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Variables Affecting Periprocedural Haemostatic Response in Patients With Haemophilia: Real-World Retrospective Study

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ABSTRACT

Introduction: Patients with haemophilia (PWH) undergoing invasive procedures are at increased risk of periprocedural bleeding, and optimal haemostatic response (HR) depends on patient- and procedure-related factors. We aimed to evaluate variables associated with HR in PWH undergoing invasive procedures.

Methods: We performed a retrospective, single-centre study of all invasive procedures in males with haemophilia A or B recorded in a regional reference centre database (2010–2025). Data from electronic records included age, body weight, haemophilia type and severity, inhibitor status, prophylaxis regimen and haemostatic product, pre-procedural haemostatic preparation, genetic mutation (when available) and procedure characteristics. HR was assessed using World Federation of Haemophilia criteria and dichotomised as good/excellent versus fair/poor. Categorical comparisons were performed using Fisher's exact test or Fisher–Freeman–Halton exact tests. Continuous sensitivity analyses were also performed.

Results: Overall, 158 procedures were performed in 61 patients. HR was good/excellent in 151/158 procedures (95.6%) and fair/poor in 7/158 (4.4%). Fair/poor HR occurred in 3/11 procedures (27.3%) in patients weighing >100 kg, compared with 1/87 (1.1%) in those weighing 61–100 kg and 2/51 (3.9%) in those ≤ 60 kg (exact $p = 0.003$). Major procedures showed a higher proportion of fair/poor HR than minor procedures, although this difference did not reach statistical significance (4/38 [10.5%] vs. 3/120 [2.5%]; Fisher $p = 0.058$).

Conclusion: High body weight may be associated with suboptimal HR in PWH undergoing invasive procedures, supporting targeted strategies to address overweight and obesity.

Trial Registration: The authors have confirmed clinical trial registration is not needed for this submission.

1 | Introduction

Haemophilia A (HA) and B (HB) are X-linked congenital bleeding disorders caused by a deficiency of coagulation factor VIII (FVIII) and factor IX (FIX), respectively [1, 2]. Haemophilia is classified as mild (> 5–40 IU/dL), moderate (1–5 IU/dL) or severe (< 1 IU/dL) [1, 3]. Both deficiencies result in ineffective haemostasis, leading to bleeding episodes that typically occur in joints, often following minor trauma or even spontaneously. This can ultimately lead to chronic arthropathy, pain and reduced mobility, significantly impacting patients' quality of life [2, 4]. During interventional procedures, the haemorrhagic risk in patients with haemophilia (PWH) is significantly increased [3]. Therefore, careful pre-procedural haemostatic preparation is required for each intervention [5, 6]. However, peri-procedural bleeding is influenced by multiple variables that must be considered, such as

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patient age, haemophilia severity, the presence of inhibitors and the type of haemostatic agent used [7]. Haemostatic response (HR) assessment encompasses the presence of bleeding, unexpected factor requirements and peri-procedural transfusion needs. In addition, it allows categorization of the effectiveness of haemostatic preparation, when performed [3, 8].

The aim of this study is to evaluate the variables that modify HR in haemophilia patients who underwent invasive procedures in a retrospective cohort.

2 | Materials and Methods

A retrospective, observational study was conducted including all interventional procedures performed in male patients diagnosed with HA or HB. These procedures were registered in our institutional database, which belongs to the Haemophilia and Congenital Coagulopathies Unit of the Virgen de la Arrixaca University Hospital (Murcia, Spain), the regional reference centre. The study period spanned from January 2010 to January 2025 and encompassed patients from birth with no upper age limit. Data were collected from electronic medical records. Procedures performed in women with haemophilia and symptomatic carriers were not included, as a systematic registry of these patients was not available in the database during the analysed period. All interventions meeting the inclusion criteria were consecutively enrolled, as this was an all comers study with no prior sample size calculation. Interventions carried out at external institutions, those lacking sufficient documentation in the electronic medical records, and those performed in patients with other coagulation disorders were excluded from analysis. No additional exclusion criteria were applied. The study was approved by the local Research Ethics Committee.

2.1 | HR Categorization

The HR was categorized according to the recommendations of the World Federation of Haemophilia (WFH) [3, 8]: Excellent (no excessive bleeding, no additional factor replacement required, no transfusions), Good (mild bleeding without the need for factor adjustment or transfusions), Fair (bleeding requiring factor dose adjustment and/or transfusion), or Poor (excessive bleeding requiring urgent additional treatment, transfusion of two or more blood products, and/or surgical reintervention). HR was retrospectively adjudicated by the study investigators from haematology, surgical, transfusion and discharge records. When the available information was compatible with more than one category, the least favourable category was assigned. HR was subsequently dichotomized into poor/fair and good/excellent categories.

2.2 | Clinical Variables Related to the Procedures

The following variables related to interventional procedures were collected: Patient age, body weight, severity of haemophilia (classified as mild, moderate, or severe), and type of haemophilia (A or B). Body weight was analysed both as a continuous variable and as a categorical variable. For the categorical analysis, patients were classified into three pragmatic weight groups (≤ 60, 61–100 and >100 kg). These cut-offs were not intended to define nutritional status, because height and BMI were not systematically available. Instead, they were selected to separate patients with low body weight, the main adult weight range of the cohort, and patients with high body weight (>100 kg), in whom actual body weight-based factor dosing may be less predictable. The 61–100 kg group was used as the reference category because it represented the largest and most clinically usual weight group in our cohort. When available, genetic mutation type was also recorded and categorized as missense, inversion, deletion, splicing mutation or other variants. Additional variables included the presence of inhibitors, the use of prophylaxis and the type of product administered, as well as the use of haemostatic preparation prior to the procedure and the product employed.

For procedures treated with factor concentrate, loading dose, Day-0 post-procedure dose, duration of maintenance treatment and cumulative maintenance dose were also collected when available.

All procedures that required general or spinal anaesthesia, respiratory support, the opening and exposure of a major body cavity or orthopaedic surgeries involving joints were classified as major surgical procedures [9]. The remaining procedures were classified as minor. In addition, procedures were further specified as abdominal or digestive surgery, orthopaedic procedures, interventional and non-interventional endoscopies, central venous catheter manipulation or other interventions. Interventional endoscopy included procedures with biopsy, polypectomy or therapeutic intervention, whereas diagnostic endoscopy included procedures without biopsy or therapeutic manoeuvres.

In addition to the HR as the primary outcome, secondary outcome variables included the occurrence of bleeding complications and the requirement for blood transfusion.

2.3 | Statistical Analysis

Continuous variables were expressed as median and interquartile range (IQR) and categorical variables were presented as frequencies and percentages.

Because only seven procedures had fair/poor HR and several contingency tables had small expected counts, categorical comparisons were performed using Fisher's exact test for 2×2 tables and Fisher–Freeman–Halton exact tests for larger tables. Age and weight were also explored as continuous variables using the Mann–Whitney U test. A p-value < 0.05 was considered statistically significant for all tests. Statistical analyses were conducted using SPSS software, version 21.0 (IBM Corporation, Armonk, NY, USA).

3 | Results

A total of 119 males with haemophilia were registered in the institutional database (98 [82.4%] HA and 21 [17.6%] HB). Of these, 61 patients underwent invasive procedures during the study period (49 [80.3%] HA and 12 [19.7%] HB). A total of 158

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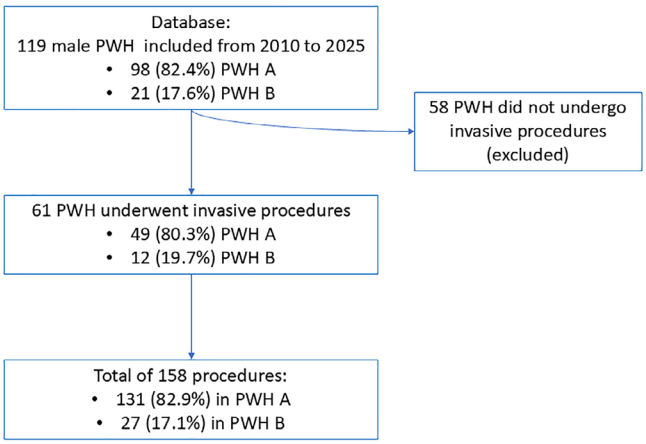


FIGURE 1 | Flowchart for selecting the included interventional procedures. PWH: Patients with haemophilia.

procedures were performed. The flow diagram for the selection of interventional procedures is shown in Figure 1. Baseline characteristics are detailed in Table 1.

Overall HR was rated as good/excellent in 151/158 procedures (95.6%) and fair/poor in 7/158 (4.4%) (Table 2). Fair/poor HR was more frequent in major than in minor procedures (4/38 [10.5%] vs. 3/120 [2.5%]), although this difference did not reach statistical significance using Fisher's exact test ($p = 0.058$). When procedures were analysed by type, digestive and abdominal wall surgery showed the highest proportion of fair/poor HR (4/23 [17.4%]), followed by interventional endoscopy (2/21 [9.5%]); the exact test across procedure categories was significant ($p = 0.030$) (Table 2).

Body weight was associated with HR in the categorical analysis: Fair/poor HR occurred in 3/11 procedures (27.3%) in patients weighing > 100 kg versus 1/87 (1.1%) in those weighing 61–100 kg and 2/51 (3.9%) in those ≤ 60 kg (exact $p = 0.003$) (Table 2). In the continuous analysis, median weight was higher in procedures with fair/poor HR (82.0 kg [IQR 60.0–110.0]) than in those with good/excellent HR (79.0 kg [IQR 60.0–85.0]), but this did not reach statistical significance ($p = 0.066$). Genetic category was also associated with HR in the exact test ($p = 0.041$), with fair/poor HR observed in procedures performed in patients with deletions (1/6 [16.7%]) and inversions (3/17 [17.6%]) but not in missense, splicing or other variants; however, this result should be interpreted cautiously because genetic testing was not available for 66 procedures (Table 2).

Peri-procedural haemostatic management is summarized in Table 3. Haemostatic preparation was used in 127/158 procedures (80.4%), including 37/38 major procedures (97.4%) and 90/120 minor procedures (75.0%). Major procedures required longer maintenance treatment and higher cumulative factor doses than minor procedures.

4 | Discussion

Our findings indicate that body weight > 100 kg was associated with a higher proportion of fair/poor HR in the categorical analysis. However, this finding should be interpreted as exploratory, because only seven fair/poor HR events were observed and the multivariable model was not retained due to sparse data. In addition, the continuous weight analysis showed the same direction but did not reach statistical significance. Overweight and obesity represent a growing challenge and constitute a serious health problem both in the general population and in PWH in developed countries. Obesity, defined as a body mass index (BMI) ≥ 30 kg/m^2, accounts for more than 42.5% of the adult population in the United States [10]. In Spain, where the present study was conducted, 39.8% of the adults were overweight (25 kg/m^2 ≤ BMI <30 kg/m^2) and 15.2% were obese [11]. Kleiboer et al. reported that obesity is a specific risk factor for haemorrhagic complications in orthopaedic surgery, even when appropriate haemostatic preparation has been administered [12]. Our results are in line with this finding, although they should be interpreted cautiously because of the low number of fair/poor HR events.

It is well known that PWH with obesity present greater limitations in daily activities, as well as a higher number of bleeding episodes and increased factor requirements [13, 14]. Paradoxically, it has been described that in this patient group, haemostatic recovery is higher than in underweight patients, and circulating FVIII levels may not be reliable predictors of optimal HR during procedures [15]. It has even been suggested that factor dosing should be based on BMI rather than body weight [16].

These findings support the need to reinforce prevention and treatment programs for high body weight and obesity in PWH to the same or even greater extent than in the general population [17], encouraging a multidisciplinary approach.

Beyond this main finding, variables classically associated with bleeding risk—particularly the type of procedure (minor/major)—showed the expected pattern, with major procedures presenting less favourable haemostatic outcomes (10.5% poor/fair HR) compared with minor procedures (2.5% poor/fair HR), although this difference did not reach statistical significance with Fisher's exact test [1, 9, 18]. Considering specific procedure types, digestive and abdominal wall surgeries showed worse HR (17.4% poor/fair HR), likely reflecting the predominance of major interventions in this group [9].

Interestingly, the proportion of poor/fair HR in procedures with mild haemophilia (4.9%) was similar to that seen procedures with severe haemophilia (5.1%), although this difference did not reach statistical significance. A plausible explanation in our cohort is that mild PWH often do not undergo preoperative haemostatic assessment—either because clinicians do not routinely schedule it or because patients perceive a lower need for such preparation [19]—and therefore do not attend pre-procedure visits where haemostatic planning would typically take place.

In our centre, peri-procedural haemostatic management was systematically planned or supervised by the haemophilia unit in patients with severe or moderate haemophilia. In patients with mild haemophilia, haematology supervision was not systematic

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TABLE 1 | Basaline characteristics of the procedures. CVC: Central venous catheter. DDAVP: Desmopressin; EHL: Extended half-life; FIX: Factor IX; FVIII: Factor VIII; IQR: Interquartile range.

Interventions, *N* = 158			
Age (years), median (IQR)	46,0 (27.0–64.0)	**Inhibitor presence, *n* (%)**	
Age (years) ranges, *n* (%)		No	146 (92.4)
≤18.0	30 (19.0)	Yes	12 (7.6)
19–45	46 (29.1)	**Procedure type, *n* (%)**	
46–65	54 (34.2)	Minor	120 (75.9)
> 65	28 (17.7)	Major	38 (24.1)
Weight (kg), median (IQR)	80.0 (60.0–86.0)	**Specific procedure type, *n* (%)**	
Weight ranges, *n* (%)[a]		Digestive and abdominal wall	23 (14.6)
≤ 60 kg	51 (34.2)	Orthopedic	13 (8.2)
61–100	87 (58.4)	Interventional endoscopy	21 (13.3)
> 100 kg	11 (7.4)	Diagnostic endoscopy	30 (19.0)
Haemophilia A, *n* (%)	131 (82.9)	CVC manipulation	23 (14.6)
Mild	78 (49.4)	Other major surgeries	3 (1.9)
Moderate	15 (9.5)	Other minor surgeries	45 (28.5)
Severe	38 (24.1)	**Haemostatic preparation, *n* (%)**	
Haemophilia B, *n* (%)	27 (17.1)	Yes	127 (80.4)
Severe	21 (13.3)	No	31 (19.6)
Moderate	3 (1.9)	**Haemostatic preparation type, *n* (%)**	
Mild	3 (1.9)	Factor	108 (68.4)
Genetics, *n* (%)[b]		Bypass agent	9 (5.7)
Deletion	6 (3.8)	DDAVP	10 (6.3)
Inversion	17 (10.8)	No preparation	31 (19.6)
Missense	54 (34.2)		
Splicing	10 (6.3)		
Others	5 (3.2)		
Prophylaxis, *n* (%)			
FVIII	14 (8.8)		
EHL FVIII	8 (5.1)		
FIX	14 (8.9)		
EHL FIX	4 (2.5)		
Emicizumab	3 (1.9)		
No prophylaxis	115 (72.8)		

[a]Weight was available for 149 procedures.

[b]Genetic test not performed: 66 procedures.

and depended on referral before the procedure, recognition of the bleeding disorder by the treating team and the clinical context.

This study has limitations that should be considered when interpreting the results. First, height was inconsistently recorded, preventing the routine calculation of BMI in daily practice. Therefore, the body weight categories used in this study should be interpreted as pragmatic exploratory strata rather than validated haemophilia-specific thresholds. BMI would have been more appropriate to assess overweight or obesity, but body weight in kilograms is directly used for factor dose calculation in routine practice and was available for most patients. Previous pharmacokinetic studies and reviews have shown that BMI and body composition influence FVIII recovery and may affect the accuracy of actual body weight–based dosing in overweight or obese patients [14, 16, 20, 21]. To improve the standardization and comparability of results across patients and studies, systematic recording of height and the availability of BMI would be desirable in future analyses. Second, the retrospective design did not allow a uniform evaluation of planned target factor levels, achieved factor levels or pharmacokinetic parameters. A direct comparison

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TABLE 2 | Exact test for haemostatic response. CVC: Central venous catheter; DDAVP: Desmopressin.

	Good/ Excellent	Poor/ Fair	*p*-value
Age (years), *n* (%)			0.349
≤ 18	30 (100.0)	0	
19–45	42 (91.3)	4 (8.7)	
46–65	52 (96.3)	2 (3.7)	
> 65	27 (96.4)	1 (3.6)	
Weight (kg), *n* (%)			0.003
≤ 60	49 (96.1)	2 (3.9)	
61–100	86 (98.9)	1 (1.1)	
> 100	8 (72.7)	3 (27.3)	
Severity, *n* (%)			0.763
Severe	56 (94.9)	3 (5.1)	
Moderate	18 (100.0)	0	
Mild	77 (95.1)	4 (4.9)	
Genetics, *n* (%)			0.041
Deletions	5 (83.3)	1 (16.7)	
Inversions	14 (82.4)	3 (17.6)	
Missense	54 (100.0)	0	
Splicing	10 (100.0)	0	
Others	5 (100.0)	0	
Prophylaxis, *n* (%)			0.384
Yes	39 (92.9)	3 (7.1)	
No	112 (96.6)	4 (3.4)	
Inhibitor, *n* (%)			1.000
Yes	12 (100.0)	0	
No	139 (95.2)	7 (4.8)	
Type of procedure, *n* (%)			0.058
Minor	117 (97.5)	3 (2.5)	
Major	34 (89.5)	4 (10.5)	
Specific type of procedure, *n* (%)			0.030
Digestive and abdominal wall	19 (82.6)	4 (17.4)	
Orthopaedic	13 (100.0)	0	
Interventional endoscopy	19 (90.5)	2 (9.5)	
Diagnostic endoscopy (no intervention)	30 (100.0)	0	
CVC manipulation	23 (100.0)	0	
Other major surgeries	3 (100.0)	0	
Other minor surgeries	44 (97.8)	1 (2.2)	
Haemostatic preparation, *n* (%)			0.347
Yes	120 (94.5)	7 (5.5)	
No	31 (100.0)	0	
Type of haemostatic preparation, *n* (%)			0.419
Factor concentrate	102 (94.4)	6 (5.6)	
Bypassing agent	9 (100.0)	0	
DDAVP	9 (90.0)	1 (10.0)	
No preparation	31 (100.0)	0	

with non-haemophilia patients was not possible because this study did not include a matched control group and WFH HR categories include haemophilia-specific elements, such as additional factor requirement or dose adjustment. In addition, haemophilia severity was analysed using standard clinical categories, which may not capture differences across the full range of baseline factor levels. Third, the 15-year study period spans major changes in haemophilia care and periprocedural management [3, 22]. Consequently, patients treated in more recent years may have benefited from improved haemostatic preparation and, therefore, a more favourable HR, introducing potential temporal bias in the observed results. Fourth, genetic information was not uniformly available—some patients entered the database in adulthood without prior molecular testing, limiting our ability to assess genotype–risk relationships. Although poor/fair HR occurred in 16.7% of procedures with deletions and 17.6% with inversions, no robust conclusions can be drawn due to the high number of procedures without genetic testing. Finally, the analysis was performed at procedure level. Some patients contributed more than one procedure, and a clustering-adjusted analysis was not feasible because the number of fair/poor HR events was very low.

In addition, although a substantial number of procedures were analysed, the retrospective and single-centre design may introduce biases inherent to local clinical practices and limits the generalizability of the results. Therefore, confirmation of our findings will require a future multicentre study with prospectively collected and standardized data.

5 | Conclusion

Our data suggest that high body weight may be associated with a higher likelihood of suboptimal periprocedural HR in PWH undergoing invasive procedures. However, this finding should be considered exploratory due to the low number of fair/poor HR events.

From a practical standpoint, body weight could be used as a simple flag to prompt more intensive pre-procedural planning (including dosing strategy review and postoperative monitoring), while longer-term multidisciplinary programmes addressing overweight and obesity may have benefits, potentially improving periprocedural safety. Confirmation in multicentre prospective cohorts with standardized data capture (including BMI, pharmacokinetics and genotype) is warranted.

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TABLE 3 | Peri-procedural haemostatic management by procedure intensity. Values are *n* (%) or median (IQR). *Only procedures treated with factor concentrate and with available numeric dosing were included in dose summaries. DDAVP: Desmopressin; HR: Haemostatic response.

Variable	All procedures	Minor procedures	Major procedures
n	158	120	38
Any preparation, *n* (%)	127 (80.4)	90 (75.0)	37 (97.4)
Factor concentrate, *n* (%)	108 (68.4)	74 (61.7)	34 (89.5)
Bypassing agent, *n* (%)	9 (5.7)	7 (5.8)	2 (5.3)
DDAVP, *n* (%)	10 (6.3)	9 (7.5)	1 (2.6)
No preparation, *n* (%)	31 (19.6)	30 (25.0)	1 (2.6)
Loading dose, IU/kg*	41.7 (33.3–50.0)	40.0 (32.3–52.6)	45.2 (33.3–50.0)
Day-0 post-procedure dose, IU/kg*	0.0 (0.0–34.9)	0.0 (0.0–22.1)	33.3 (20.0–42.9)
Maintenance treatment, days*	3.0 (1.0–7.0)	2.0 (0.0–3.0)	9.0 (6.0–14.0)
Cumulative maintenance dose, IU/kg*	105.9 (27.3–273.7)	72.3 (0.0–147.8)	290.7 (133.3–575.3)
Fair/poor HR, *n* (%)	7 (4.4)	3 (2.5)	4 (10.5)

Author Contributions

José Antonio Sánchez Salas contributed to data collection, data analysis, interpretation of the results and drafting of the manuscript. Eva Soler Espejo contributed to data analysis and interpretation of the results. Faustino García Candel contributed to the generation of clinical data, interpretation of the results and critical revision of the manuscript for important intellectual content. Vanessa Roldán Shilling contributed to the critical revision of the manuscript and supervised the work. All authors reviewed and approved the final version of the manuscript and agree to be accountable for all aspects of the work.

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The authors have nothing to report.

Ethics Statement

The study was approved by the local Research Ethics Committee in compliance with the Declaration of Helsinki.

Consent

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request. Due to ethical and privacy restrictions, the data are not publicly available.

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