Diagnostic and management practices for inherited fibrinogen disorders: a nationwide survey of Italian Hemophilia Treatment Centers

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ABSTRACT

Background: inherited fibrinogen disorders are characterized by a spectrum of quantitative or qualitative fibrinogen deficiency associated with both a haemorragic and thrombotic risk.

Methods: A nationwide survey was conducted in 19 Italian Hemophilia Treatment Centers in order to investigate current diagnostic and management practices for inherited fibrinogen disorders (afibrinogenemia, hypofibrinogenemia, and dysfibrinogenemia).

Results: the survey revealed a strong consensus (95% of centers) on the necessity of both functional and antigenic fibrinogen assays for diagnosis, and a preference for fibrinogen concentrate-based treatment (used by >85% of centers). However, significant heterogeneity was observed in critical areas: for hypofibrinogenemia, the definition of a «severe» form varied among centers, and the perceived risk of spontaneous intracranial hemorrhage remained a major point of uncertainty (up to 47% of respondents answered 'don't know' for this risk in hypofibrinogenemia and dysfibrinogenemia). Furthermore, intervention thresholds for major surgical procedures showed a high degree of variability across all three disorders.

Conclusions: the findings highlight areas of consistent practice alongside those requiring further standardization and collaborative research to optimize the care of individuals with these rare bleeding and thrombotic conditions.

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Introduction

Inherited fibrinogen disorders, encompassing quantitative deficiencies (afibrinogenemia/ hypofibrinogenemia) and qualitative defects (dysfibrinogenemia/hypo-dysfibrinogenemia), are rare congenital conditions primarily associated with bleeding, though thrombotic events may occasionally occur.[1-7] Afibrinogenemia is characterized by severely reduced or absent fibrinogen levels, often leading to a significant bleeding diathesis and in some cases to arterial and venous thrombosis, regardless of the replacement therapy.[8] Hypofibrinogenemia involves a proportional decrease of both activity and antigen fibrinogen concentration with a more variable bleeding phenotype well correlated with fibrinogen levels.[9] Dysfibrinogenemia is defined by the presence of a dysfunctional fibrinogen molecule, resulting in a discrepancy between antigenic and functional levels, and can be associated with both bleeding and thrombotic risks.[10,11] Hypodysfibrinogenemia is characterized by reduced antigen levels associated with disproportionately low functional activity.[12]

Due to the rarity and heterogeneity of these conditions, comprehensive data on current clinical practices is limited. Understanding the approaches employed by specialized haemophilia treatment centers (HTCs) is crucial for identifying areas of consensus and variability, which can inform the development of standardized recommendations and improve patient care. This study aimed to provide a national overview regarding the diagnostic and management strategies for inherited fibrinogen disorders adopted by Italian HTCs. A nationwide survey was conducted to gather detailed information on the definition of these disorders, diagnostic approaches, target hemostatic levels for various clinical scenarios, the use of prophylactic treatment, and preferred therapeutic options. The results of this survey offer valuable insights into the current clinical landscape and highlight areas where further research and harmonization of practices may be beneficial.

Materials and Methods

The information presented in this research was gathered via a nationwide survey administered to 43 HTCs members of the Italian Association of Hemophilia Centers (AICE). This survey encompassed rare coagulation factor deficiencies, with the results being reported in two distinct publications: one focusing on fibrinogen disorders and another on other rare coagulation factor deficiencies.

The survey consisted of a few initial questions on the experience in the management of people with rare bleeding disorders (RBDs) and diagnostic approaches in different HTCs, followed by the investigation of 17 specific items in each RBDs.

The following different aspects in fibrinogen, factor (FII, FVII, FX, FV, FV+FVIII, FXI and FXIII) deficiencies were investigated:

- the coagulation factor 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 coagulation factor threshold 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.

All the survey questions were closed-ended; the levels of the factors related to the responses were indicated by the members of the AICE Scientific Committee and Guidelines Working Group based on the literature and each person's clinical experience.

This article describes the results for inherited fibrinogen deficiency.

Results

Responses were received from 19 out 43 distinct HTCs, offering valuable data concerning their patient characteristics, professional background, and the services they offer.

Concerning the patient groups overseen by these centers, the predominant share (84.2%, n=16) indicated they manage individuals with inherited bleeding disorders spanning all age ranges. A smaller segment of centers focused on either pediatric patient management (5.3%, n=1) or primarily attended to adult patients (10.5%, n=2).

The level of expertise among the participating centers in the management of congenital bleeding disorders showed variation. Roughly half of the centers (47.4%, n=9) possessed between 5 and 20 years of experience, while the other half (52.6%, n=10) reported an experience level exceeding 20 years in this area. It is worth noting that no participating center reported having less than 5 years of experience.

All participating centers (100%, n=19) confirmed that they offer consultative services to other departments within their respective institutions or to external healthcare facilities for individuals with congenital bleeding disorders. This underscores the significant role that these specialized Hcts play in supporting the wider healthcare system.

Moreover, all 19 responding centers (100%) stated they had experience in the care of patients with rare bleeding disorders undergoing prophylactic treatment. This implies a widespread familiarity with this crucial aspect of management for individuals affected by these conditions.

While this publication focuses on inherited fibrinogen disorders, the initial section of the survey included general questions about the diagnostic strategies used for rare congenital bleeding disorders (*Table S1*).

Firstly, a unanimous agreement (100%, n=19 of participating centers) was observed regarding the limitations of standard screening assays, such as prothrombin time (PT), activated partial thromboplastin time (aPTT), and fibrinogen levels, in definitively excluding a mild deficiency of coagulation factors. This shared perspective emphasizes the importance of employing more specialized diagnostic tools when clinical suspicion of a bleeding disorder arises, even in the context of normal initial screening results.

Secondly, insights were gathered concerning the perceived necessity of assessing both antigenic levels and functional activity in the diagnostic process for coagulation factor defects. While a minority of centers (10.5%, n=2) advocated for the routine determination of both parameters, the majority (73.7%, n=14) indicated that antigenic level assessment is required in specific situations. These situations were identified as cases involving functional protein abnormalities or instances where a poor correlation exists between the severity of laboratory findings and the clinical presentation, particularly relevant in fibrinogen-related disorders. A small fraction of centers (10.5%, n=2) did not consider antigenic level determination necessary, and one center (5.3%) expressed uncertainty. This suggests a general recognition of the supplementary value of antigenic testing in particular diagnostic scenarios.

Finally, the survey explored the strategies for risk stratification in individuals with confirmed congenital bleeding disorder. Most centers (84.2%, n=16) deemed it appropriate to investigate

the potential co-occurrence of other hemostatic abnormalities, such as von Willebrand disease (vWD) or platelet function disorders, to achieve a comprehensive understanding of the hemorrhagic risk profile. A smaller number of centers (15.8%, n=3) did not consider this necessary, and no center expressed uncertainty. This underscores the prevalent view that a thorough evaluation of bleeding risk in patients with known congenital bleeding disorders should encompass the consideration of other potential contributing factors.

The specific responses pertaining to afibrinogenemia, hypofibrinogenemia and dysfibrinogenemia are detailed in Table 1. The data gathered on these specific defects provides a more detailed understanding of the current practices within the national network of HTCs concerning these conditions.

Table 1. Responses expressed as percentage from 19 participating hemophilia treatment centers.

	Afibrinogenemia		Hypofibrinogenemia		Dysfibrinogenemia	
What Fbg level do you think allows us to define a patient with a severe form?	a) <10 mg/dL	84%	a) <80 mg/dL	36%	a) Fbg antigen normal, Fbg activity <150 mg/dL	53%
	b) <20 mg/dL	5%	b) <100 mg/dL	32%	b) Fbg antigen normal, Fbg activity <50 mg/dL	42%
	c) <50 mg/dL	11%	c) <150 mg/dL	32%	c) I don't know	5%
Do you think that subjects with a severe Fbg deficiency are at risk of spontaneous cerebral hemorrhage?	a) Yes, at all ages	95%	a) Yes, at all ages	32%	a) Yes, at all ages	32%
	b) Only neonatal	5%	b) Only neonatal	21%	b) Only neonatal	47%
	c) I don't know	0%	c) I don't know	47%	c) I don't know	21%
What tests do you think are necessary for the diagnosis of Fbg deficiency?	a) PT, aPTT	0%	a) PT, aPTT	0%	a) PT, aPTT	0%
	b) PT, aPTT, Fbg activity dosage	0%	b) PT, aPTT, Fbg activity dosage	0%	b) PT, aPTT, Fbg activity dosage	0%
	c) PT, aPTT, Fbg activity and antigen dosage	100%	c) PT, aPTT, Fbg activity and antigen dosage	100%	c) PT, aPTT, Fbg activity and antigen dosage	100%
Do you think genetic testing is necessary to define the diagnosis of Fbg deficiency?	a) Yes	79%	a) Yes	74%	a) Yes	69%
	b) No	0%	b) No	0%	b) No	5%
	c) I don't know	21%	c) I don't know	26%	c) I don't know	26%
What are the levels of haemostatic safety that you believe is necessary to achieve during minor surgery or minor bleeding in subjects with Fbg deficiency?	a) > 50 mg/dL	58%	a) >80 mg/dL	68%	a) > 80 mg/dL	63%
	b) >100 mg/dL	42%	b) >150 mg/dL	11%	b) >150 mg/dL	11%
	c) I don't know	0%	c) I don't know	21%	c) I don't know	26%
In the case of invasive dental procedures, what are the Fbg levels for which you believe it is necessary to use post-procedure prophylaxis with tranexamic acid?	a) < 50 mg/dL	42%	a) < 80 mg/dL	63%	a) <80 mg/dL	58%
	b) < 100 mg/dL	58%	b) <150 mg/dL	26%	b) <150 mg/dL	16%
	c) I don't know	0%	c) I don't know	11%	c) I don't know	26%
What are the levels of haemostatic safety that you believe is necessary to achieve during major surgery or major bleeding in subjects with Fbg deficiency?	a) >50 mg/dL	42%	a) > 80 mg/dL	0%	a) >80 mg/dL	0%
	b) >100 mg/dL	58%	b) >100 mg/dL	42%	b) >100 mg/dL	53%
	c) > 150 mg/dL	0%	c) >150 mg/dL	58%	c) >150 mg/dL	47%

To be continued on next page

Table 1. Continued from previous page.

	Afibrinogenemia		Hypofibrinogenemia		Dysfibrinogenemia	
Do you think it is necessary to start prophylaxis in all subjects affected by fibrinogen deficiency?	a) Yes	58%	a) Yes	0%	a) Yes	11%
	b) No	26%	b) No	89%	b) No	78%
	c) I don't know	16%	c) I don't know	11%	c) I don't know	11%
What do you think are the safety Fbg levels during pregnancy?	a) >50 mg/dL	42%	a) > 50 mg/dL	26%	a) > 50 mg/dL	21%
	b) >150 mg/dL	53%	b) >150 mg/dL	69%	b) >150 mg/dL	74%
	c) >200 mg/dL	5%	c) > 200 mg/dL	5%	c) >200 mg/dL	5%
What do you think are the safety factor levels during vaginal delivery?	a) > 80 mg/dL	26%	a) > 80 mg/dL	21%	a)>80 mg/dL	16%
	b) > 150 mg/dL	58%	b) >150 mg/dL	74%	b) >150 mg/dL	79%
	c) > 200 mg/dL	11%	c) >200 mg/dL	5%	c) >200 mg/dL	5%
	d) I don't know	5%				
What do you think are the safety Fbg levels during surgical delivery?	a) > 80 mg/dL	16%	a) > 80 mg/dL	5%	a) >80 mg/dL	5%
	b) >150 mg/dL	68%	b) >150 mg/dL	79%	b) >150 mg/dL	84%
	c) > 200 mg/dL	16%	c) > 200 mg/dL	16%	c) > 200 mg/dL	11%
What do you think are the Fbg levels below which heavy menstrual bleeding is expected?	a) <50 mg/dL	68%	a) <80 mg/dL	74%	a) <80 mg/dL	84%
	b) <80 mg/dL	16%	b) <100 mg/dL	21%	b) <100 mg/dL	11%
	c) <100 mg/dL	16%	c) < 150 mg/dL	5%	c) < 150 mg/dL	5%
What is the range of Fbg levels that you consider normal in newborns/infants between 0 and 6 months of age?	a) 80-150mg/dL	47.5%				
	b) 100-300 mg/dL	47.5%				
	c) 80-250 mg/dL	5%				
Which of the following therapies do you consider useful in the treatment of Fbg deficiency?	a) FFP	0%	a) FFP	0%	a) FFP	0%
	b) Fbg concentrate, TA	74%	b) Fbg concentrate, TA	95%	b) Fbg concentrate, antifibrinolytics	16%
	c) Fbg concentrate	26%	c) Fbg concentrate	5%	c) FBg concentrate, TA, LMWH (case by case)	84%
Do you think it is possible the development of inhibitors during treatment of factor deficiency?	a) Yes	32%	a) Yes	11%	a) Yes	11%
	b) No	26%	b) No	42%	b) No	47%
	c) I don't know	42%	c) I don't know	47%	c) I don't know	42%

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

Discussion

This comprehensive survey of 19 Italian HTCs provides a valuable comparative insight into the current clinical practices for managing the spectrum of inherited fibrinogen disorders, including afibrinogenemia, hypofibrinogenemia, and dysfibrinogenemia. Our survey provides valuable real-world practice information that must be compared with the data of the literature currently available concerning the classification and the management of these disorders.[13-15] The results reveal both areas of consensus and notable variations in approach, reflecting the differing severities and complexities of these rare bleeding and thrombotic disorders.

Afibrinogenemia: the management of afibrinogenemia demonstrated the highest degree of uniformity. The near-universal agreement on the definition of severe deficiency (<10 mg/dl), the perceived high risk of spontaneous ICH, and the unanimous preference for fibrinogen concentrate-based treatment highlight a well-established and aggressive approach to this severe condition. The majority also favored routine long-term prophylaxis, underscoring the need for continuous hemostatic support.

Hypofibrinogenemia: in contrast, the management of hypofibrinogenemia exhibited greater heterogeneity. The lack of a consistent definition and the uncertainty surrounding the risk of spontaneous ICH likely reflect the broader clinical spectrum associated with varying levels of reduced fibrinogen. While fibrinogen concentrate remained the preferred treatment, the threshold for intervention in surgical settings and the necessity of routine prophylaxis were less clearly defined, suggesting a more individualized, often event-driven approach.

Dysfibrinogenemia: the management of dysfibrinogenemia also showed a generally consistent approach, particularly in the diagnostic requirement of both functional and antigenic fibrinogen assays. The preference for fibrinogen concentrates, often combined with tranexamic acid and, in selected cases, low molecular weight heparin (LMWH), reflects the dual potential for bleeding and thrombosis in this qualitative disorder.[11] However, the variability in defining the functional fibrinogen threshold for clinical significance and the uncertainty regarding ICH risk indicate areas needing further clarification.

Several key themes emerged from the comparison across these three fibrinogen disorders. Firstly, the severity of the deficiency correlated with the intensity and uniformity of the management approach. Afibrinogenemia, the most severe form, elicited the most consistent and proactive strategies. Secondly, fibrinogen concentrate was overwhelmingly the preferred treatment across all three disorders, highlighting its efficacy and safety compared to fresh frozen plasma. Thirdly, the role of genetic investigation was consistently recognized as important for diagnosis and understanding the underlying pathophysiology.

Pregnancy in patients with fibrinogen disorders is highly challenging, due to the increased risk of bleeding, thrombosis and obstetric complications.[16,17] Regarding target fibrinogen levels in pregnant women, the data highlights the varying target hemostatic fibrinogen levels adopted by different HTCs for managing pregnant women with congenital fibrinogen disorders. Across afibrinogenemia, hypofibrinogenemia, and dysfibrinogenemia, there is a strong preference among most centers to maintain fibrinogen levels above 150 mg/dL both throughout pregnancy and delivery, regardless of the delivery method. This target appears to be considered crucial across all three types of disorders and for both vaginal and surgical deliveries. The preference for higher targets (above 150 mg/dL, and sometimes above 200 mg/dL) becomes even more pronounced during surgical deliveries, likely due to the increased risk of bleeding. The variability in targets among centers, particularly the lower thresholds, suggests a need for further standardized guidelines to optimize patient outcomes.

Despite the overall coherence, areas of variability warrant further attention. The inconsistent definitions of severe hypofibrinogenemia, as well as the different thresholds reported for intervention in surgical and dental procedures across all three disorders could be expression of a simple clinical perception by treaters who do not frequently deal with this rare disorder. In particular, our survey found a notable inconsistency in the terminology and thresholds used by Italian centers to define "severe deficiency" of fibrinogen, a finding that is itself a fundamental result of our study.To contextualize this variability, it is crucial to refer to the classification established by the International Society of Haemostasis and Thrombosis (ISTH) Subcommittee on Factor XIII and Fibrinogen, which defines severe hypofibrinogenemia as a functional fibrinogen level below 0.5 g/L.[13] The critical gap we have documented lies in the fact that, while the ISTH classification provides a clear quantitative threshold, our survey responses indicate that a significant percentage of centers still operate using less uniform definitions or different thresholds. This non-adherence to the established definition (or the use of lower/higher thresholds to justify prophylaxis) highlights how the translation of international consensus into everyday clinical practice remains heterogeneous. Therefore, the inconsistency in terminology is further evidence supporting our conclusion about the urgent need for national guidelines to ensure diagnostic and therapeutic uniformity in Italy.

The perception of ICH risk is, furthermore, another critical point illustrating the knowledge gaps in the natural history of inherited fibrinogen disorders. The high rate of "I don't know" responses (up to 47%) regarding ICH risk in patients with hypofibrinogenemia and dysfibrinogenemia is particularly concerning. This elevated level of clinical uncertainty indicates that there are insufficient epidemiological data or validated risk assessment tools to allow clinicians to formulate an accurate and homogeneous estimate. To bridge this gap, we once again advocate for the urgent need for prospective and longitudinal studies and the establishment of dedicated national registries that can more precisely define the incidence of ICH and other severe bleeding events, thereby supporting more uniform and risk-based prophylaxis strategies in Italy.

Another critical issue that emerged from the survey is the variability in responses regarding safe threshold levels of fibrinogen during surgery, especially major surgery. These results once again highlight a deviation of our clinical practice from what is suggested by current recommendations, namely maintaining fibrinogen levels above 150 mg/dL to ensure effective hemostasis in this clinical setting.[14-15]

Finally, a noteworthy observation arising from the survey is the consideration by some centers of the potential formation of inhibitors during replacement therapy. Although the development of alloantibodies against exogenous fibrinogen is an extremely rare event in congenital fibrinogen disorders, unlike in other coagulopathies such as hemophilia, the perception of this risk by some clinicians suggests a high degree of caution in the management of rare diseases. This finding may reflect the lack of standardized monitoring protocols for inhibitor risk in this specific context, highlighting another area where harmonization of clinical and laboratory practices would be beneficial.

Despite the value of the data collected, the present study has certain limitations inherent to questionnaire-based surveys. First, we must consider the potential self-reporting bias and recall bias, as the responses reflect the subjective perception of clinical practice and the past experiences of the professionals. Furthermore, our sampling was limited exclusively to medical specialists affiliated with AICE. Although this approach could technically exclude non-adherent institutions, it must be emphasized that, within the context of the National Health Service, AICE Centers

are universally recognized as the specialist reference network for the management, diagnosis, and long-term treatment of rare bleeding disorders. It is established practice that consultation for the management of these conditions, even when the patient is hospitalized in non-hematological settings, is requested from these centers. Therefore, while sporadic cases of patients, particularly those not yet diagnosed, may fall outside the AICE circuit, we believe the interviewed sample represents the best and most comprehensive snapshot of Italian specialist clinical practice, conferring solid internal validity to our results in the context of rare coagulopathies.

The findings of this survey underscore the importance of continued research into genotype-phenotype correlations and the optimal management strategies for inherited fibrinogen disorders. Prospective studies evaluating the efficacy of prophylactic regimens in hypofibrinogenemia and dysfibrinogenemia, as well as further investigation into the thrombotic risk associated with specific dysfibrinogenemia variants, are warranted. The development of evidence-based recommendations, informed by collaborative studies and registry data, could help to harmonize clinical practices and improve outcomes for individuals with these rare and complex disorders.

Conclusions

This nationwide survey provides a crucial snapshot of clinical practice for inherited fibrinogen disorders in Italian HTCs. We found strong consistency in diagnostic work-up and in treatment options, but the study also reveals significant heterogeneity. Variability was notable in the definition of hypofibrinogenemia, the hemostatic thresholds for surgical procedures, and the perception of spontaneous ICH risk in hypofibrinogenemia and dysfibrinogenemia, where uncertainty was high. This individualized approach for less severe forms contrasts with the more uniform management of afibrinogenemia. In conclusion, while a foundation of consensus exists, the identified variability underscores an urgent need for standardized national guidelines. Further collaborative, evidence-based research is essential to refine clinical definitions, reduce uncertainty regarding risk profiles, and ultimately optimize and harmonize care for patients with inherited fibrinogen disorders.

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Online supplementary material:

Table S1. Survey responses from the 19 participating centres.
Appendix 1. List of contributing centres.