. Individually rare, they pose a significant challenge for diagnosis and management due to diverse clinical presentations and low awareness. This study aimed to provide an overview of RBDs.

Methods: An online survey was sent to Italian hemophilia treatment centers.

Results: Nineteen centers responded. The diagnostic approach was tiring, but key definitions showed significant variability. This included defect severity, target hemostatic levels for surgery, eligibility thresholds for rare disease exemptions. The use of prophylaxis varied, although favored in severe FII, FVII, FX, and FXIII defects. Treatment primarily involved factor-specific concentrates and tranexamic acid. While inhibitor development was considered uncommon, it was a recognized risk. Bleeding management during dental procedures, pregnancy, and delivery also showed variability. Additionally, normal factor levels in neonates differed across centers.

Conclusions: This study highlights a good consensus for managing certain RBDs (FII, FVII, FX, FXIII) in Italy. However, significant heterogeneity persists, emphasizing the need for greater standardization and further research in several key areas.

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Key words: rare bleeding disorders; hemorrhagic risk; prophylaxis.

Contributions: RCS, study concept, data analysis and interpretation, manuscript original drafting; SL, RM, data analysis and interpretation, manuscript original drafting; ML, AC, PDG, FAB, FP, CS, EZ, contribution to manuscript writing and editing. All the authors read and approved the definitive version of the manuscript and agreed to be accountable for all aspects of the work.

Conflict of interests: the authors declare no competing interests and all authors confirm accuracy.

Availability of data and materials: all data generated or analyzed during this study are included in this published article.

Acknowledgements: to the contributing hemophilia treatment centers (see Appendix).

Received: 9 August 2025.
Accepted: 28 October 2025.

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Bleeding, Thrombosis and Vascular Biology 2025; 4:369
doi:10.4081/btvb.2025.369

Introduction

The intricate process of hemostasis involves a cascade of coagulation factors working in concert to prevent and control bleeding. While the most common inherited bleeding disorders, such as von Willebrand disease (VWD), hemophilia A and hemophilia B, have been extensively studied, a spectrum of less frequent conditions, collectively termed rare bleeding disorders (RBDs), pose unique diagnostic and therapeutic challenges. These disorders arise from quantitative or qualitative defects in coagulation factors such as factor (F) I (fibrinogen), FII (prothrombin), FV, FVII, FXI, FXIII, as well as combined factor deficiencies and platelet function disorders beyond VWD.

Research by Peyvandi and colleagues[1-7] have significantly contributed to our understanding of the genetic and clinical aspects of various RBDs, highlighting the heterogeneity in their prevalence, clinical manifestations, and severity. Furthermore, studies such as the one on FVII deficiency by Mariani *et al*.[8] provided valuable insights into the prevalence and clinical features of this specific RBD. Additionally, research on FXIII deficiency[9] has advanced our understanding of its crucial role in maintaining hemostatic plug stability.

Despite the rarity of each individual disorder, the cumulative impact of RBDs on patient morbidity and healthcare resource utilization is substantial. Accurate diagnosis,[10-12] often requiring spe-

cialized laboratory testing, is crucial for appropriate management, which can range from prophylactic or on-demand replacement therapy to supportive care. However, awareness of these conditions among healthcare professionals can be limited, potentially leading to diagnostic delays and suboptimal treatment.

To date, comprehensive nationwide data on the clinical management of RBDs in Italy have been unavailable. This gap underscores the importance of our current survey in guiding both clinical practice and the development of health policy. To characterize the current state of RBDs in Italy, we conducted a nationwide survey across 19 Italian hemophilia treatment centers (HTCs). This survey aimed to gather comprehensive data on the diagnosis, clinical management, and challenges associated with RBDs within this specific geographical context. Building upon existing knowledge and incorporating novel survey data, this study seeks to enhance understanding and improve the care of individuals living with these rare but significant conditions. The subsequent sections of this paper will detail the methodology of this survey and present an analysis of the collected data, providing valuable insights into the real-world landscape of RBDs in Italy.

Materials and Methods

The data for this study were obtained through a survey distributed to HTCs across the nation. Clinicians were invited to respond based on their clinical experience.

The survey consisted of a few initial questions on the experience in the management of people with RBDs and diagnostic approaches in different HTCs, followed by the investigation of seventeen specific items in each RBDs, except for FXII deficiency, as it is not clinically significant for hemorrhagic risk.

The following various aspects in fibrinogen, FII, FVII, FX, FV, FV+FVIII, FXI and FXIII deficiencies were investigated:

- The coagulation factor activity plasma level which defines a severe deficiency
- The possibility that a severe coagulation factor deficiency could cause spontaneous intracranial hemorrhage (ICH)
- The laboratory tests needed for diagnosis and the role of genetic testing
- The threshold level of coagulation factor for rare disease exemption
- The required coagulation factor plasma level to manage surgeries or bleeding
- The coagulation factor plasma level which confers a bleeding risk such that prophylaxis is recommended
- The required coagulation factor plasma level during pregnancy and to manage a vaginal or surgical delivery, in addition to that which may justify the presence of menorrhagia
- The normal coagulation factor ranges in the first 6 months of life and the plasma level which confers a bleeding risk such that prophylaxis is recommended in newborn
- The recommended hemostatic treatments for the management of coagulation factor deficiency
- The possibility of developing inhibitors following treatment with coagulation factor concentrate.

Data relating to fibrinogen defects are described in another article.

All survey questions were closed-ended and plasma factor levels for closed-ended responses were decided by the AICE Guidelines group based on literature and clinical experience. The suggested answers for each specific factor are shown in Tables 1 and 2.

Results

A total of 19 HCTs completed the survey, providing insights into their patient demographics, experience, and service provision.

Regarding the patient populations managed by these centers, the majority (84.2%, n=16) reported caring for individuals with congenital bleeding disorders across all age groups. A smaller proportion of centers specialized either in pediatric care (5.3%, n=1) or managed adult patients (10.5%, n=2).

The experience levels of the participating centers in managing congenital bleeding disorders varied. Half of the centers (47.4%, n=9) had between 5 and 20 years of experience, while the other half (52.6%, n=10) reported having over 20 years of experience in this field. Notably, none of the responding centers had less than 5 years of experience.

All participating centers (100%, n=19) indicated that they provide consultation services to other departments within their own institutions or to other healthcare facilities for patients with congenital bleeding disorders. This highlights the role of these specialized centers in supporting the broader healthcare network.

Furthermore, all nineteen responding centers (100%) reported having experience in managing patients with congenital bleeding disorders who were receiving prophylactic treatment. This suggests a widespread familiarity with this important aspect of care for individuals with these conditions.

All participating HTCs (100%, n=19) agreed that standard screening tests, such as prothrombin time (PT), activated partial thromboplastin time (aPTT), and fibrinogen levels, are insufficient to rule out the presence of a mild coagulation factor deficiency. This consensus underscores the need for more specific testing when clinical suspicion for a bleeding disorder exists, even with normal initial screening results.

Moreover, opinions were gathered on the necessity of determining both antigenic levels and functional activity in the diagnosis of coagulation factor defects. A minority of centers (10.5%, n=2) believed that both should always be performed. However, the majority (73.7%, n=14) indicated that determining antigenic levels is necessary in some cases. These cases were specified as instances of functional protein alterations or when there is a poor correlation between the severity of the laboratory defect and the clinical presentation, particularly noted in fibrinogen disorders. A small percentage of centers (10.5%, n=2) did not believe antigenic level determination was necessary, while one center (5.3%) was unsure. This suggests a general awareness of the added value of antigenic testing in specific diagnostic scenarios.

Finally, the survey explored the approach to risk stratification in individuals with a known congenital bleeding disorder. The majority of centers (84.2%, n=16) considered it appropriate to investigate the potential co-occurrence of other hemostatic defects, such as VWD or platelet function disorders, to comprehensively determine the hemorrhagic risk profile, mainly in cases where low levels of factor activity do not fully explain the severity of clinical bleeding. A smaller proportion of centers (15.8%, n=3) did not believe this was necessary, and no centers were unsure. This highlights the prevailing view that a thorough assessment of bleeding risk in patients with known congenital bleeding disorders should include consideration of other potential contributing factors.

The specific responses pertaining to individual coagulation factor deficiencies are detailed in Tables 1 and 2. The results for FII, FVII, FX (vitamin K-dependent factors) are described in Table 1, those for all other defects in Table 2.

The data collected on these specific defects provides a more detailed understanding of the current practices within the national network of HTCs.

Table 1. Results for vitamin K-dependent factors deficiencies.

	Factor II deficiency		Factor X deficiency		Factor VII deficiency	
	Type of response	% of response	Type of response	% of response	Type of response	% of response
What is the factor plasma level to define a severe defect?	a) <5% b) <10% c)<20% d) I don't know	42.0 37.0 16.0 5.0	a) <10% b) <20% c) <25% d) I don't know	89.5 0.0 10.5 0.0	a)<5% b) <10% c) <20% d) I don't know	79.0 21.0 0.0 0.0
Do you think that subjects with severe defects are at risk of spontaneous ICH?	a) Yes, at all ages b) Only neonatal c) I don't know	58.0 5.0 37.0	a) Yes, at all ages b) Only neonatal c) I don't know	73.7 5.3 21.0	a) Yes, at all ages b) Only neonatal c) I don't know	74.0 10.5 15.5
Which laboratory tests are needed for diagnosis?	a) PT, aPTT b) PT, aPTT, assay of FII activity and FII antigen c) PT, aPTT, assay of FII activity and other Vitamin K-dependent coagulation factors d) I don't know	0.0 47.4 47.4 5.2	a) PT, aPTT b) PT, aPTT, assay of FX activity and FX antigen c) PT, aPTT, assay of FX activity and other Vitamin K-dependent coagulation factors d) I don't know	0.0 31.6 68.4 0.0	a) PT, aPTT b) PT, aPTT, assay of FVII activity and FVII antigen c) PT, aPTT, assay of FVII activity and other vitamin K-dependent coagulation factors d) I don't know	0.0 31.6 68.4 0.0
Is genetic testing necessary to diagnose the coagulation factor defect?	a) Yes b) No c) I don't know	26.0 37.0 37.0	a) Yes b) No c) I don't know	26.3 52.7 21.0	a) Yes b) No c) I don't know	21.0 63.2 15.8
What do you consider to be the required plasma levels of coagulation factor for rare disease exemption?	a) <30% b) <40% c) I don't know	53.0 26.0 21.0	a) <10% b) <30% c) I don't know	10.5 84.2 5.3	a) <20% b) <40% c) I don't know	52.6 47.4 0.0
What coagulation factor plasma levels are required to manage minor surgery or mild bleeding?	a) >10% b) >30% c) I don't know	26.0 53.0 21.0	a) >20% b) >40% c) I don't know	68.5 21.0 10.5	a) >10% b) >30% c) I don't know	31.6 63.1 5.3
In the management of invasive dental procedures, what coagulation factor requires post-operative prophylaxis with TA?	a) <10% b) <25% c) I don't know	10.0 69.0 21.0	a) <10% b) <25% c) I don't know	26.3 73.7 0.0	a) <10% b) <35% c) I don't know	63.1 31.6 5.3
What coagulation factor plasma levels are required to manage major surgery or severe bleeding?	a) >20% b) >35% c) >50% d) I don't know	0.0 37.0 58.0 5.0	a) >20% b) >35% c) >50% d) I don't know	15.6 21.1 63.3 0.0	a) >20% b) >35% c) >50% d) I don't know	21.4 15.5 63.1 0.0
What coagulation factor plasma levels confer a bleeding risk that suggests prophylaxis?	a) <5% b) <20% c) I don't know	74.0 0.0 26.0	a) <10% b) <25% c) I don't know	79.0 0.0 21.0	a) <10% b) <25% c) I don't know	73.7 0.0 26.3
What coagulation factor plasma levels are required during pregnancy?	a) >10% b) >25% c) >40% d) I don't know	16.0 42.0 37.0 5.0	a) >10% b) >25% c) >50% d) I don't know	46.0 26.0 31.0 0.0	a) >10% b) >25% c) >40% d) I don't know	21.3 47.3 26.2 5.2
What coagulation factor plasma levels are required for vaginal delivery?	a) >20% b) >50% c) I don't know	42.0 32.0 26.0	a) >20% b) >50% c) I don't know	58.0 26.4 15.6	a) >20% b) >50% c) I don't know	47.4 52.6 0.0
What coagulation factor plasma levels are required for surgical delivery?	a) >20% b) >50% c) I don't know	21.0 63.0 16.0	a) >20% b) >50% c) I don't know	15.5 74.0 10.5	a) >20% b) >50% c) I don't know	31.6 63.1 5.3
What coagulation factor plasma levels can justify the presence of menorrhagia in affected women?	a) <5% b) <20% c) <40% d) I don't know	27.0 63.0 10.0 0.0	a) <10% b) <20% c) <40% d) I don't know	42.1 42.1 10.5 5.3	a) <10% b) <20% c) <40% d) I don't know	26.3 68.4 5.3 0.0
What plasma coagulation factor level range is normal in the first 6 months of life?	a) 10-70% b) 25-95% c) 35-95% d) I don't know	42.0 32.0 16.0 10.0	a) 10-70% b) 25-95% c) 40-120% d) I don't know	42.1 42.1 10.5 5.3	a) 10-70% b) 25-95% c) 40-100% d) I don't know	57.9 31.6 10.5 0.0
What coagulation factor plasma levels in newborn confer a bleeding risk that suggests prophylaxis?	a) <5% b) <20% c) I don't know	48.0 10.0 42.0	a) <5% b) <25% c) I don't know	63.1 5.3 31.6	a) <5% b) <15% c) I don't know	68.5 10.5 21.0
Which of the following therapies are useful in the management of coagulation factor deficiency?	a) FFP b) PCC, TA c) FFP, PCC, TA d) I don't know	0.0 53.0 42.0 5.0	a) FFP b) PCC, TA c) FX concentrate, TA d) I don't know	5,3 26.3 68.4 0.0	a) FFP b) FVII concentrates c) FVII concentrates, TA d) I don't know	0.0 5.3 89.4 5.3
Is it possible the development of inhibitors following treatment with coagulation factor concentrate?	a) Yes b) No c) I don't know	48.0 4.0 48.0	a) Yes b) No c) I don't know	42.1 5.3 52.6	a) Yes b) No c) I don't know	36.8 36.8 26.4

PT, prothrombin time; aPTT, activated partial thromboplastin time; ICH, intracranial hemorrhage; TA, tranexamic acid; FFP, fresh frozen plasma; PCC, prothrombin complex concentra.

Table 2. Results for FXI, FV, FV+FVIII, and FXIII deficiencies

	Factor XI deficiency		Factor V deficiency		Combined factor V and VIII deficiency		Factor XIII deficiency	
	Type of response	% of response	Type of response	% of response	Type of response	% of response	Type of response	% of response
What is the factor plasma level to define a severe defect?	a) <1% b) <10% c) <20% d) I don't know	63.1 22.2 16.6 0.0	a) <5% b) <10% c) <20% d) I don't know	43.0 26.0 26.0 5.0	a) <10% for both b)<5% FVIII + <10% FV c)<5% FV + <10% FVIII d) I don't know	21.0 58.0 21.0 0.0	a) <5% b) <10% c) <20% d) I don't know	84.3 15.7 0.0 0.0
Do you think that subjects with severe defects are at risk of spontaneous ICH?	a) Yes, at all ages b) Only neonatal c) I don't know	33.3 11.1 55.5	a) Yes, at all ages b) Only neonatal c) I don't know	64.0 10.0 26.0	a) Yes, at all ages b) Only neonatal c) I don't know	42.0 16.0 42.0	a) Yes, at all ages b) Only neonatal c) I don't know	79.1 15.7 0.0
Which laboratory tests are needed for diagnosis?	a) PT, aPTT b) PT, aPTT, assay of FXI activity and FXI antigen c) PT, aPTT, assay of FXI activity d) I don't know	0.0 22.2 77.8 0.0	a) PT, aPTT b) PT, aPTT, assay of FV activity (and FV antigen) c) PT, aPTT, assay of FV and FVIII activity d) I don't know	0.0 26.0 65.0 5.0	a) PT, aPTT b) PT, aPTT, assay of FVIII and FV activity c) PT, aPTT, assay of FVIII and FV activity and antigen d) I don't know	0.0 48.0 48.0 4.0	a) PT, aPTT b) PT, aPTT, assay of FXIII activity and FXIII antigen c) PT, aPTT, assay of FXIII activity d) I don't know	0.0 63.1 36.9 0.0
Is genetic testing necessary to diagnose the coagulation factor defect?	a) Yes b) No c) I don't know	33.3 38.9 27.8	a) Yes b) No c) I don't know	48.0 26.0 26.0	a) Yes b) No c) I don't know	53.0 26.0 21.0	a) Yes b) No c) I don't know	47.4 21.0 31.6
What do you consider to be the required plasma levels of coagulation factor for exemption?	a) <20% b) <40% c) I don't know	50.0 50.0 0.0	a) <20% b) <40% c) I don't know	58.0 37.0 5.0	a) <20% for both b) <40%for both c) I don't know	27.0 63.0 10.0	a) <20% b) <30% c) I don't know	21.0 68.5 10.5
What coagulation factor plasma levels are required to manageminor surgery /mild bleeding?	a)>10% b)>30% c) I don't know	22.2 55.6 22.2	a)>20% b)>40% c) I don't know	63.0 32.0 5.0	a)>10% for both b)>30% for both c) I don't know	10.0 74.0 16.0	a)>10% b)>30% c) I don't know	63.2 26.3 10.5
In the management of invasive dental procedures, what coagulation factor requires post-operative prophylaxis with TA?	a) <10% b) <35% c) I don't know	22.2 72.2 5.6	a) <10% b) <30% c) I don't know	16.0 68.0 16.0	a) <20% for both b) <30% for both c) I don't know	21.0 64.0 15.0	a) <10% b) <25% c) I don't know	42.1 47.4 10.5
What coagulation factor plasma levels are required to manage major surgery or severe bleeding?	a)>20% b)>35% c) >50% d) I don't know	11.1 33.3 55.6 0.0	a)>20% b)>40% c) >60% d) I don't know	26.0 48.0 21.0 5.0	a)>30% for both b)>50% for both c) >60% for both d) I don't know	16.0 53.0 26.0 5.0	a)>20% b)>35% c) >50% d) I don't know	15.5 58.1 26.4 0.0
What coagulation factor plasma levels confer a bleeding risk that suggests prophylaxis?	a) <1% b) <20% c) I don't know	38.9 5.5 55.6	a) <10% b) <30% c) I don't know	64.0 5.0 31.0	a) <10% for both b) <20% for both c) I don't know	53.0 16.0 31.0	a) <5% b) <20% c) I don't know	73.8 10.5 15.7
What coagulation factor plasma levels are required during pregnancy?	a)>10% b)>25% c) >40% d) I don't know	38.9 33.3 27.8 0.0	a)>20% b)>30% c) >50% d) I don't know	53.0 21.0 21.0 5.0	a)>20% for both b)>30% for both c) >40% for both d) I don't know	32.0 32.0 32.0 4.0	a)>10% b)>25% c) >40% d) I don't know	21.0 63.2 15.8 0.0
What coagulation factor plasma levels are required for vaginal delivery?	a) >20% b) >50% c) I don't know	44.5 33.3 22.2	a) >20% b) >50% c) I don't know	53.0 32.0 15.0	a) >20% for both b) >50% for both c) I don't know	26.3 47.4 26.3	a) >20% b) >50% c) I don't know	42.1 42.1 15.8

To be continued on next page

Table 2. Continued from previous page.

	Factor XI deficiency		Factor V deficiency		Combined factor V and VIII deficiency		Factor XIII deficiency	
	Type of response	% of response	Type of response	% of response	Type of response	% of response	Type of response	% of response
What coagulation factor plasma levels are required for surgical delivery?	a) >20% b) >50% c) I don't know	16.6 66.8 16.6	a) >20% b) >50% c) I don't know	32.0 53.0 15.0	a) >20% for both b) >50% for both c) I don't know	5.3 68.4 26.3	a) >20% b) >50% c) I don't know	15.8 73.7 10.5
What coagulation factor plasma levels can justify the presence of menorrhagia in affected women?	a) <5% b) <20% c) <40% d) I don't know	27.8 50.0 22.2 0.0	a) <10% b) <30% c) <50% d) I don't know	42 53 0 5	a) <10% for both b) <20% for both c) <40% for both d) I don't know	26.3 47.4 21.0 5.3	a) <1% b) <20% c) <40% d) I don't know	36.8 52.7 10.5 0.0
What plasma coagulation factor level range is normal in the first 6 months of life?	a) 20-70% b) 40-95% c) 50-130% d) I don't know	55.6 27.8 16.6 0.0	a) 20-70% b) 30-95% c) 50-100% d) I don't know	37.0 32.0 21.0 10.0	a) 40-70% for both b) 50-120% for both c) 50-150% for both d) I don't know	42.1 36.8 21.1 0.0	a) 10-70% b) 40-95% c) 60-120% d) I don't know	42.1 36.8 15.8 5.3
What coagulation factor plasma levels in newborn confer a bleeding risk that suggests prophylaxis?	a) <1% b) <20% c) I don't know	44.5 5.5 50.0	a) <1% b) <25% c) I don't know	58.0 10.0 32.0	a) <1% for both b) <20% for both c) I dont' know	47.4 15.8 36.8	a) <1% b) <25% c) I don't know	68.5 10.5 21.0
Which of the following therapies are useful in the management of coagulation factor deficiency?	a) FFP, TA b) FXI concentrate, TA c) TA d) I don't know	38.9 55.6 5.5 0.0	a) FFP b) FFP, Plt T c) FFP, Plt T, TA d) I don't know	26.0 5.0 64.0 5.0	a) FFP, DSP/FVIII C b) FFP, Plt T, DSP/FVIII C c) TA d) I don't know	36.8 57.9 0.0 5.3	a) FFP b) FXIII C, TA c) FFP, TA d) I don't know	0.0 100.0 0.0 0.0
Is it possible the development of inhibitors following treatment with coagulation factor concentrate?	a) Yes b) No c) I don't know	66.7 11.1 22.2	a) Yes b) No c) I don't know	58 5 37	a) Yes b) No c) I don't know	31.6 10.5 57.9	a) Yes b) No c) I don't know	57.9 26.3 15.8

PT, prothrombin time; aPTT, activated partial thromboplastin time; ICH, intracranial hemorrhage; TA, tranexamic acid; TA, tranexamic acid; Plt T, platelet transfusion; DSP, Desmopressin; FVIII C, FVIII concentrate; FXIII C, FXIII concentrate; FFP, fresh frozen plasma.

Discussion

This comprehensive survey of 19 Italian HTCs provides a valuable snapshot of the current diagnostic and management approaches for a spectrum of rare coagulation factor deficiencies within the national healthcare network. The results highlight areas of consensus as well as notable variability in clinical practice across different coagulation defects, underscoring the complexities in managing these RBDs.

Definition of severity and risk of spontaneous ICH: The definition of severe deficiency showed variability across factors, with thresholds differing for FV and FXI. In contrast, a greater alignment was observed for FII, FVII, FX, and FXIII. The perceived risk of spontaneous ICH also varied. While a strong belief in this risk across all ages in severe FXIII, FVII, and FX defects was evident, uncertainty or a perception of risk limited to the neonatal period was noted for FII, FV, and FXI. This heterogeneity underscores the need for more detailed natural history studies and collaborative data collection to better define the true risk of this devastating complication in different RBDs and across age groups.

Diagnostic approaches: The diagnostic workup involved a tiered approach, starting with basic screening tests (PT, aPTT) followed by specific factor activity assays. The inclusion of antigen testing varied, suggesting differing perceptions on its clinical utility depending on the factor. Notably, a considerable proportion of HTCs routinely assessed other related coagulation factors (e.g., vitamin K-dependent factors in FII and FVII deficiency), indicating a cautious approach to exclude broader coagulopathies, congenital or acquired. The necessity of genetic testing also showed variability, reflecting the heterogeneity of these disorders and the perceived clinical utility of genetic information beyond diagnostic confirmation.

Threshold level of coagulation factor for rare disease exemption: The thresholds identified for rare disease exemption eligibility exhibited variability for FII and FV deficiency, potentially impacting patient access to resources and specialized care. A more harmonized national approach to defining these criteria for RBDs would ensure equitable access.

Target hemostatic levels for surgical procedures: Target hemostatic levels for minor and major surgery showed significant variation across all factor deficiencies surveyed, suggesting a lack

of definitive evidence-based guidelines and a strong reliance on individual center experience. While a general trend towards higher target levels for more invasive procedures was evident, the wide range of responses highlights the urgent need for prospective studies to establish optimal perioperative management strategies and minimize bleeding risks in these rare patient populations.

Prophylactic strategies: The use of prophylaxis varied considerably. While routine prophylaxis was favored for severe FXIII deficiency and a substantial proportion of severe FII, FV, FVII and FX deficiency, a more selective approach was evident for FXI, reflecting its more variable bleeding phenotypes. The triggers for prophylaxis initiation (based on factor levels) also showed divergence, highlighting the need for further research to identify individuals who would benefit most from this preventative strategy across different rare bleeding disorders.

Treatment modalities: The mainstay of treatment involved factor-specific concentrates when available (FX, FXI, FXIII, and FVII). For the treatment of FVII deficiency, Italian HTCs have two therapeutic options: plasma-derived FVII (pd-FVII) concentrate and recombinant activated FVII (r-FVIIa) concentrate. Both therapies share the challenge of a short plasma half-life, necessitating frequent dosing for effective hemostasis. The clinical choice between them reflects differences in their mechanism and origin: pd-FVII concentrate offers direct factor replacement, aiming to restore functional plasma levels. Conversely, r-FVIIa functions as a bypass agent, rapidly promoting thrombin generation. The latter is often favored in international protocols due to its recombinant origin, which avoids potential pathogen transmission risk. Both agents are effective for treating bleeds and perioperative prophylaxis, as confirmed by their respective Italian Summary of Product Characteristics (SmPCs). However, the FVII concentrate selection must be carefully individualized based on the patient's bleeding severity, the specific clinical setting, and their underlying thrombotic risk profile.

Fresh frozen plasma (FFP) played a more significant role in FV and combined FV+FVIII deficiency, due to the limited availability of specific concentrates while prothrombin complex concentrate (PCC) has a role in FII defect. The use of tranexamic acid (TA) for mucocutaneous bleeding (e.g., in dental procedures and menorrhagia), was a common adjunctive therapy across various deficiencies. The awareness of potential inhibitor development, although perceived as relatively uncommon for some factors (e.g., FVII), was acknowledged across the spectrum of deficiencies, necessitating long-term monitoring.[13-16]

Management in specific clinical scenarios: The management of bleeding during dental procedures, pregnancy, and delivery also revealed variability in target factor levels and the use of adjunctive therapies. These findings underscore the need for specific guidelines tailored to these clinical situations in the context of rare bleeding disorders, often based on limited available evidence. The reported normal ranges of factor levels in neonates/infants also showed some variation, emphasizing the importance of establishing age-specific reference ranges for accurate diagnosis and management in this vulnerable population.

The findings highlight six key areas requiring further attention:

Standardization of definitions: Establishing universally accepted definitions of severity for each rare coagulation factor deficiency is crucial for consistent patient classification and management decisions.

Evidence-based guidelines: There is an urgent need for further research, including prospective studies and international collaborations, to generate high-quality evidence that can inform the development of evidence-based national and international guidelines for diagnosis and treatment across all clinical scenarios.

Risk stratification: More research is needed to better define the risk of spontaneous bleeding, particularly life-threatening events like ICH or gastrointestinal bleeding in different RBDs and to identify specific risk factors.

Optimization of prophylaxis: Prospective studies are warranted to identify individuals who would benefit most from prophylactic treatment and to establish clinical situations, optimal initiation thresholds, and regimens for different factor deficiencies.

Harmonization of administrative criteria: Efforts to harmonize national criteria for rare disease exemption eligibility would ensure equitable access to specialized care and resources for all affected individuals.

Age-specific management: Further studies are needed to establish age-specific reference ranges for coagulation factors and to optimize management strategies in neonates, infants, and pregnant women with RBDs. This observed heterogeneity underscores the urgent need for more research, including large-scale collaborative studies and prospective investigations, to generate robust clinical evidence that can inform best practices. The development and implementation of evidence-based national guidelines, and in some cases international guidelines (particularly for ultra-rare conditions), are crucial to standardize diagnostic and therapeutic approaches and optimize the care and outcomes for individuals with these RBDs in Italy.

Limitations of the study

As a questionnaire-based survey, the present study has obvious inherent methodological limitations, such as potential self-reporting bias and recall bias, which might influence the respondents' perception of clinical practice. Furthermore, our sampling was limited to Centers belonging to the AICE network (Italian Association of Hemophilia and Thrombosis Centers). Although this approach technically excludes other facilities, it is crucial to recognize that AICE Centers constitute the primary focal point and national reference network for the long-term management and consultation regarding RBDs in Italy. Therefore, while not 100% exhaustive, the sample represents the best and most reliable mapping of specialist clinical practice in the country. However, these limitations are acceptable and often unavoidable in the field of rare diseases. Due to the low prevalence of congenital coagulation factor disorders, it is extremely difficult to conduct larger studies, such as randomized controlled trials or observational studies with significant sample sizes. For this reason, surveys like ours are particularly important in this context, as they document real-world clinical practice. Our findings, by mapping areas of consensus and high heterogeneity, provide a solid foundation for future standardization efforts, which are essential in a field where both national and international guidelines remain scarce and largely based on expert consensus.

Conclusions

In conclusion, this comprehensive national survey provides a multi-faceted overview of the current management strategies for a spectrum of rare coagulation factor deficiencies – FV, FII, FVII, FX, FXI, FXIII (subunit A), combined FV+FVIII deficiency, – across Italian HCTs.

Our findings reveal a variable landscape of clinical practice. For certain deficiencies, such as FII, FVII, FX, and FXIII, a good degree of consensus exists, particularly in fundamental aspects of diagnosis and treatment. However, significant heterogeneity persists across several key domains, including the definition of disease severity, diagnostic approaches (particularly for FVII and FX), and the establishment of target hemostatic levels for various clinical scenarios, including surgical procedures and bleeding episodes. Furthermore, the role and implementation of prophylactic treatment strategies demonstrate considerable variability across different factor deficiencies and even within specific disorders like FV deficiency. The management of the ultra-rare combined FV+FVIII deficiency was notably characterized by significant heterogeneity, underscoring the challenges posed by the limited clinical evidence for such conditions. The management of FXI deficiency also demonstrated a less uniform approach, potentially attributable to its milder and more variable bleeding phenotype. This observed heterogeneity highlights the challenges inherent in managing these rare conditions, often in the absence of robust, high-level evidence.

The data presented in this survey serve as a valuable resource, providing a comprehensive snapshot of current clinical practices and highlighting specific areas where standardization and further investigation are warranted. These findings can form a critical foundation for future initiatives aimed at improving the management of these rare coagulation factor deficiencies within the Italian healthcare system and beyond.

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Online supplementary material:

Appendix: List of Contributing centers.