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ORIGINAL RESEARCH

Characterization of Inherited Bleeding Disorders in Egyptian Children in a Tertiary Care Center: A 10 Years Experience

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Background: Inherited bleeding disorders (IBDs) require accurate diagnosis and long-term management. This study characterized the clinical and hematologic profile of Egyptian children with IBDs managed at Cairo University Children's Hospital and Misr University for Science and Technology.

Methods: This retrospective longitudinal observational study included 200 pediatric patients with inherited coagulation or platelet disorders followed between 2015 and 2025. Data collected included demographics, family history, bleeding manifestations, complications, treatment exposure, functional scores, imaging findings, and confirmatory laboratory investigations.

Results: Hemophilia A (HA) and von Willebrand disease (vWD) were the most common disorders, accounting for 32.0% and 28.5% of cases, respectively. Among rare inherited coagulation defects, fibrinogen disorders and factor VII deficiency were the most frequent. HA showed the highest hospitalization rate, annual bleeding rate, and ISTH bleeding score, while joint disease was most prominent in hemophilia. Intracranial hemorrhage occurred most often in factor VII deficiency. In HA, the Functional Independence Score of Hemophilia (FISH) was the best discriminator of chronic hemophilic arthropathy (AUC 0.715; cutoff $\leq$ 26), followed by annual bleeding rate (AUC 0.695; cutoff > 6/year). Persistent high-titer inhibitors developed in 17.2% of HA patients. Most vWD cases were type 1 (75.4%), and Glanzmann thrombasthenia was the most common inherited platelet disorder.

Conclusion: Egyptian children with IBDs show heterogeneous clinical presentations and outcomes. Severe phenotypes, particularly HA and type 3 vWD, were associated with earlier bleeding onset, greater morbidity, and the need for individualized management.

Keywords: inherited bleeding disorders, egyptian children, hemophilia, von Willebrand disease, inherited platelet disorder

Introduction

Inherited bleeding disorders are relatively common in pediatric practice, requiring accurate diagnosis and timely management. Most are chronic, complex, and need lifelong, often costly, treatment. Reported prevalences and clinical presentations vary across populations, with hemophilia and von Willebrand disease (vWD) being the most common. Research on inherited platelet function defects (IPFDs) is even more limited.[1] According to the Global Annual Survey 2024 by the World Federation of Hemophilia (WFH), the most commonly reported Inherited bleeding disorders are Hemophilia A (HA) and vWD.[2] Other rare coagulation defects are less common and show heterogeneous clinical phenotypes ranging from mild bleeding to potentially serious or life-threatening bleeding.[3] IPFDs commonly present with mucocutaneous bleeds. In Egypt, only a few studies of local populations reported unique distributions and patterns among patients with Inherited bleeding disorders.[4,5] Most of the data are derived from the WFH annual global survey, with HA, hemophilia B (HB), vWD, and Glanzmann thrombasthenia (GT) being the most common reported, respectively.[2] Maintaining an updated, established registry of Inherited bleeding disorders is vital for delivering optimal, prompt management and improvement of quality of care for our patients.[6] This study examined the distribution, clinical

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Graphical Abstract

spectrum, severity, complications, and clinical-laboratory profiles of Inherited bleeding disorders in our patients, enhancing understanding of these disorders in our population, thus helping us to evaluate our management outcomes, and guiding effective care policies. It aimed to assess the patterns and identify the clinical and hematological characteristics of Inherited bleeding disorders among Egyptian patients over a 10-year follow-up.

Patients and Methods

This retrospective longitudinal observational study was conducted at the Pediatric Hematology Unit, Cairo University Children's Hospital, a major tertiary referral center in Egypt receiving about 320 hematology patients weekly, with approximately 10 children presenting with a bleeding history and around two children per week suspected of having an inherited bleeding disorder, and at the pediatric clinic at Misr University for Science and Technology. Children with suggestive bleeding manifestations, a positive family history, and/or abnormal screening coagulation tests were referred for confirmatory evaluation and follow-up in the specialized bleeding clinic. The study included 200 Egyptian pediatric patients (≤18 years) of both sexes with inherited bleeding disorders (inherited coagulation and platelet disorders), registered between 2015 and 2025.

Ethical Considerations

The study was approved by the Ethics Committee of the Faculty of Medicine, Misr University for Science & Technology Hospital (2022/0076) on May 31, 2023, and by the Department Councils of the Faculty of Medicine, Cairo University,

and Misr University for Science & Technology. Written informed consent/assent was obtained from all subjects and/or legal guardians before enrollment in the study. All conducted procedures complied with the Helsinki Declaration of 1975, as revised in 2013.

All patients underwent detailed history-taking, including demographics, Age at presentation and diagnosis, residence, family history, pedigree analysis, and a comprehensive bleeding history covering manifestations, sites, triggers, frequency, severity, and hospital/pediatric intensive care unit (PICU) admissions. History of replacement and non-replacement therapies and related complications was recorded. All patients had a full physical examination with emphasis on the musculoskeletal system. Scoring of bleeding symptoms using the International Society of Thrombosis and Hemostasis (ISTH) score, and joint bleeding symptoms using Hemophilia Joint Health Score (HJHS) and Functional Independence Score of Hemophilia (FISH) were presented.

Treatment-related data collected from the records included on-demand versus prophylactic therapy, replacement products used when available (including cryoprecipitate, fresh frozen plasma, factor concentrates, and FVIII/VWF-containing products), adjunctive tranexamic acid, treatment-related allergies, inhibitor development, and major management changes such as use of bypassing therapy or emicizumab when documented.

HJHS and FISH assessments were performed only in patients with documented recurrent hemarthrosis and chronic joint involvement, irrespective of the underlying inherited bleeding disorder. Although these scoring systems were originally developed and validated for hemophilia, they were applied in this study to provide standardized functional assessment of joint status in patients with significant musculoskeletal bleeding. This represents an extrapolation beyond their original validation scope and is acknowledged as a methodological limitation.

Quantitative factor XIII activity and platelet function tests were performed when PT and aPTT were normal. vWD was suspected based on early-onset bleeding, positive family history, normal or decreased platelet count, and prolonged aPTT; it was further characterized by vWF antigen and vWF activity assays together with factor VIII assay, and ristocetin-induced platelet aggregation when indicated, using the phenotypic assays available in routine clinical practice. If inherited platelet function defects were suspected because of early-onset bleeding, positive family history, suggestive bleeding pattern, mild thrombocytopenia, or other supporting features, additional investigations were performed, including blood film examination, bone marrow studies in thrombocytopenic cases, platelet aggregation to ADP, collagen, epinephrine, and ristocetin using light transmission aggregometry, and/or flow cytometry assessing platelet surface glycoprotein expression whenever feasible. Whole exome sequencing was performed for one patient diagnosed with glycoprotein IV (CD36) deficiency. Further tests for possible complications were included whenever available or indicated, such as inhibitor titers and virology tests. Imaging studies such as ultrasonography, computed tomography, or magnetic resonance imaging were performed when indicated.

Quantitative factor XIII activity and platelet function tests were performed when PT and aPTT were normal. vWD was suspected based on early-onset bleeding, positive family history, normal or decreased platelet count, and prolonged aPTT; it was further diagnosed by vWF-Ag and activity assays and a factor VIII level assay using Sysmex CN 6000 by the clotting method. If IPFDs were suspected as with early onset of bleeding, positive family history, suggestive bleeding pattern, mild thrombocytopenia or other features, investigations as blood film examination, bone marrow studies (in case if thrombocytopenia), platelet function tests were done including: platelet aggregation to ADP, Collagen, Epinephrine, and Ristocetin using LTA (light transmission aggregometry), and/or flow cytometry assessing surface glycoprotein expression of the platelets whenever feasible. Whole exome sequencing was performed for one patient diagnosed with Glycoprotein IV (CD36) deficiency. Further tests for possible complications were included whenever available or indicated, such as inhibitor titers and virology tests. Imaging studies, such as ultrasonography, computed tomography (CT), or magnetic resonance imaging (MRI), were performed when indicated.

We defined target joints as joints in which 3 or more consecutive bleeds occurred within 6 consecutive 6-month periods[7] and/or radiologically as a joint with chronic synovitis (synovial hypertrophy by MRI) regardless of the explicit number of recent bleeds.[8]

Diagnosis and Disease Severity

HA and HB were diagnosed by factor VIII or IX activity ≤30% and classified as mild (6–30%), moderate (1–5%), or severe (<1%). Diagnosis of vWD type 1 was defined by a vWF level <30% regardless of bleeding, and for patients with abnormal bleeding, a vWF level <50% of normal, while extremely low or undetectable vWF-Ag levels defined type 3 disease (severe Type).

Afibrinogenemia/hypofibrinogenemia were diagnosed when fibrinogen was absent or very low, respectively, while FII, V, FVII, FX, FXI, and FXII deficiencies were diagnosed when specific factor assay was below normal (n = 70–120%). Diagnosis of GT was based on clinical assessment confirmed by normal platelet count, normal platelet size, defective platelet aggregation with ADP, with normal aggregation with ristocetin, while that of Bernard–Soulier syndrome (BS) was confirmed by the presence of giant platelets and normal aggregation with ADP and defective aggregation to ristocetin not corrected by the addition of normal plasma.

Outcomes

The primary aim was to determine the distribution and clinical and hematological features of Inherited bleeding disorders in an Egyptian patient cohort at our tertiary care center. Secondary outcomes included assessing the frequency and pattern of IBD complications and evaluating the treatment regimens and approaches used for these patients.

Sample Size

The sample size calculation was performed using EpI-Info 2002 software statistical package designed by World Health Organization (WHO) and by Centers for Disease Control and Prevention (CDC).

The sample size was calculated based on the following considerations: 95% confidence level and the incidence of Hemophilia in a bulk of IBD was 57% according to a previous study[9] ± 7% confidence limit. Seven cases were added to overcome dropout. Therefore, we recruited 200 cases.

Statistical Analysis

Statistical analysis was done by SPSS v27 (IBM©, Chicago, IL, USA). Normality was assessed with the Shapiro–Wilks test and histograms. Quantitative parametric data were expressed as mean ± SD and analyzed using ANOVA with Tukey post hoc test. Nonparametric quantitative data were presented as median (IQR) and analyzed using the Kruskal–Wallis test and the Mann–Whitney test for group comparisons. Qualitative variables were expressed as frequency (%) and analyzed with the Chi-square test. A two-tailed $P \leq 0.05$ was considered statistically significant.

Results

Additional expanded results, supplementary analyses, and supporting tabulations are provided in Supplementary Material: Results and Data Collection, Tables S1–S22 and Supplementary Figure S1and S2.

Two hundred ninety-five records were thoroughly reviewed; 45 were excluded due to inadequate data, and 50 were excluded due to failure to follow up. Two hundred patients fulfilling the inclusion criteria were consecutively enrolled in the study, as shown in Figure 1.

The distribution of our studied patients is shown in Table 1 with HA and vWD being the most prevalent (32% and 28.5%, respectively). Fibrinogen disorders followed by Factor VII deficiency were the most common rare inherited coagulation defects (ICDs). Most of our HA and HB patients were severe or moderate based on their factor levels (53.1% and 29.7% for HA, 56.3% and 31.3% for HB, respectively), while the majority of vWD patients were type 1 (75.4%) Table 1.

Inherited Coagulation Disorders (ICDs)

Table 2 presents the demographic characteristics, initial clinical presentation, and complication frequency among patients with ICDs. Demographic analysis revealed complete male predominance in HA and HB, contrasting sharply with the mixed gender distribution in other coagulation disorders. High consanguinity rates were observed in fibrinogen disorders,

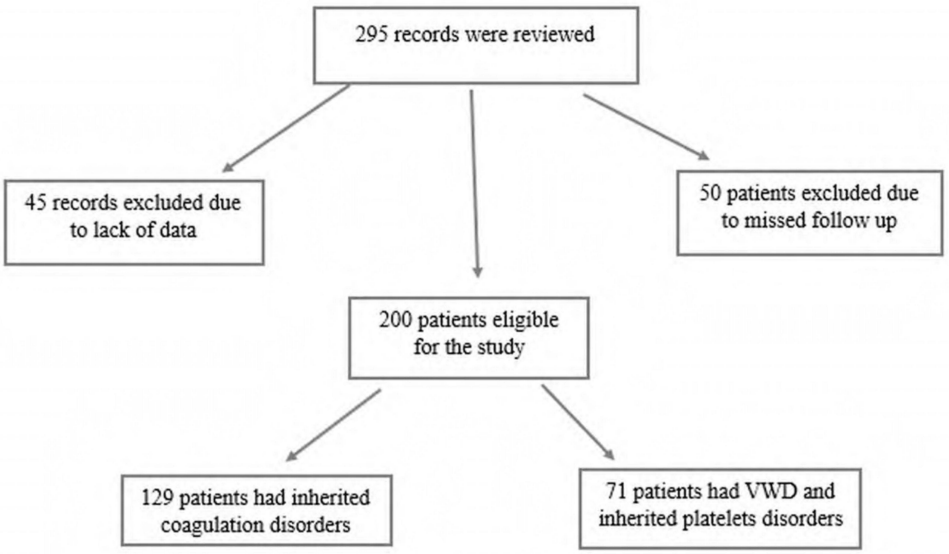

Figure 1 Flowchart for studied patients.

followed by HA, HB, and Factor VII deficiency. The majority of our patients resided in Giza and Cairo (44% for HA, 50% for HB, 16% for fibrinogen disorders, 47% for FVII deficiency, and 67% and 11% for other rare coagulation defects, respectively). In contrast, other governorates showed less representation in our cohort (data not shown). Skin was the predominant initial site of bleeding in fibrinogen disorders (60%), while mucous membrane bleeds were most frequent in

Table 1 Distribution of Studied Patients with Inherited Coagulation and Platelet Disorders (n = 200)

Diagnosis		**N (%)**
Inherited coagulation disorders (n = 129)		
Hemophilia A (n = 64, 49.6%)	**Severe**	34(53.1%)
	Moderate	19(29.7%)
	Mild	11(17.2%)
Fibrinogen disorders (n = 25, 19.4%)	**Afibrinogenemia**	19(14.7%)
	Hypofibrinogenemia	6(4.7%)
Hemophilia B (n = 16, 12.4%)	**Severe**	9(56.3%)
	Moderate	5(31.3%)
	Mild	2(12.5%)
Factor VII deficiency		15(11.6%)
Other Rare Coagulation	**Factor V deficiency**	2(1.6%)
	Factor X deficiency	3(2.3%)
	Factor XI deficiency	2(1.6%)
	Factor XII deficiency	1(0.8%)
	Factor XIII deficiency	1(0.8%)

(*Continued*)

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Table 1 (Continued).

Diagnosis		N (%)
vWD and Inherited platelet disorders (n = 71)		
vWD (n = 57, 80.3%)	**Type 1**	43(75.4%)
	Type 3	14(24.6%)
Inherited platelet (n = 14, 19.7%)	**Bernard Soulier syndrome**	4(28.6%)
	Glanzmann's disease	9(64.3%)
	CD36 deficiency	1(7.1%)

Notes: Data presented as frequency (%), vWD: Von Willebrand disease. Bold text indicates major category or subgroup headings within the table.

HA (67.2%), Factor VII deficiency (53.3%), and rare coagulation disorders (44.4%). As an initial presentation, umbilical stump and organ bleeding occurred most frequently in fibrinogen disorders and Factor VII deficiency (44% and 26.7%, respectively). Most HA patients experienced their first bleeding episode within their first year of life (76.6%), with a median age of 1.0 month, and were diagnosed at a median age of 0.5 years, in contrast to other coagulation disorders, which first presented and were diagnosed at later ages (Table 2). Joint complications emerged as a distinguishing feature of HA and HB, with chronic hemophilic arthropathy evident in 64% and 32%, respectively, whereas intracranial hemorrhage (ICH) occurred most frequently in Factor VII deficiency (20%), despite its relatively small sample size, highlighting the need for strict monitoring in this population. Notably, 17.2% of HA patients developed persistent high-titer inhibitors, upon which they were shifted to Emicizumab therapy. Allergic reactions were reported in 23.4% of HA patients (12.5% to Factor VIII concentrate and 10.9% to Cryoprecipitate), while Fresh frozen plasma (FFP) related allergic reactions were reported in 18.6% and 6.7% of HB and Factor VII deficiency patients, respectively, who have received it in emergencies due to limited access to specific factor replacement. Age, consanguinity, family history of similar condition, family history of bleeding, regarding site of first bleeding attack (gum bleeding, subconjunctival hemorrhage, skin, puncture site, easy bruising, eyelid wound, organ, rectal, hematemesis, hematuria, intracranial hemorrhage, vaginal, retinal, musculoskeletal, hemarthrosis and muscle), duration of disease, intracranial hemorrhage and allergy were insignificantly different among the five groups. Sex and Age at first bleeding were significantly different among the five groups (P value < 0.05). The site of the first bleeding attack (mucous membrane, circumcision) was markedly higher in hemophilia A than in other groups, while epistaxis was considerably higher in hemophilia B than in other groups (P value < 0.05). Age at first bleeding attack and Age at first bleeding attack were markedly lower in hemophilia A than in hemophilia B, factor VII deficiency, and rare coagulation disorders; they were insignificantly different between hemophilia A and fibrinogen disorders, and among the other groups. Disease-related complications (contracture and chronic hemophilic arthropathy) were significantly higher in hemophilia A and hemophilia B than in other groups.

Table 3 presents longitudinal follow-up data, bleeding triggers, and severity scores for patients with ICDs. Target joints affection, MRI Denver, and HEAD ultrasound scores among HA and HB patients are also shown. HA patients exhibited the highest hospitalization rate (primarily due to musculoskeletal bleeds), ABR and ISTH scores reflecting the severity of bleeding in this group. PICU admissions were mainly related to ICH and circumcision-related complications. The most common target joints in HA patients were the knee, elbow, and ankle joints (50%, 26.6%, and 20.4%, respectively). Multiple joint affections were also reported in 24.4% and 20% of HA and HB patients, respectively. Although validated in HA and HB, FISH and HJHS were applied in this cohort to patients with factor VII deficiency, fibrinogen disorders, and rare bleeding disorders with joint involvement as surrogate measures of joint health and functional status. Hospital admission indications (gum bleeding, epistaxis, sub conjunctival, circumcision (preoperative), extensive bruising, umbilical stump, rectal, hematemesis, hematuria, intra-cranial hemorrhage and sepsis), PICU admission indications (circumcision (postoperative), umbilical stump, hematemesis and intracranial hemorrhage), surgical

Table 2 Demographics, Initial Clinical Presentation, and Frequency of Complications Among Patients with Inherited Coagulation Disorders (n = 129)

		Diagnosis					P value
		Hemophilia A (n = 64)	Hemophilia B (n = 16)	Fibrinogen Disorders (n = 25)	Factor VII Deficiency (n = 15)	Rare Coagulation (n = 9)	
Age (Years)		7.0(4.0–9.0)	6.0(5.0–9.50)	5.0(3.0–9.0)	5.0(4.0–8.0)	8.0(7.0–9.0)	0.829
Sex	**Male**	64(100.0%)	16(100.0%)	13(52.0%)	5(33.3%)	4(44.4%)	<0.001
	Female	0(0.0%)	0(0.0%)	12(48.0%)	10(66.7%)	5(55.6%)	
Consanguinity	**Positive**	26(40.6%)	7(43.8%)	15(60.0%)	4(26.7%)	5(55.6%)	0.267
Family History of similar condition		38(59.4%)	7(43.8%)	14(56.0%)	6(40.0%)	5(55.6%)	0.618
Family History of Bleeding		38(59.4%)	7(43.8%)	14(56.0%)	6(40.0%)	5(55.6%)	0.618
Initial clinical presentation							
Site of first bleeding attack	**Mucous Membrane**	43(67.2%)	6(37.5%)	5(20.0%)	8(53.3%)	4(44.4%)	0.005
	Gum bleeding	10(15.6%)	0(0.0%)	1(4.0%)	1(6.7%)	2(22.2%)	0.189
	Epistaxis	6(9.4%)	4(25.0%)	2(8.0%)	7(46.7%)	1(11.1%)	0.004
	Circumcision	27(42.2%)	1(6.3%)	2(8.0%)	0(0.0%)	1(11.1%)	0.001
	Subconjunctival hemorrhage	0(0.0%)	1(6.3%)	0(0.0%)	0(0.0%)	0(0.0%)	0.129
	Skin	19(29.6%)	6(37.5%)	15(60.0%)	3(20.0%)	3(33.3%)	0.059
	Puncture site	4(6.3%)	1(6.3%)	2(8.0%)	0(0.0%)	1(11.1%)	0.826
	Easy bruising	4(6.3%)	4(25.0%)	2(8.0%)	2(13.3%)	1(11.1%)	0.261
	Umbilical stump	11(17.2%)	1(6.3%)	11(44.0%)	0(0.0%)	1(11.1%)	0.003
	Eyelid wound	0(0.0%)	0(0.0%)	0(0.0%)	1(6.7%)	0(0.0%)	0.105
	Organ	1(1.6%)	3(18.8%)	5(20.0%)	4(26.7%)	1(11.1%)	0.012
	Rectal	1(1.6%)	0(0.0%)	0(0.0%)	1(6.7%)	0(0.0%)	0.499
	Hematemesis	0(0.0%)	2(12.5%)	1(4.0%)	1(6.7%)	1(11.1%)	0.118
	Hematuria	0(0.0%)	1(6.3%)	2(8.0%)	0(0.0%)	0(0.0%)	0.151
	Intracranial hemorrhage	0(0.0%)	0(0.0%)	1(4.0%)	1(6.7%)	0(0.0%)	0.321
	Vaginal	0(0.0%)	0(0.0%)	0(0.0%)	1(6.7%)	0(0.0%)	0.129
	Retinal	0(0.0%)	0(0.0%)	1(4.0%)	0(0.0%)	0(0.0%)	0.381
	Musculoskeletal	1(1.6%)	1(6.3%)	0(0.0%)	0(0.0%)	1(11.1%)	0.262
	Hemarthrosis	1(1.6%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0.906
	Muscle	0(0.0%)	1(6.3%)	0(0.0%)	0(0.0%)	1(11.1%)	0.053
Age at first bleeding attack (months)		1.0 (0.0–12.0)	15.0 (7.6–39.2)	12.0 (0.0–16.0)	12.0 (8.7–44.1)	12.0 (7.3–45.3)	<0.001
P1			<0.001	0.154	0.002	0.005	
P2				0.036	0.781	0.982	
P3					0.080	0.089	
P4						0.830	

(*Continued*)

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Table 2 (Continued).

		Diagnosis					P value
		Hemophilia A (n = 64)	**Hemophilia B (n = 16)**	**Fibrinogen Disorders (n = 25)**	**Factor VII Deficiency (n = 15)**	**Rare Coagulation (n = 9)**	
<1 year old		49(76.6%)	7(43.8%)	16(64.0%)	8(53.3%)	2(22.2%)	0.005
1–6 years old		15(23.4%)	9(56.2%)	9(36.0%)	7(46.7%)	7(77.8%)	
7–12 years old		0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	
12–18 years old		0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	
Age at diagnosis (years)		0.50(0.12–2.0)	1.50(1.0–3.50)	1.0(1.0–2.0)	2.0(1.0–4.50)	2.0(1.0–4.0)	0.001
P1			0.006	0.211	0.002	0.006	
P2				0.133	0.795	0.618	
P3					0.079	0.0.076	
P4						0.786	
Duration of disease (years)		6.0(4.0–8.0)	4.0(2.0–6.0)	4.0(2.0–8.0)	3.0(2.0–5.5)	6.0(2.0–6.0)	0.170
Disease related complications	**Intracranial Hemorrhage**	5(7.8%)	0(0.0%)	0(0.0%)	3(20.0%)	1(11.1%)	0.121
	Contracture	19(29.7%)	5(31.2%)	0(0.0%)	0(0.0%)	0(0.0%)	0.001
	Chronic Hemophilic Arthropathy	41(64.06%)	5(31.2%)	0(0.0%)	0(0.0%)	0(0.0%)	<0.001
Treatment related complications							
Inhibitors to Factor VIII concentrate	**Transient low titre***	9(14.0%)	–	–	–	–	-
	Persistent high titre**	11(17.2%)	–	–	–	–	-
Allergy		15(23.4%)	3(18.6%)	1(4.0%)	1(6.7%)	0(0.0%)	0.082

Notes: Data presented as frequency (%) or median (IQR). * <5 Bethesda units/mL that temporarily disappears or resolves on its own; **≥5 Bethesda units/mL and does not resolve over time Bold text indicates major category or subgroup headings within the table.

history (adenoidectomy, tonsillectomy, GI endoscope, ICH evacuation, intestinal obstruction bypass, lipoma excision and vitreous hemorrhage evacuation), triggers of bleeding (spontaneous) were insignificantly different among the five groups. Hospital admission indications (retinal hemorrhage, joint bleeds, postoperative, and muscle hematoma), surgical history (circumcision), were significantly different among the five groups (P value < 0.05). Frequency of hospitalization/year and HJHS score were substantially higher in hemophilia A than in hemophilia B, factor VII deficiency, fibrinogen disorders, and rare coagulation disorders (P value < 0.05) and were insignificantly different among the other groups. The ISTH score was significantly higher in hemophilia A than in hemophilia VII deficiency (P value = 0.047), was insignificantly different between hemophilia A and hemophilia B, and was insignificantly different among the other groups. ABR was significantly higher in hemophilia A than (factor VII deficiency and fibrinogen disorders) (P value < 0.05), were insignificantly different between hemophilia A and (hemophilia B, factor VII deficiency and rare coagulation) and were insignificantly different among the other groups. The FISH score was significantly lower in hemophilia A than in hemophilia B, factor VII deficiency, fibrinogen disorders, and rare coagulation disorders. (P value < 0.05) and were insignificantly different among the other groups.

Comparative analysis between different ICDs showed no statistical significance across Age, gender or consanguinity (p > 0.05) but revealed statistically significant higher ISTH score, ABR, target joint affection and chronic arthropathy frequencies and lower mean hemoglobin levels among HA compared to other coagulation disorders (p = 0.02, <0.001, <0.001, <0.001 and 0.01 respectively) [data not shown]. Compared to HB, HA consistently demonstrated greater severity, with significantly higher ABR and ISTH scores, lower hemoglobin levels, and longer aPTT (p = 0.01, 0.01, 0.01, and

Table 3 Longitudinal Follow-Up Data, Bleeding Triggers, Severity Scores, Target Joint Affection, MRI Denver, and HEAD Ultrasound Scores of Patients with Inherited Coagulation Disorders (n = 129)

		Diagnosis					P value
		Hemophilia A (n = 64)	Hemophilia B (n = 16)	Fibrinogen Disorders (n = 25)	Factor VII Deficiency (n = 15)	Rare Coagulation (n = 9)	
		(n = 63)	(n = 12)	(n = 22)			
Frequency of hospitalization/year		6.0(4.0–8.0)	3.50(2.0–5.50)	4.0(2.0–5.0)	4.0 (2.50–5.50)	3.50(1.0–6.0)	<0.001
P1			<0.001	<0.001	<0.001	0.011	
P2				0.501	0.899	0.770	
P3					0.603	0.809	
P4						0.857	
Hospital admission indications	**Gum bleeding**	11(17.2%)	1(6.3%)	1(4.0%)	1(6.7%)	1(11.1%)	0.496
	Epistaxis	23(35.9%)	3(18.8%)	7(28.0%)	5(33.3%)	2(22.2%)	0.881
	Sub conjunctival	0(0.0%)	0(0.0%)	2(8.0%)	0(0.0%)	0(0.0%)	0.057
	Circumcision (preoperative)	2(3.2%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0.759
	Extensive bruising	29(45.3%)	4(25.0%)	10(40.0%)	6(40.0%)	2(22.2%)	0.669
	Umbilical stump	0(0.0%)	0(0.0%)	1(4.0%)	0(0.0%)	0(0.0%)	0.338
	Rectal	1(1.6%)	0(0.0%)	0(0.0%)	2(13.3%)	1(11.1%)	0.085
	Hematemesis	4(6.3%)	2(12.5%)	2(8.0%)	2(13.3%)	2(22.2%)	0.493
	Hematuria	0(0.0%)	1(6.3%)	1(4.0%)	0(0.0%)	0(0.0%)	0.212
	Intracranial hemorrhage	5(7.8%)	0(0.0%)	0(0.0%)	3(20.0%)	1(11.1%)	0.173
	Retinal hemorrhage	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	1(11.1%)	0.014
	Joint bleeds	49(76.6%)	10(62.5%)	3(12.0%)	3(20.0%)	2(22.2%)	<0.001
	Postoperative	0(0.0%)	2(12.5%)	0(0.0%)	0(0.0%)	1(11.1%)	0.004
	Sepsis	0(0.0%)	1(6.3%)	0(0.0%)	1(6.7%)	0(0.0%)	0.126
	Muscle hematoma	50(78.12%)	11(68.7%)	4(16.0%)	2(13.3%)	3(33.3%)	<0.001
PICU admission indications	**Circumcision (postoperative)**	4(6.3%)	0(0.0%)	1(4.2%)	0(0.0%)	0(0.0%)	0.673
	Umbilical stump	4(6.3%)	0(0.0%)	1(4.2%)	0(0.0%)	1(11.1%)	0.663
	Hematemesis	1(1.6%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0.921
	Intracranial hemorrhage	3(4.7%)	0(0.0%)	0(0.0%)	0(0.0%)	1(11.1%)	0.433
Surgical history	**Circumcision**	53(82.8%)	14(87.5%)	9(36.0%)	6(40.0%)	3(33.3%)	<0.001
	Adenoidectomy	1(1.6%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0.916
	Tonsillectomy	1(1.6%)	0(0.0%)	0(0.0%)	1(6.7%)	0(0.0%)	0.526
	GI endoscope	2(3.1%)	1(6.3%)	1(4.0%)	0(0.0%)	0(0.0%)	0.760
	ICH evacuation	3(4.7%)	0(0.0%)	0(0.0%)	1(6.7%)	0(0.0%)	0.597
	Intestinal obstruction bypass	0(0.0%)	0(0.0%)	1(4.0%)	0(0.0%)	1(11.1%)	0.097
	Lipoma excision	1(1.6%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0.906
	Vitreous hemorrhage evacuation	0(0.0%)	0(0.0%)	2(8.0%)	0(0.0%)	0(0.0%)	0.076

(*Continued*)

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Table 3 (Continued).

		Diagnosis					P value
		Hemophilia A (n = 64)	Hemophilia B (n = 16)	Fibrinogen Disorders (n = 25)	Factor VII Deficiency (n = 15)	Rare Coagulation (n = 9)	
		(n = 63)	(n = 12)	(n = 22)			
Triggers of Bleeding	**Spontaneous**	34(53.1%)	7(43.7%)	7(28.0%)	6(40.0%)	3(33.3%)	0.261
	Traumatic	64(100.0%)	16(100.0%)	25(100.0%)	15(100.0%)	9(100.0%)	-
ISTH score		8.64 ± 2.19	7.0 ± 2.22	7.24 ± 1.85	8.0 ± 2.17	7.11 ± 2.15	0.009
P1			0.052	0.047	0.832	0.052	
P2				0.997	0.688	1	
P3					0.810	1	
P4						0.859	
ABR		5.95 ± 2.13	4.31 ± 2.06	3.96 ± 2.17	4.0 ± 2.14	5.22 ± 2.59	<0.001
P1			0.057	0.001	0.017	0.876	
P2				0.986	0.994	0.850	
P3					1	0.563	
P4						0.666	
FISH score		22.1 ± 6.3	23.2 ± 6.9	27.9 ± 0.33	27.4 ± 0.5	27.8 ± 0.44	<0.001
P1			<0.001	<0.001	<0.001	<0.001	
P2				1	1	0.997	
P3					1	0.987	
P4						0.991	
HJHS score		13.5(6.8–19.3)	7.5(3.0–15.5)	1(0–2)	1(0–2.5)	1(0–5)	<0.001
P1			0.032	<0.001	<0.001	0.002	
P2				0.026	0.043	0.229	
P3					0.962	0.590	
P4						0.594	

Notes: Data presented as frequency (%), median (IQR), or mean ± SD Bold text indicates major category or subgroup headings within the table.
Abbreviations: MRI, Magnetic resonance imaging; PICU, Pediatric intensive care unit; GI, Gastrointestinal; ICH, Intracranial haemorrhage; ISTH, International Society on Thrombosis and Haemostasis; ABR, Annual bleeding rate; FISH, Functional Independence Score of Hemophilia; HJHS, Hemophilia Joint Health Score.

<0.001, respectively), supporting the clinical impression of a more severe bleeding phenotype. Worth noting, comparing severe and moderate HA across all scores showed no statistically significant differences ($p > 0.05$) [data not shown].

Treatment modalities and laboratory data among studied patients with ICDs are shown in Table 4 Tranexamic acid (TXA) was widely used across all groups. All patients across all groups received on-demand treatment. For HA, 45 patients (70.3%) received prophylactic therapy (factor or non-factor replacement). Patients on Emicizumab were on a bi-weekly maintenance regimen. HB and fibrinogen disorder patients received once-weekly prophylaxis in 56.3% and 40%, respectively. Three patients with Factor VII deficiency received prophylactic doses of Factor VII due to a history of ICH. One patient with Factor V deficiency and another with Factor XIII deficiency received prophylactic doses of FFP and Cryoprecipitate, respectively, for the same reason. Tranexamic acid, Cryoprecipitate, fibrinogen, FFP, F VIII, F IX, F VII, emicuzimab, and frequency of prophylaxis (1/W and 2/W) were significantly different among the five groups (P value < 0.05). Duration, prophylactic factor, PLT, and TLC were not significantly different among the five groups. Hb was

Table 4 Treatment Modalities and Laboratory Data Among Studied Patients with Inherited Coagulation Disorders (n = 129)

		Diagnosis					P value
		Hemophilia A (n = 64)	Hemophilia B (n = 16)	Fibrinogen Disorders (n = 25)	Factor VII Deficiency (n = 15)	Rare Coagulation (n = 9)	
Product							
Tranexamic acid		64(100.0%)	16(100.0%)	25(100.0%)	15(100.0%)	7(77.8%)	<0.001
Cryoprecipitate		31(48.4%)	0(0.0%)	15(60.0%)	0(0.0%)	1(11.1%)	<0.001
Fibrinogen		0(0.0%)	0(0.0%)	25(100.0%)	0(0.0%)	0(0.0%)	<0.001
FFP		12(18.8%)	16(100.0%)	14(56.0%)	13(86.7%)	1(11.1%)	<0.001
F VIII		63(98.4%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	<0.001
F IX		0(0.0%)	16(100.0%)	0(0.0%)	0(0.0%)	0(0.0%)	<0.001
F VII		11(17.2%)	0(0.0%)	0(0.0%)	15(100.0%)	0(0.0%)	<0.001
Emicuzimab		11(17.2%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0.016
Duration (years)		6.0 (4.0–8.0)	4.0 (2.0–6.0)	4.0 (2.0–8.0)	3.0 (2.0–5.5)	6.0 (2.0–6.0)	0.170
Type	On-demand	64(100.0%)	16(100.0%)	25(100.0%)	15(100.0%)	9(100.0%)	-
	Prophylactic Factor	34(53.2%)	9(56.3%)	10(40.%)	3(20.0%)	2(22.2%)	0.076
	Non-factor (Emicuzimab)	11(17.2%)	-	-	-	-	
Frequency of prophylaxis	1/W	15(23.4%)	9(56.3%)	10(40.%)	2(13.3%)	2(22.2%)	0.039
	2/W	30(46.9%)	0(0.0%)	0(0.0%)	1(6.7%)	0(0.0%)	0.001
Laboratory data							
Hb (g/dl)		10.05 ± 1.54	11.23 ± 1.31	10.31 ± 1.15	11.35 ± 1.51	10.59 ± 1.32	0.004
P1			0.031	0.940	0.016	0.830	
P2				0.266	0.999	0.816	
P3					0.174	0.987	
P4						0.709	
PLT (X10^3/m)		339.6 ± 120.5	375.4 ± 154.7	396.2 ± 142.6	287.8 ± 99.15	362.8 ± 112.8	0.096
TLC (X10^3/m)		7.93 ± 3.10	8.46 ± 4.19	8.29 ± 3.52	7.61 ± 1.54	6.68 ± 2.50	0.678
PT (sec.)		13.0 (12.10–14.50)	13.40 (12.20–14.50)	24.0 (16.0–44.0)	31.7 (21.70–37.05)	25.50(15.0–27.80)	<0.001
P1			<0.001	<0.001	<0.001	<0.001	
P2				0.806	0.671	0.395	
P3					0.479	0.266	
P4						0.633	
aPPT (sec.)		64.5 ± 18.81	53.9 ± 8.75	60.4 ± 15.8	40.05 ± 4.40	69.48 ± 33.19	0.003
P1			0.371	0.337	0.004	0.977	
P2				1	0.567	0.337	
P3					0.354	0.454	
P4						0.029	

(*Continued*)

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Table 4 (Continued).

	Diagnosis					P value
	Hemophilia A (n = 64)	**Hemophilia B (n = 16)**	**Fibrinogen Disorders (n = 25)**	**Factor VII Deficiency (n = 15)**	**Rare Coagulation (n = 9)**	
FVIII %	0.1 ± 0.09	–	–	–	–	
FIX %	–	3.0 ± 1.0	–	–	–	
Fibrinogen %	–	–	1.4 ± 0.6	–	–	
FVII %	–	–	–	35.0 ± 23.0	–	

Notes: Data presented as frequency (%) or median (IQR) or mean ± SD. Bold text indicates major category or subgroup headings within the table.
Abbreviations: FFP, Fresh Frozen Plasma; F VII, VIII, IX: Factor VII, VIII, IX concentrates, 1/w, Once per week, 2/w: Twice per week, Hb, Hemoglobin, PLT, Platelet, TLC, Total leukocytic count, PT, Prothrombin time, aPPT, Activated partial thromboplastin time.

markedly lower in hemophilia A than in hemophilia B and factor VII deficiency (P value < 0.05), was insignificantly different between hemophilia A and fibrinogen disorders and rare coagulation disorders, and was insignificantly different among the other groups. PT was significantly lower in hemophilia A than in hemophilia B, factor VII deficiency, fibrinogen disorders, and rare coagulation disorders. (P value < 0.05) and was insignificantly different among the other groups. aPPT was significantly lower in factor VII deficiency than in hemophilia A and rare coagulation disorders (P value < 0.05) and was insignificantly different among the other groups.

Correlative analysis identified FISH functional score as the strongest predictor of chronic hemophilic arthropathy, while ABR represented the main modifiable risk factor as shown in Table 5. Haemoglobin level and ISTH bleeding score showed moderate correlations, indicating their value as accessible clinical markers. Weak association with disease severity and lack of correlation with Age highlight that management quality and bleeding control outweigh factor level or disease duration. Overall, results support a multifactorial, risk-stratified approach emphasizing function and bleeding frequency over laboratory severity.

ROC analysis was performed to evaluate the discriminative performance of selected clinical and laboratory variables in distinguishing patients with and without chronic hemophilic arthropathy. The FISH functional score showed the highest discriminative accuracy among the evaluated variables (AUC = 0.715), with an optimal cutoff of ≤26 offering 73.2%

Table 5 Correlation Between Chronic Hemophilic Arthropathy in Hemophilia A Patients and Demographic, Clinical and Laboratory Parameters (n = 64)

Risk Factor	Correlation (r)	95% CI	P	Interpretation
FISH Functional Score	−0.430	−0.60 to −0.22	**<0.01***	Moderate negative
ABR	0.390	0.17 to 0.58	**<0.01***	Moderate positive
Hemoglobin level (g/dl)	−0.383	−0.57 to −0.16	**<0.01***	Moderate negative
ISTH Bleeding Score	0.353	0.13 to 0.55	**<0.01***	Moderate positive
HJHS Joint Score	0.250	0.03 to 0.45	**<0.05***	Weak positive
Disease Severity	0.230	0.02 to 0.42	>0.05	Weak positive
Consanguinity	0.180	−0.07 to 0.41	>0.05	No correlation
Family History	0.160	−0.09 to 0.39	>0.05	No correlation
Age (years)	−0.006	−0.25 to 0.24	>0.05	No correlation

Note: *Significant P value <0.05, Bold text indicates major category or subgroup headings within the table.
Abbreviations: CI, Confidence interval; ISTH, International Society on Thrombosis and Haemostasis; FISH, Functional independence score of hemophilia; HJHS, Hemophilia Joint Health Score; ABR, Annual bleeding rate.

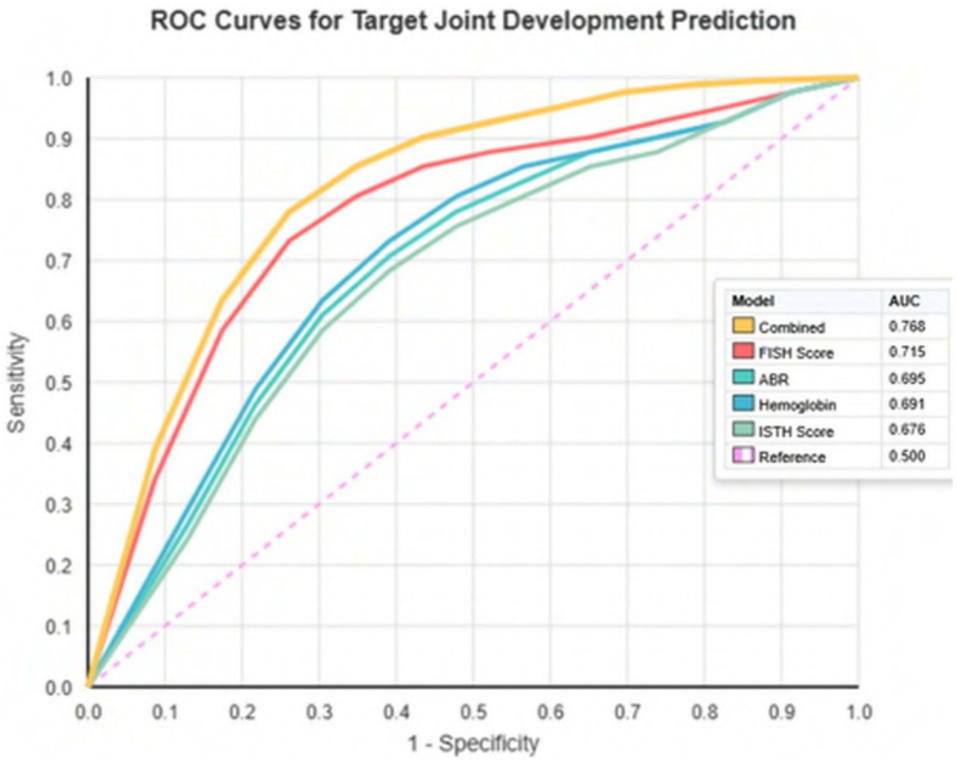

Figure 2 ROC analysis of hemophilia A risk factors for predicting chronic hemophilic arthropathy development.

sensitivity and 69.6% specificity followed by ABR (AUC = 0.695) with a cutoff of >6 episodes per year. Disease severity demonstrated limited discriminative ability (AUC = 0.615), while Age showed no discriminatory value (AUC = 0.503).

These Findings Indicate an Association Rather Than a Predictive or Causal Relationship (Figure 2).

In univariate regression, Age at diagnosis, duration of the disease, ABR, HJHS Joint score and FISH functional score were independent predictors of chronic hemophilic arthropathy (P value < 0.05). In Multivariate regression, Age at diagnosis, ABR, HJHS Joint score and FISH functional score were independent predictors of chronic hemophilic arthropathy (P value < 0.05) and remained independent predictors, while disease duration lost significance (Table 6).

Table 6 Univariate and Multivariate Regression Predictors of Chronic Hemophilic Arthropathy

	Univariate			**Multivariate**		
	Odds ratio	**95% CI**	**P**	**Odds ratio**	**95% CI**	**P**
Age (years)	1.036	0.934–1.148	0.505	-	-	-
Age at diagnosis (years)	0.545	0.3881 −0.764	0.004	0.5319	0.348–0.814	0.036
Duration of the disease (years)	1.141	1.0249–1.271	0.016	1.0659	0.938–1.211	0.327
ABR	1.139	1.1787–1.662	0.001	1.0899	0.883–1.345	0.422
HJHS Joint Score	1.733	1.365–2.200	<0.001	1.8759	1.275–2.759	0.001
FISH Functional Score	0.249	0.1201–0.519	0.002	0.2610	0.110–0.6173	0.002

Note: Bold text indicates major category or subgroup headings within the table.

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Von Willebrand Disease and Inherited Platelet Disorders (IPDs)

Demographics, initial clinical presentation, bleeding triggers and severity scores, longitudinal follow up, complications, treatment modalities and laboratory data among our vWD and IPDs studied patients are shown in Table 7.

Table 7 Demographics, Initial Clinical Presentation, Longitudinal Follow Up Data, Bleeding Severity Scores, Laboratory Data, and Treatment Modalities of Patients with Von Willebrand Disease and Inherited Platelet Disorders (N = 70) *

		Diagnosis			P value	Post hoc
		vWD Type I (n = 43)	vWD Type III (n = 14)	Inherited Platelet (n = 13)		
Sex	**Male**	23(53.5%)	7(50.0%)	7(53.8%)	0.972	
	Female	20(46.5%)	7(50.0%)	6(46.2%)		
Age (years)		9.0 (5.0–11.0)	9.50 (5.50–11.0)	5.0 (4.0–7.0)	0.040	P1 = 0.293 P2 = 0.140 P3 = 0.040
Consanguinity	**Positive**	22(51.2%)	4(28.6%)	11(84.6%)	0.013	
Family History of similar condition		22(48.8%)	7(50.0%)	8(61.5%)	0.783	
Family History of Bleeding		22(48.8%)	7(50.0%)	8(61.5%)	0.783	
Clinical data at initial presentation						
Site of first bleeding attack	**Mucous Membrane**	22(51.1%)	4(28.6%)	4(30.8%)	0.207	
	Gum bleeding	10(23.2%)	2(14.3%)	2(15.4%)	0.689	
	Epistaxis	7(16.2%)	1(7.1%)	0(0.0%)	0.321	
	Circumcision	4(9.3%)	1(7.1%)	2(15.4%)	0.752	
	Tongue injury	1(2.3%)	0(0.0%)	0(0.0%)	0.727	
	Skin	21(48.9%)	3(21.4%)	7(53.8%)	0.149	
	Puncture site	2(4.7%)	1(7.1%)	1(7.7%)	0.888	
	Easy bruising	10(23.3%)	1(7.1%)	5(38.5%)	0.153	
	Umbilical stump	9(20.9%)	1(7.1%)	0(0.0%)	0.117	
	Eyelid wound	0(0.0%)	0(0.0%)	1(7.7%)	0.108	
	Organ	0(0.0%)	7(50.0%)	2(15.4%)	<0.001	
	Rectal	0(0.0%)	1(7.1%)	1(7.7%)	0.193	
	Menorrhagia	0(0.0%)	4(28.6%)	0(0.0%)	0.002	
	Hematemesis	0(0.0%)	1(7.1%)	0(0.0%)	0.132	
	Hematuria	0(0.0%)	1(7.1%)	1(7.7%)	0.193	
Age at first bleeding attack (months)		12.0 (6.0–24.0)	12.0 (6.13–18.0)	5.0 (2.0–24.0)		0.185
<1 year old		22(51.2%)	10(71.4%)	10(76.9%)	0.156	
1–6 years old		21(48.8%)	4(28.6%)	3(23.0%)		
7–12 years old		0(0.0%)	0(0.0%)	0(0.0%)		
12–18 years old		0(0.0%)	0(0.0%)	0(0.0%)		
Age at diagnosis (months)		18.0 (7.0–60.0)	18.0 (14.0–21.0)	12.0 (6.0–24.0)	0.185	

(*Continued*)

Table 7 (Continued).

		Diagnosis			P value	Post hoc
		vWD Type I (n = 43)	vWD Type III (n = 14)	Inherited Platelet (n = 13)		
Duration of disease (years)		6.0 (3.0–9.0)	9.0 (5.50–9.50)	4.0 (3.0–5.0)	0.080	
Bleeding triggers	**Spontaneous**	13(30.2%)	10(71.4%)	8(61.5%)	0.010	
	Traumatic	43(100.0%)	14(100.0%)	13(100.0%)	-	
ISTH score		7.75 ± 2.50	8.13 ± 1.61	7.85 ± 2.08		0.650
ABR		6.0 (4.0–7.0)	7.50 (6.0–8.50)	5.0 (4.0–6.0)		0.133
Longitudinal follow up clinical data						
Frequency of hospitalization/Year		2.0 ± 0.84	10.14 ± 3.48	5.33 ± 2.15	<0.001	P1 < 0.001 P2 < 0.001 P3 < 0.001
Hospital admission indications	**Gum bleeding**	0(0.0%)	5(35.7%)	2(15.4%)	0.004	
	Epistaxis	20(45.6%)	10(71.4%)	6(46.2%)	0.246	
	Bruising easily	9(21.0%)	0(0.0%)	5(38.5%)	0.043	
	Rectal	0(0.0%)	1(14.3%)	2(15.4%)	0.047	
	Hematemesis	5(11.6%)	4(28.6%)	0(0.0%)	0.080	
	Hematuria	0(0.0%)	0(00.0%)	1(7.7%)	0.108	
	Intracranial hemorrhage	0(0.0%)	2(14.3%)	1(7.7%)	0.058	
	Retinal hemorrhage	0(0.0%)	2(14.3%)	1(7.7%)	0.058	
	Joint bleeds	0(0.0%)	5(35.7%)	0(0.0%)	<0.001	
	Sepsis	1(2.3%)	0(0.0%)	0(0.0%)	0.727	
PICU admission indications	**Hematemesis**	0(0.0%)	1(7.1%)	0(0.0%)	0.132	
	Intracranial hemorrhage	0(0.0%)	2(14.3%)	1(7.7%)	0.058	
	Sepsis	1(2.3%)	0(0.0%)	0(0.0%)	0.727	
Surgical history	**Circumcision**	20(46.5%)	7(50.0%)	6(46.2%)	0.972	
	Adenoidectomy	0(0.0%)	1(7.1%)	0(0.0%)	0.132	
	Cholecystectomy	0(0.0%)	1(7.1%)	0(0.0%)	0.132	
	Splenectomy	0(0.0%)	1(7.1%)	0(0.0%)	0.132	
	Tonsillectomy	2(4.7%)	0(0.0%)	0(0.0%)	0.524	
	GI endoscope	0(0.0%)	2(14.3%)	2(15.4%)	0.034	
	ICH evacuation	0(0.0%)	2(14.3%)	1(7.7%)	0.058	
Disease-related complications	**Intracranial Hemorrhage**	0(0.0%)	2(14.3%)	1(7.7%)	0.058	
	Chronic arthropathy	0(0.0%)	5(35.7%)	0(0.0%)	<0.001	
	Angiodysplasia	0(0.0%)	2(14.3%)	0(0.0%)	0.016	
Treatment-related complications						
Inhibitor to Factor VIII concentrate		0(0.0%)	3(21.4%)	–		0.012

(*Continued*)

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Table 7 (Continued).

		Diagnosis			P value	Post hoc
		vWD Type I (n = 43)	vWD Type III (n = 14)	Inherited Platelet (n = 13)		
Allergic reactions		4(9.3%)	6(42.8%)	4(30.8%)	0.014	
Treatment modalities						
Product	**Tranexamic acid**	43(100.0%)	14(100.0%)	13(100.0%)	-	
	Platelets	0(0.0%)	0(0.0%)	13(100.0%)	<0.001	
	Cryoprecipitate	18(41.9%)	12(85.7%)	0(0.0%)	<0.001	
	FFP	4(9.3%)	1(7.1%)	0(0.0%)	0.521	
	F VIII + VonWillebrand	23(53.5%)	14(100.0%)	0(0.0%)	<0.001	
	F VII	0(0.0%)	2(14.2%)	4(30.8%)	0. 017	
Duration (in years)		6.0(3.0–9.0)	9.0(5.50–9.50)	4.0(3.0–5.0)		0.080
Type	**On-Demand**	43(100.0%)	14(100.0%)	13(100.0%)	-	
	Prophylactic 1/W	0(0.0%)	11(78.5%)	0(0.0%)	<0.001	
	Prophylactic 2/W	0(0.0%)	3(21.4%)	0(0.0%)	0. 019	
Laboratory data						
Hb (g/dl)		11.0 (9.50–11.70)	10.40 (9.30–11.75)	10.0 (9.0–10.50)		0.070
PLT count (X10^3/m)		339.0(262.0–414.0)	342.5(266.5–401.0)	239.0(174.0–282.0)	<0.001	P1 < 0.001 P2 < 0.001 P3 = 955
TLC (X10^3/m)		7.35(6.50–8.40)	7.15(5.95–8.50)	8.20(6.0–10.0)		0.390
PT (sec.)		13.0(12.30–14.20)	12.45(12.10–13.0)	13.0(13.0–16.0)		0.199
aPPT (sec.)		54(48.80–70.0)	61.75(56.0–70.75)	35(15.70–35.0)	<0.001	P1 = 0.845 P2 < 0.001 P3 < 0.001
			Glanzmann's Thrombasthenia (n = 9)		**Bernard Soulier Syndrome (n = 4)**	
ADP %		–	–	5.0(3.0–14.0)	91.0(84.9–97.1)	
Ristocetin %		–	–	89.5(83.3–92.0)	22.5(15.6–29.4)	
Collagen %		–	–	74(60–87)		
VIII %		31 (35–47)	9.5 (8–11)			
VW AG %		18(6–37)	8(6–8)	–		
VW Activity %		16(13–50)	0.21(3–6.44)	–		

Notes: * One patient with CD36 deficiency was excluded from the analysis. Data presented as frequency (%), median (IQR) or mean ± SD Bold text indicates major category or subgroup headings within the table.

Abbreviations: vWD, Von Willebrand disease; ISTH, International society on thrombosis and haemostasis; GI, Gastrointestinal; ICH, Intracranial haemorrhage; ABR, Annual bleeding rate; PICU, Pediatric intensive care unit; FFP, Fresh frozen plasma; 1/w, Once per week; 2/w, Twice per week; Hb, Hemoglobin; PLT, Platelet; TLC, Total leukocytic count; PT, Prothrombin time; aPPT, Activated partial thromboplastin time.

Angiodysplasia was evident in 14.3% of vWD type III patients (n = 2); one patient had vascular malformations of parapharyngeal space, and another one had rectal vascular malformations that were treated by embolization. Tranexamic acid (TXA) was used universally in all groups. Worth noting, rVII was used as a bypassing agent in 14.2% (n = 2) of vWD type III due to development of inhibitors to Factor VIII concentrates and as alternative management in 30.8% of patients with IPDs due to platelet transfusion reactions. Comparative analysis between vWD types and IPDs showed significantly lower mean Age and higher consanguinity rate among IPDs versus vWD ($p = 0.04$ for both) while gender, ISTH score and Hb levels did not differ significantly ($p > 0.05$) [data not shown].

Sex, family history of similar condition, family history of bleeding, site of first bleeding attack (mucous membrane, gum bleeding, epistaxis, circumcision, tongue injury, skin, puncture site, easy bruising, umbilical stump, eyelid wound, rectal, hematemesis and hematuria), Age at first bleeding attack, Age at diagnosis, duration of disease, ISTH score, ABR, hospital admission indications (epistaxis, hematemesis, hematuria, intracranial hemorrhage, retinal hemorrhage, and sepsis), PICU admission indications (hematemesis, intracranial hemorrhage and sepsis), surgical history circumcision (adenoidectomy, cholecystectomy, splenectomy, tonsillectomy and GI endoscope), disease-related complications (intracranial hemorrhage), treatment product (FFP), duration, Hb, TLC and PT were insignificantly different among the three groups.

Consanguinity, site of first bleeding attack (organ and menorrhagia), bleeding triggers (spontaneous), hospital admission indications (gum bleeding, bruising easily, rectal and joint bleeds), surgical history circumcision (GI endoscope), disease-related complications (chronic arthropathy and angiodysplasia), inhibitor to factor VIII concentrate, allergic reactions, treatment product (platelets, Cryoprecipitate, F VIII + Von Willebrand and F VII), type (prophylactic 1/W and prophylactic 2/W) were significantly different among the three groups (P value < 0.05). Age was significantly higher in vWD Type III than inherited platelet (P value = 0.040) and was insignificantly different between vWD Type I (vWD Type III and inherited platelet). Frequency of hospitalization/Year was significantly higher in vWD Type III than (vWD Type I and inherited platelet). PLT count was significantly higher in vWD Type I than inherited platelet, was significantly lower in vWD Type I than vWD Type III and was insignificantly different between vWD Type III and inherited platelet. aPPT was insignificantly different between vWD Type I and vWD Type III and was significantly lower in vWD Type III than inherited platelet and vWD Type I.

Discussion

Inherited bleeding disorders pose a major challenge in pediatric practice because of their chronic course, clinical complexity, and need for long-term, costly treatment. Accurate diagnosis and early intervention are essential, given their variable presentation and prevalence.[1]

In our cohort, HA was the most prevalent ICD, succeeded by fibrinogenopathies and HB. Consistent with the X-linked transmission and the rare/under recognition of hemophilia among females, HA and HB occurred exclusively in males, whereas fibrinogen disorders and rare coagulation defects showed a near-equal or female predominance. These sex distributions accord with the observations of Hussain et al[9] who classified HA as the preeminent bleeding disorder in their populations. The female prevalence and comparable frequency in fibrinogen and rare disorders reflect their autosomal inheritance and corroborate findings in both regional and global registries. High consanguinity rate noted among our patients with fibrinogen and rare coagulation disorders aligns with findings in Middle Eastern and South Asian populations Naz et al,[10] and supports the notion that autosomal recessive transmission is common in these disorders, particularly with higher rates of consanguineous marriages. Worth noting, absence of family history of similar condition or bleeding was evident in considerable frequency (40–60%) across all our ICDs cohort. This goes in line with Bannow and Konkle (2018)[11] who cautioned that differences in bleeding phenotype and variations in individual clinical presentations carry greater prognostic weight than pedigree data alone, emphasizing the importance of systematically integrating bleeding severity scores and individualized clinical evaluation into diagnostic algorithms.

Most of our cohort resided in Cairo and Giza which relates to their proximity to our referral center. However, presence of a wide-ranging and diverse population from Upper and Lower Egypt governorates in our sample sheds light on the growing, and nation-wide burden of Inherited bleeding disorders and the need to create decentralized diagnostic

and treatment services. The presence of patients from remote and underserved regions demonstrates the need for increased awareness, screening, and care that is affordable and accessible across the country.

Within our cohort, HA was characterized by the earliest Age of first bleeding and diagnosis, typically in infancy, reflecting early clinical recognition due to severe bleeding symptoms and increasing awareness about the disease among healthcare professionals and consistent with Chalmers et al[12] linking early-onset ICH to severe phenotypes. In contrast, fibrinogenopathies and rare coagulation disorders were diagnosed later reflecting milder or nonspecific initial presentations or clinical awareness gaps among healthcare professionals about these heterogeneous rare disorders, echoing Shahbazi et al[13] regarding diagnostic delays in non-hemophilia disorders.

Clinically, HA showed the highest hospitalization rate and dominant joint bleeding (76.6%), confirming findings by Hussain et al[9] and Collins et al[14] ICH requiring PICU care occurred mainly in HA and rare deficiency groups, consistent with Chalmers et al[12] highlighting early-life vulnerability in severe disease. Circumcision was the most frequent first bleeding site in males (42.2% in HA), aligning with prior reports.[15,16]

Our analysis documented recurrent arthropathies and target joints among our hemophilia patients with chronic arthropathy evident in 64% of HA and 31.2% of HB patients in line with reports by Zavala et al (2024)[17] and Bordbar et al[18] HJHS assessment showed the highest arthropathy burden in HA, followed by HB, while other disorders had near-normal joint scores, consistent with Hussain et al[(11)]. No association was found between Age and joint deterioration, highlighting that management quality, not disease duration, determines musculoskeletal outcomes. Despite current prophylaxis being received by 70.4% and 56.3% of our HA and HB patients, respectively, our data emphasize the severe bleeding phenotype and significant burden of joint damage among our patients and calls for the utmost need for early initiation of prophylaxis and increasing awareness and health education among our patients/caregivers and all healthcare teams dealing with the patients along their disease course to preserve joints health and improve disease outcomes and patients' quality of life.

While our HA patients showed a more severe bleeding phenotype than HB, evidenced by significantly lower mean Age at first bleeding, higher ISTH score and ABR and lower hemoglobin, both FISH and HJHS were comparable with no statistically significant difference emphasizing the comparable burden of joint damage in HB patients.

Worth noting, comparisons between patients with severe and moderate HA as per factor VIII levels showed no statistically significant differences across all studied scores (ISTH, ABR, FISH and HJHS) supporting the hypothesis that patients with moderate hemophilia might still exhibit a severe disease phenotype. However, the relatively small sample size of patients with moderate HA might be a limitation to this observation.

Inhibitors Developed in 31.2% of HA Patients (14% Transient, 17.2% Persistent), Consistent with Global Data

Among 71 patients with vWD and IPDs, vWD predominated (80.3%), mainly Type I (75.4%), with Type III comprising 24.6%. IPDs represented 19.7%, mainly Glanzmann's thrombasthenia (64.3%), followed by Bernard–Soulier syndrome (28.6%). These findings align with Bannow & Konkle[11] who identified vWD as the most common IBD and corroborate the predominance of Type I vWD reported globally. The proportion of platelet function disorders exceeded the 7% prevalence reported by Hussain et al[9] reflecting enhanced diagnostic rigor and referral practices.

Consanguinity was frequent, observed in 28.6% of Type III vWD and 84.6% of IPD cases, consistent with Naz et al[10] and Hussain et al[9] supporting an autosomal recessive inheritance pattern. Atiq et al[19] reported a similar prevalence of 60% among individuals with vWD.

Clinically, mucocutaneous bleeding predominated across all groups. Cutaneous bleeding occurred in 53.8% of IPD cases. Type III vWD showed more severe organ hemorrhage (50%) and the highest ABR with ICH and joint bleeds observed in 14.3% and 35.7%, respectively, underscoring its significant associated morbidity. Spontaneous bleeding was most frequent in Type III vWD (71.4%) and IPDs (61.5%), reinforcing their severe phenotypes.[11] Epistaxis (45.6%), gum bleeding (23.2%), and easy bruising (23.3%) were common in Type I vWD but less frequent than those reported by Yu et al[20] Angiomatous malformations were identified in 14.3% of Type III vWD patients, consistent with Chornenki et al.[21]

Menorrhagia was notably less prevalent in our vWD patients (11.6% and 28.6% in Type I and III respectively) compared to other reports[22] possibly due to our younger age group (not yet reaching menarche or had limited exposure to menstrual cycles) reducing the likelihood of reporting menorrhagia. These findings underscore the importance of Age and reproductive history in evaluating bleeding symptoms in pediatric and adolescent populations with Inherited bleeding disorders.

Therapeutically, TXA was administered universally. FVIII/VWF concentrates were used in all type III vWD patients, adhering to WFH (2020) guidelines,[23] while cryoprecipitate use (85.7%) underscored reliance on plasma-derived therapy in resource-limited contexts.[24] Platelet transfusion (100%) and rFVIIa (30.8%) were commonly employed in IPDs, consistent with Buchanan et al[25] and Naz et al[10] Prophylactic regimens were implemented in 78.5% of Type III vWD cases, a higher rate than previously documented, indicating improved clinical awareness and adherence to WFH recommendations.

Within our cohort, type III vWD demonstrated the most concerning adverse treatment outcomes, with inhibitors to factor VIII in 21.4% of patients and allergic reactions occurring in 42.8%, necessitating a therapeutic shift. These rates are higher than those in European registries,[12] yet are consistent with findings from Naz et al[10] reported higher incidences of inhibitor and allergic reactions in settings characterized by delayed diagnosis and predominant use of plasma-derived products among patients with severe vWD and Glanzmann's thrombasthenia. Among IPDs, allergic platelet transfusion-related reactions occurred in 30.8% of cases, with an equal proportion requiring conversion to rFVIIa, consistent with the observations of Bannow and Konkle.[11]

Hemoglobin levels were reduced across all groups, with the lowest mean in platelet disorder cohort, reflecting significant bleeding and anemia, a pattern in line with Wolf et al.[24]

Platelet counts were normal or elevated in our vWD, while IPDs showed variable counts reflecting phenotypic heterogeneity (normal in Glanzmann's thrombasthenia and mild thrombocytopenia in Bernard–Soulier syndrome). Prolonged aPTT in vWD types I and III—but not in IPDs—further distinguished these disorders, consistent with the diagnostic framework of Gresele et al.[26]

Our study was limited by a relatively small sample size and being conducted at a single center. Early screening and genetic counseling, especially in consanguineous populations along with individualized, severity-based management and improved access to advanced diagnostics and therapies are essential to improve outcomes.

Conclusions

This study highlights the diverse presentation, management, and outcomes of pediatric inherited bleeding disorders. HA and vWD were the most prevalent, each with distinct bleeding patterns, complications, and therapeutic needs. IPDs and rare coagulation defects, though less common, posed significant diagnostic and treatment challenges, especially with consanguinity and family history. Severe phenotypes like vWD type III and HA showed early-onset bleeding, significant joint involvement, and complications such as ICH which calls for equitable access to multidisciplinary care, early prophylaxis programs, preservation of joint health regimens and enhancing physical therapy and psychosocial support. Our findings underscore the importance of individualized, diagnosis-specific management based on detailed clinical, laboratory, and imaging assessments.

Abbreviations

ABR, Annual Bleeding Rate; ADP, Adenosine Diphosphate; Aptt, Activated Partial Thromboplastin Time; AUC, Area Under the Curve; BS, Bernard–Soulier Syndrome; CBC, Complete Blood Count; CD36, Cluster of Differentiation 36; CI, Confidence Interval; CT, Computed Tomography; FFP, Fresh Frozen Plasma; FII, Factor II; FISH, Functional Independence Score of Hemophilia; FISH score, Functional Independence Score of Hemophilia score; FV, Factor V; F VII, Factor VII; F VIIa, Recombinant Activated Factor VII; F VIII, Factor VIII; F IX, Factor IX; FX, Factor X; FXI, Factor XI; FXII, Factor XII; FXIII, Factor XIII; GI, Gastrointestinal; GT, Glanzmann Thrombasthenia; HA, Hemophilia A; HB, Hemophilia B; Hb, Hemoglobin; HJHS, Hemophilia Joint Health Score; Inherited bleeding disorders – Inherited Bleeding Disorders; ICDs, Inherited Coagulation Disorders; ICH, Intracranial Hemorrhage; IPDs, Inherited Platelet Disorders; IPFDs, Inherited Platelet Function Defects; IQR, Interquartile Range; ISTH, International Society of

Thrombosis and Hemostasis; LTA, Light Transmission Aggregometry; MRI, Magnetic Resonance Imaging; PICU, Pediatric Intensive Care Unit; PLT, Platelet Count; PT, Prothrombin Time; rFVIIa, Recombinant Activated Factor VII; ROC, Receiver Operating Characteristic; SD, Standard Deviation; SPSS, Statistical Package for the Social Sciences; TLC, Total Leukocytic Count; TXA, Tranexamic Acid; vWD, von Willebrand Disease; vWF, von Willebrand Factor; WFH, World Federation of Hemophilia.

Standards of Reporting

STROBE guidelines were followed.

Data Sharing Statement

All data generated or analyzed during this study are included in this published article.

Author Contributions

Investigation: SMF; draft manuscript: ME, MA, MSEMAK. All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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