Validation of the ISTH/SSC bleeding assessment tool for inherited platelet disorders

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SUPPLEMENTARY MATERIALS

Statistical analysis

Based on previous data on the prevalence of hemorrhagic symptoms in VWD-1, patients with IPFD or IT and HC [1-3], we expected that a significant difference in the BS would be shown by enrolling at least 300 subjects per group (β=0.8, α=0.05).

Descriptive analyses have been performed to assess the sample composition: age, sex, type of diagnosis, age at diagnosis. Data are reported as medians and 25th-75th percentiles (IQR) when continuous, and as counts and percentages when categorical.

Distributions of WHO bleeding score and ISTH-BAT bleeding score in the four groups (HC, VWD-1, IT, IPFD) have been compared using Sidak's multiple comparisons test.

Pearson correlation coefficient was calculated to assess the association between WHO bleeding score and ISTH-BAT bleeding score with age, age at diagnosis and platelet number.

The kappa statistic was used to test interrater reliability [4]. Receiver operating characteristic (ROC) curves were calculated for diagnostic prediction rule to discriminate between different groups and area under curve (AUC), with binomial exact confidence interval for AUC [5,6], sensitivity, specificity, negative predictive value (NPV) and positive predictive value (PPV) for the analyzed populations were assessed. Cut-off values using the Youden index for the most relevant comparisons were also calculated.

The R software (R Foundation for Statistical Computing, Vienna, Austria. www.R-project.org) was used for all analyses. A two-sided $p<0.05$ was considered as statistically significant.

References

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Supplementary table 1. Diagnostic criteria for IT required for the enrollment in the study.

Disease (abbreviation, OMIM entry)	**Inheritance**	**Gene (chromosome localization)**	**Diagnostic criteria**
SYNDROMIC FORMS			
X-linked thrombocytopenia (XLT, 313900)	XL	*WAS* (Xp11)	Genetic analysis
MYH9-related disease (*MYH9*-RD,155100)	AD	*MYH9* (22q12-13)	Genetic analysis or positive immunofluorescence screening test for MYH9 protein aggregates
Paris-Trousseau thrombocytopenia (TCPT, 188025/600588), Jacobsen syndrome (JBS, 147791)	AD	Large deletion (11q23-ter)	Genetic analysis
Thrombocytopenia with absent radii (TAR, 274000)	AR	*RBM8A* (1q21.1)	Genetic analysis or typical phenotype
Congenital thrombocytopenia with radio-ulnar synostosis (CTRUS, 605432)	AD	*HOXA11* (7p15-14)	Genetic analysis or typical phenotype
Thrombocytopenia associated with sitosterolaemia (STSL, 210250)	AR	*ABCG5*, *ABCG8* (2p21)	Genetic analysis
NON-SYNDROMIC FORMS			
Monoallelic Bernard-Soulier syndrome (mBSS, 153670)	AD	*GP1BA* (17p13), *GP1BB* (22q11)	Genetic analysis
ANKRD26-related thrombocytopenia (THC2, 313900)	AD	*ANKRD26* (10p2)	Genetic analysis
TUBB1-related thrombocytopenia (TUBB1-RT, 613112)	AD	*TUBB1* (6p21.3)	Genetic analysis
CYCS-related thrombocytopenia (THC4, 612004)	AD	*CYCS* (7p15.3)	Genetic analysis
Congenital amegakaryocytic thrombocytopenia (CAMT, 604498)	AR	*MPL* (1p34)	Genetic analysis or typical phenotype
GATA1-related diseases *(GATA1*-RDs, Dyserythropoietic anemia with thrombocytopenia, 300367 – X-linked thrombocytopenia with thalassemia, 314050)	XL	*GATA1* (Xp11)	Genetic analysis
ACTN1-related thrombocytopenia *(ACTN1-RT,* 615193*)*	AD	*ACTN1* (14q24)	Genetic analysis
FLNA-related thrombocytopenia *(FLNA-RT, nd)*	XL	*FLNA* (Xq28)	Genetic analysis

AD= autosomal dominant; AR= autosomal recessive; XL= X-linked

Supplementary table 2. Diagnostic criteria for IPFD required for the enrollment in the study.

Disease (abbreviation, OMIM entry)	***Inheritance***	***Gene (chromosome localization)***	**Diagnostic criteria**
SYNDROMIC FORMS			
Hermansky–Pudlak syndrome (HPS, 203300)	AR	*HPS1, ADTB3A, HPS3, HPS4, HPS5,HPS6, DTNBP1, BLOC1S3* BLOC1S3 (different locations) HPS4, HPS5,HPS6, DTNBP1 BLOC1S3 (different locations)	Genetic analysis or typical phenotype + delta granule deficiency or decrease in platelet nucleotide content and increased ATP/ADP ratio (+decreased 5HT content)
Chediak-Higashi Syndrome (CHS, 214500)	AR	*CHS1 (1q42.1-42.2)*	
NON SYNDROMIC FORMS			
Glanzmann thrombasthenia (GT, 273800)	AR	*ITGA2B* (17q21.31), *ITGB3* (17q21.32)	Genetic analysis or absent platelet aggregation to all agonists but ristocetin or absent GPIIb-IIIa
§*ITGA2B*/*ITGB3*-related thrombocytopenia (*ITGA2B*/*ITGB3-RT*, 187800)	AD	*ITGA2B* (17q21.31), *ITGB3* (17q21.32)	Genetic analysis
§Biallelic (bBSS, 231200)	AR	*GP1BA* (17p13), *GP1BB* (22q11), *GP9* (3q21)	Genetic analysis or absent GPIb/IX/V or absent RIPA and normal to other agonists
§Familial platelet disorder and predisposition to acute myelogenous leukemia (FPD/AML, 601399)	AD	*RUNX1* (21q22)	Genetic analysis
$P2Y_{12}$ deficiency (nd, 609821)	AR	*P2RY12* (3q24-q25)	Genetic analysis or selective, severe defect of platelet aggregation by ADP, defect of inhibition o adenylyl cyclase by ADP (VASP phosphorylation assay)
Defect of thromboxane A2 receptor (nd, 188070)	AD	*TBXA2R* (19p13.3)	Genetic analysis or defective platelet aggregation by U46619 and by arachidonic acid

Scott syndrome (SCTS, 262890)	AR	*TMEM16F* (12q12)	Genetic analysis
Quebec platelet disorder (QPD, 601709)	AD	*PLAU* (10q24)	Genetic analysis
Delta granule deficiency	AR/AD	*Unknown*	Absence of delta-granules (TEM) or decrease in platelet nucleotide content and increased ATP/ADP ratio (+decreased 5HT content)
Combined alpha-delta granule deficiency (nd, 185050)	AR/AD	Unknown	Severe deficiency of alpha and delta granules
§*Platelet-type Von Willebrand Disease (VWDP, 177820)*	AD	*GP1BA (17p13.2)*	Genetic analysis
§*Gray platelet syndrome (GPS, 139090)*	AR	*NBEAL2* (3p21.1)	Genetic analysis or absence of alpha-granules
§*Gray platelet syndrome with mutation in GFI1B (*187900)	AD	*GFI1B* (9q34.13)	Genetic analysis
Primary secretion defect (nd, nd)	AR/AD	*Unknown*	Reduced primary platelet granule secretion upon stimulation by different platelet aggregation agonists, normal TxB2 production induced by AA (or serum TxB2) and normal granule content.
Defects in collagen receptors (nd, nd)	AR	*Unknown*	Defective platelet aggregation in the response to collagen
Stormorken syndrome (nd, 185070)	*AD*	*ORAI1 (12q24.31)* *STIM1 (11p15.5)*	*Genetic analysis*
COX-1 deficiency	*AD*	*Unknown*	*Defective aggregation in response to arachidonic acid; defective serum TXB2;*
cPLA2 deficiency	*AR*	*PLA2G4A (1q31.1)*	*Genetic analysis*
Tx synthase deficiency	*AD*	*TBXAS1 (7q34)*	*Genetic analysis*
PKC deficiency	*unknown*	*Unknown*	*Defective aggregation in response to Thrombin and PAF; defective GPIIb/IIIa activation*

§= IPFD associated with thrombocytopenia.

AD= autosomal dominant; AR= autosomal recessive; XL= X-linked

Supplementary Table 3. Baseline characteristics of the patients and controls.

	N	Females %	Median age (IQR)	Median platelet count ($x10^9$/L) (IQR)
IPFD	196	61.0	31 (18.5-50)	190 (120-265.5)
IT	286	54.6	41 (29-52)	57.5 (28-85)
VWD-1	303	59.1	38 (23-51)	250 (210-298.5)
HC	313	60.1	40 (29-53)	245.5 (215-283.5)
TOT	1098	58.5	39 (25-52)	211 (93-298.5)

HC= healthy controls; IPFD= inherited platelet function disorders; IT= inherited thrombocytopenias; IQR=interquartile range; VWD-1= von Willebrand disease type 1.

Supplementary Table 4. ISTH-BAT and WHO BS distribution in specific IPFDs and ITs

IPFD	N	Median ISTH-BAT (IQR)	ISTH-BAT Median (IQR) F Median (IQR) M	ISTH-BAT Min-max F Min-max M	Median WHO (IQR)
Glanzmann thrombasthenia	79	11 (8-16)	12 (8-16) 10 (7-13.5)	1-26 4-20	3 (3-3)
δ-storage pool deficiency	21	6 (3.75-10.5)	6 (5-13.5) 4 (2.75-9.25)	1-17 1-16	2 (1-2)
Biallelic Bernard Soulier syndrome	20	8.5 (7.5-12.5)	8.5 (8-11.5) 8 (1-12.75)	4-27 0-16	3 (2-3)
Primary secretion defect	20	7.5 (3.5-12.5)	12 (7-14) 6 (0.5-6)	1-21 0-11	1 (1-2)
Familial platelet disorder associated with myeloid malignancy	8	4.5 (1-5.5)	4.5 (3.5-6.2) 2.5 (0-5.2)	2-10 0-6	1.5 (0.7-2)
Gray platelet syndrome	7	12 (10-14.25)	15 (13.5-15.5) 10 (9.5-10.5)	12-16 8-12	2 (2-2.5)
Hermansky-Pudlak syndrome	7	5 (2-13.25)	6.5 (2.75-13.2) 1 -	2-18 1-1	2 (1-2.5)
Quebec platelet disorder	7	12 (9-20.75)	8 - 16 (12-20.7)	8-8 8-27	3 (3-3)
Defect of the $P2Y_{12}$ Purinergic Receptor	6	10.5 (4-15)	13 (10.5-14) 4 (3-11)	8-15 2-18	2 (1.2-2.7)
Combined alpha-delta granule deficiency	5	8 (5.75-9)	8.5 (6.5-9) 7 -	2-9 7-7	2 (1-2)
Glanzmann Thrombasthenia Variant	5	8 (1.5-8.25)	8 (2-8) -	0-9 -	2 (1-3)
CalDAG-GEFI defect	3	22 (13-23.5)	24 - 16 (13-19)	24-24 10-22	3 (3-3)
Defect of the TP receptor	3	4 (4-5.5)	4 (4-5) 2 -	4-6 2-2	2 (1.5-3)
Defects of collagen receptors	2	2.5 (2-3)	3 - 2 -	3-3 2-2	0.5 (0.2-0.7)
Paris-Trousseau syndrome	2	14.5 (12-17)	14.5 (12-17) -	12-17 -	1 (1-1)
$cPLA_2$ deficiency	1	10 -	- 10 -	- 10-10	3 -
Platelet-type Von Willebrand Disease	1	11 -	11 -	11-11	2 -

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IT	N	Median ISTH-BAT (IQR)	ISTH-BAT Median (IQR) F Median (IQR) M	ISTH-BAT Min-max F Min-max M	Median WHO (IQR)
MYH9-related disease	115	1 (0-3)	2 (0.5-3) 0 (0-2.25)	0-17 0-12	1 (0-2)
ANKRD26-related thrombocytopenia	64	2.5 (1-4.5)	3 (1-6) 2 (1-3)	0-13 0-10	2 (0.75-2)
Monoallelic Bernard-Soulier syndrome	60	1 (0-3)	2 (0-3.25) 0 (0-1)	0-12 0-13	1 (0-2)
ETV6 -related disease	23	0 (0-2.75)	0 (0-1.5) 1 (0-2.5)	0-10 0-3	1 (0-1)
ACTN1-related thrombocytopenia	16	1 (0-3)	1 (0-3) 1 (0.5-2.5)	0-5 0-4	1 (0-1.25)
X-linked thrombocytopenia	7	4 (1-8.5)	- 4 (1-8.5)	- 1-13	1 (0-2.5)
Thrombocytopenia with absent radii	2	10.5 (7-14)	14 (14-14) 7 (7-7)	14-14 7-7	1.5 (1.2-1.7)
CYCS-related thrombocytopenia	1	1 -	1 - -	1-1 -	1 (1-1)
GATA1-related diseases	1	11 -	- 11 -	- 11-11	2 (2-2)
TUBB1-related thrombocytopenia	1	0 -	- 0 -	- 0-0	0 (0-0)
Wiskott-Aldrich syndrome	1	12 -	- 12 -	- 12-12	4 (4-4)

Supplementary Table 5. The WHO and ISTH-BAT BSs in the four groups.

	WHO median (IQR)			ISTH-BAT median (IQR)			
	All	**Females**	**Males**	**All**	**Females**	**Males**	**Females excluding post-partum hemorrhage and menorrhagia**
IPFD	3 (2-3)	3 (2-3)	3 (1-3)	9 (6-14)	9 (6.75-15)	8 (4-12)	8 (4-12)
IT	1 (0-2)	1 (0-2)	1 (0-2)	2 (0-3)	2 (0-4)	1 (0-3)	1 (0-3)
VWD-1	1 (1-2)	1 (1-2)	1 (0-2)	5 (2-8)	5 (3-9)	4 (1.75-6)	4 (1-7)
HC	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-1)	0 (0-1)	0 (0-0)	0 (0-1)

HC= healthy controls; IPFD= inherited platelet function disorders; IT= inherited thrombocytopenias; IQR=interquartile range; VWD-1= von Willebrand disease type 1.

Supplementary Table 6. Frequency of the different bleeding symptoms in the different groups: (A) whole populations and (B) pediatric subjects.

A

		Symptom, n of subjects (% of subjects requiring medical attention)													
	Number of subjects	**Epistaxis**	**Cutaneous**	**Bleeding From Minor Wounds**	**Oral Cavity**	**GI Bleeding**	**Hematuria**	**Tooth Extraction**	**Surgery**	**HMB**	**PPH**	**Muscle Hematomas**	**Hemarthrosis**	**CNS**	**Other**
HC	313	25 (28%)	23 (0%)	6 (0%)	31 (0%)	6 (0%)	4 (0%)	15 (0%)	14 (43%)	25 (28%)	6 (33%)	11 (9%)	3 (0%)	0 (0%)	1 (0%)
IPFD	196	125 (71%)	118 (23%)	79 (10%)	115 (43%)	35 (57%)	17 (29%)	64 (61%)	68 (76%)	84 (61%)	18 (78%)	44 (32%)	10 (40%)	4 (75%)	20 (40%)
IT	286	77 (33%)	109 (5%)	31 (0%)	63 (9%)	6 (50%)	5 (0%)	18 (44%)	31 (55%)	61 (16%)	7 (71%)	11 (9%)	0 (0%)	5 (80%)	7 (0%)
VWD-1	303	131 (43%)	140 (7%)	72 (7%)	114 (12%)	24 (37%)	9 (0%)	86 (42%)	91 (57%)	138 (33%)	28 (46%)	19 (42%)	8 (37%)	1 (100%)	16 (12%)

B

		Symptom, n of pediatric subjects (% of pediatric subjects requiring medical attention)												
	Number of subjects	**Epistaxis**	**Cutaneous**	**Bleeding From Minor Wounds**	**Oral Cavity**	**GI Bleeding**	**Hematuria**	**Tooth Extraction**	**Surgery**	**HMB**	**Muscle Hematomas**	**Hemarthrosis**	**CNS**	**Other**
HC	25	3 (33.3%)	3 (0%)	0 (0%)	3 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (43%)	0 (0%)	1 (0%)	0 (0%)	0 (0%)	0 (0%)
IPFD	44	35 (88.5%)	20 (50%)	13 (15.3%)	32 (65%)	8 (50%)	5 (60%)	5 (40%)	3 (100%)	7 (85.7%)	6 (33.3%)	3 (66.6%)	0 (0%)	6 (33.3%)
IT	31	13 (15.3%)	13 (15.3%)	2 (0%)	5 (0%)	0 (0%)	0 (0%)	1 (0%)	3 (33.3%)	2 (50%)	1 (0%)	0 (0%)	1 (0%)	1 (0%)
VWD-1	32	19 (26.3%)	16 (12.5%)	6 (0%)	12 (50%)	1 (100%)	0 (0%)	5 (60%)	2 (100%)	4 (50%)	6 (50%)	0 (0%)	0 (0%)	0 (0%)

CNS: central nervous system bleeding; GI: gastrointestinal; HC= healthy controls; HMB: heavy menstrual bleeding; IPFD= inherited platelet function disorders; IT= inherited thrombocytopenias; PPH: Post-Partum Hemorrhage; VWD-1= von Willebrand disease type 1.
Other: excessive umbilical stump bleeding, cephalohematoma, bleeding at circumcision, venipuncture bleeding, suction bleeding, ovulation bleeding.

Supplementary Table 7. Frequency of the different bleeding symptoms in the most representative inherited platelet disorders (enrolling ≥16 patients).

		Symptom, n of patients (% of patients requiring medical attention)													
	N	Epistaxis	Cutaneous	Bleeding From Minor Wounds	Oral Cavity	GI Bleeding	Hematuria	Tooth Extraction	Surgery	HMB	PPH	Muscle Hematomas	Hemarthrosis	CNS	Other
bBSS	19	11 (72%)	8 (25%)	3 (33%)	9 (55%)	4 (100%)	2 (0%)	5 (100%)	5 (80%)	11 (82%)	2 (50%)	0 (0%)	0 (0%)	0 (5%)	2 (100%)
δ-SPD	21	9 (89%)	17 (6%)	12 (0%)	8 (25%)	0 (0%)	1 (100%)	7 (29%)	7 (43%)	8 (62%)	1 (100%)	7 (14%)	0 (0%)	1 (100%)	2 (0%)
GT	79	64 (76%)	43 (32%)	31 (9%)	60 (66%)	23 (52%)	7 (43%)	21 (66%)	17 (76%)	32 (72%)	5 (100%)	25 (36%)	5 (60%)	2 (50%)	12 (50%)
PSD	20	9 (44%)	11 (27%)	9 (0%)	14 (0%)	2 (0%)	2 (0%)	10 (20%)	10 (70%)	10 (30%)	4 (50%)	3 (0%)	1 (0%)	0 (0%)	1 (0%)
ACTN-1	16	2 (0%)	7 (0%)	0 (0%)	2 (0%)	0 (0%)	0 (0%)	0 (0%)	4 (25%)	5 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
ANKDR26	62	20 (15%)	37 (3%)	9 (0%)	21 (5%)	0 (0%)	1 (0%)	5 (80%)	5 (60%)	11 (27%)	3 (100%)	3 (0%)	0 (0%)	1 (100%)	1 (0%)
mBSS	55	8 (12%)	14 (7%)	6 (0%)	11 (9%)	3 (67%)	0 (0%)	5 (20%)	8 (62%)	16 (6%)	3 (33%)	1 (100%)	0 (0%)	0 (0%)	0 (0%)
ETV6	23	8 (37%)	5 (20%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (33%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
MYH9-RD	115	31 (39%)	36 (3%)	12 (0%)	20 (20%)	2 (50%)	2 (0%)	6 (50%)	11 (45%)	26 (19%)	1 (100%)	3 (0%)	0 (0%)	1 (100%)	3 (0%)

ACTN-1: *ACTN1*-related thrombocytopenia; ANKDR26: *ANKRD26*-related thrombocytopenia; bBSS: biallelic Bernard Soulier syndrome; CNS: central nervous system bleeding; ETV6: *ETV6*-related thrombocytopenia; δ-SPD: δ-storage pool deficiency; GT: Glanzmann thrombasthenia; HMB: heavy menstrual bleeding; mBSS: monoallelic Bernard Soulier syndrome; *MYH9*-RD: *MYH9*-related disease; PSD: primary secretion defect; PPH: post-partum hemorrhage;

Other: excessive umbilical stump bleeding, cephalohematoma, bleeding at circumcision, venipuncture bleeding, suction bleeding, ovulation bleeding.

Supplementary Table 8A. Sensitivity, specificity, positive and negative predictive values of the ISTH-BAT-BS in the overall study populations.

	Best cut-off	AUC (p)	Sensitivity	Specificity	PPV (95% CI)	NPV (95% CI)
IPFD vs HC	>3	0.951 (<0.0001)	86.73	92.33	87.63	91.75
VWD-1 vs HC	>2	0.878 (<0.0001)	73.6	87.86	85.44	77.46
IPFD vs IT	>5	0.872 (<0.0001)	77.55	84.97	77.95	84.67
IT vs VWD-1	≤3	0.735 (<0.0001)	64.03	75.52	63.33	78.20
IPFD vs VWD-1	>7	0.731 (<0.0001)	72.27	67.96	69.71	63.94
IT vs HC	>1	0.684 (<0.0001)	50.70	79.87	83.85	61.73

Supplementary Table 8B. Sensitivity, specificity, positive and negative predictive values of the WHO-BS in the global populations.

	Best cut-off	AUC (p)	Sensitivity	Specificity	PPV (95% CI)	NPV (95% CI)
IPFD vs HC	> 0	0.911 (p<0.0001)	90.8	84.0	78.1	93.6
VWD-1 vs HC	> 0	0.799 (p<0.0001)	76.4	84.0	80.8	80.2
IPFD vs IT	≥2	0.788 (p<0.0001)	78.1	69.5	57.5	80.1
IT vs VWD-1	>0	0.581 (p<0.01)	76.4	39.9	55.0	66.6
IPFD vs VWD-1	≥2	0.687 (p<0.0001)	78.1	59.3	57.7	79.1
IT vs HC	>0	0.721 (p<0.0001)	60.1	84.0	77.5	69.8

Supplementary Table 8C. Comparison of the AUCs of the ISTH-BAT and the WHO BSs

	AUC				
	ISTH-BAT	**WHO-BAT**	**Difference**	**Diff. SE**	**p**
HC vs IPFD	0.951	0.911	0.040	0.009	<0.0001
HC vs IT	0.684	0.722	0.038	0.013	0.005
HC vs VWD-1	0.873	0.799	0.074	0.013	<0.0001
IPFD vs IT	0.872	0.788	0.084	0.015	<0.0001
IPFD vs VWD-1	0.736	0.747	0.011	0.019	0.5717
IT vs VWD-1	0.729	0.563	0.166	0.018	<0.0001

AUC= area under curve; HC= healthy controls; IPFD= inherited platelet function disorders; IT= inherited thrombocytopenias; NPV= negative predictive value; PPV= positive predictive value; VWD-1= von Willebrand disease type 1.

Supplementary Table 9. Sensitivity, specificity, positive and negative predictive values of the ISTH-BAT BS as discriminator between IPFD and HC.

Cut-off	AUC	Sensitivity	Specificity	PPV	NPV
>4	0.895	80.61	96.17	92.94	88.79
>5	0.877	77.55	97.76	95.60	87.43
>6	0.850	70.92	99.04	97.89	84.47
>7	0.836	67.86	99.36	98.52	83.16

AUC= area under curve; NPV= negative predictive value; PPV= positive predictive value.

Supplementary Table 10. Baseline characteristics of the pediatric population.

	N	Females (%)	Median age (IQR)	Median platelet count ($x10^9$/L) (IQR)
IPFD	44	59	10 (7-14)	250 (150-341)
IT	31	45	12 (7-15)	57 (28-79)
VWD-1	32	31	11 (9-13)	285 (229-387)
HC	25	52	11 (6-14)	240 (210-309)
TOT	132	47	11 (7-14)	220 (96-305)

HC= healthy controls; IPFD= inherited platelet function disorders; IT= inherited thrombocytopenias; IQR=interquartile range; NPV= negative predictive value; PPV= positive predictive value; VWD-1= von Willebrand disease type 1.

Supplementary Table 11. The WHO and ISTH-BAT BSs in the pediatric population.

Pediatric	WHO median (IQR)			ISTH-BAT median (IQR)		
	All	Female	Males	All	Female	Males
IPFD	3 (2-3)	3 (2-3)	2.5 (1.75-3)	8 (6.5-14)	8 (8-13)	8 (4-11)
IT	1 (0-2)	1 (0-2)	1 (0-1.5)	1 (0-3)	1.5 (0-4.2)	1 (0-2.5)
VWD-1	1 (1-2)	1 (0-2)	1 (0.25-2)	3 (1-6)	6 (0-12.5)	3 (1-5)
HC	0 (0-0)	0 (0-0.5)	0 (0-0)	0 (0-1)	0 (0-1)	0 (0-0)

HC= healthy controls; IPFD= inherited platelet function disorders; IT= inherited thrombocytopenias; IQR=interquartile range; NPV= negative predictive value; PPV= positive predictive value; VWD-1= von Willebrand disease type 1.

Supplementary Table 12. Sensitivity and specificity of ISTH-BAT BS in the pediatric population.

	Best cut-off	AUC (p)	Sensitivity	Specificity
IPFD vs HC	>1	0.992 (<0.0001)	100	92
VWD-1 vs HC	>1	0.839 (<0.0001)	71.87	92
IPFD vs IT	>3	0.915 (<0.0001)	88.64	80.65
IT vs VWD-1	≤2	0.691 (<0.0001)	62.5	70.97
IPFD vs VWD-1	>7	0.802 (<0.0001)	81.25	75
IT vs HC	>1	0.657 (<0.0001)	45.16	92

AUC= area under curve, HC= healthy controls; IPFD= inherited platelet function disorders; IT= inherited thrombocytopenias; VWD-1= von Willebrand disease type 1.

Legends to the supplemental figures

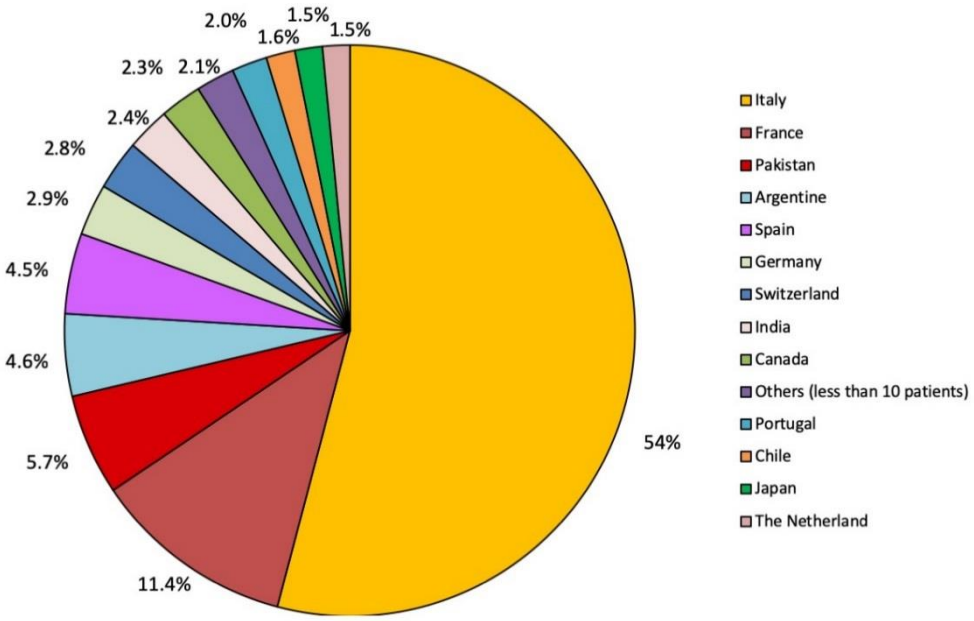
Supplementary Figure 1. World distribution of the enrolled subjects.

Supplementary Figure 2. Distribution of enrolled subjects according to study group.

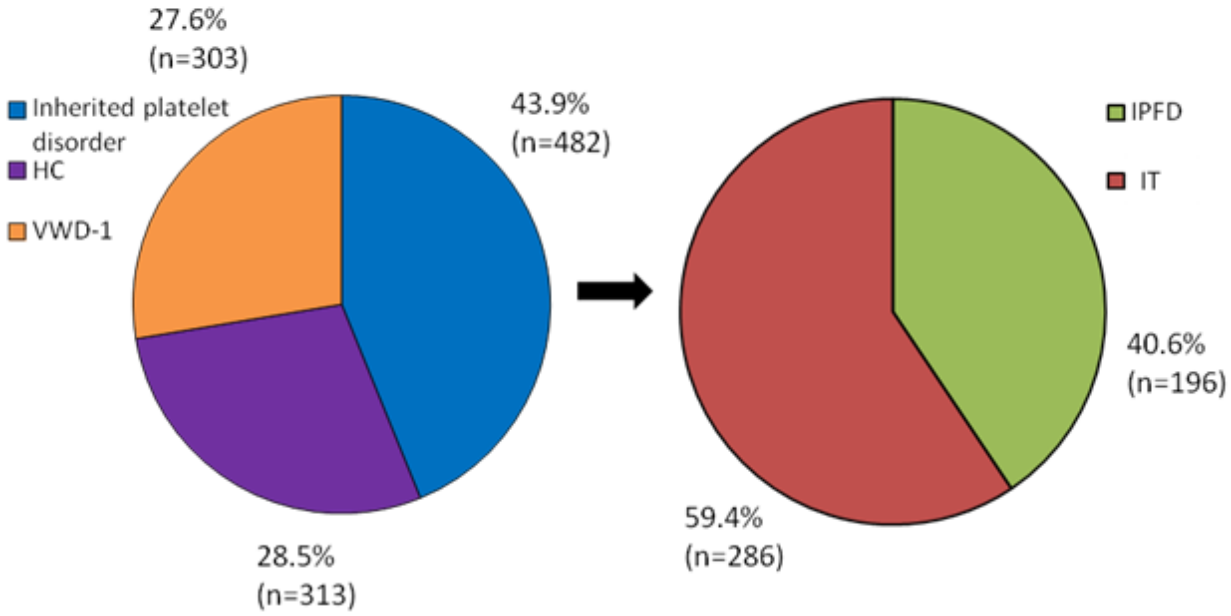
Supplementary Figure 3. Mean scores of the individual symptoms of the ISTH-BAT in the 4 groups. The severity of epistaxis, cutaneous bleeding, bleeding from minor wounds, oral cavity bleeding, GI bleeding, bleeding after tooth extraction, menorrhagia and muscle hematomas in the VWD-1 group was lower than in IPFD but higher than in IT, while the severity in HC group was the lowest. Epistaxis, oral cavity bleeding and hemarthrosis were the most severe symptoms in IPFD compared to VWD-1, IT and HC, while bleeding after tooth extraction, bleeding after surgery and menorrhagia were more severe in IPFD and VWD-1 compared to IT and HC.

Suppl. Figure 4. Frequency of the individual symptoms of the ISTH-BAT score in the four groups (% of patients manifesting the symptom).

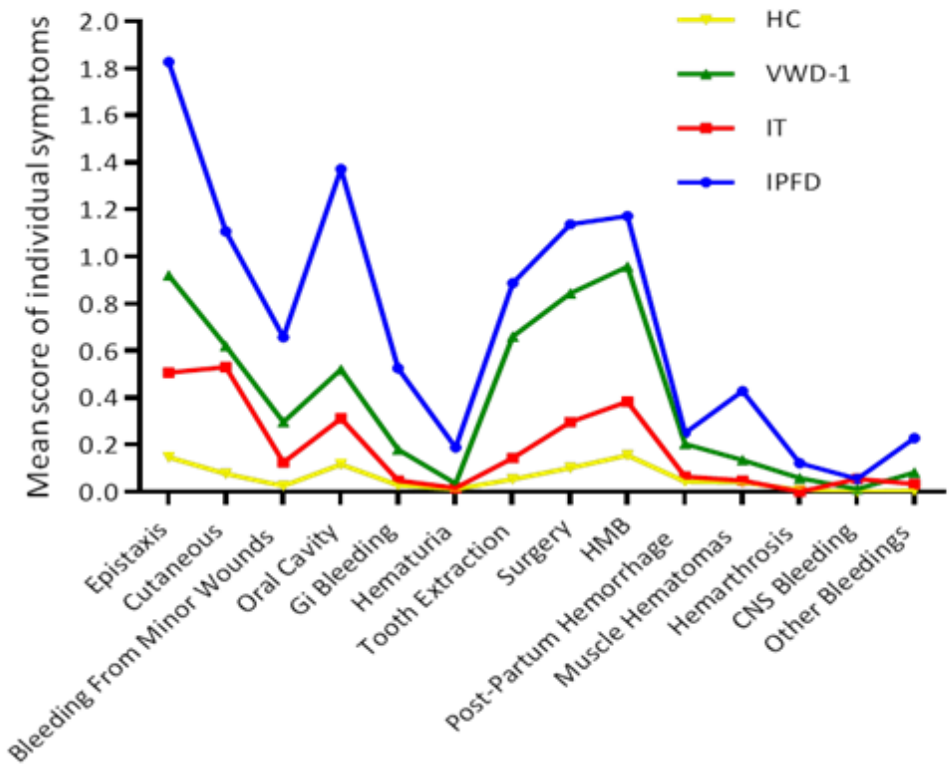
Supplementary figure 1



Supplementary figure 2



Supplementary figure 3



Supplementary figure 4