

Validation of the ISTH/SSC bleeding assessment tool for inherited platelet disorders: A communication from the Platelet Physiology SSC

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Abstract

Background: Careful assessment of bleeding history is the first step in the evaluation of patients with mild/moderate bleeding disorders, and the use of a bleeding assessment tool (BAT) is strongly encouraged. Although a few studies have assessed the utility of the ISTH-BAT in patients with inherited platelet function disorders (IPFD) none of them was sufficiently large to draw conclusions and/or included appropriate control groups.

Objectives: The aim of the present study was to test the utility of the ISTH-BAT in a large cohort of patients with a well-defined diagnosis of inherited platelets disorder in comparison with two parallel cohorts, one of patients with type-1 von Willebrand disease (VWD-1) and one of healthy controls (HC).

Patients/Methods: We enrolled 1098 subjects, 482 of whom had inherited platelet disorders (196 IPFD and 286 inherited platelet number disorders [IT]) from 17 countries.

*BAT-VAL study investigators are included in the Appendix.

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Results: IPFD patients had significantly higher bleeding score (BS; median 9) than VWD-1 patients (median 5), a higher number of hemorrhagic symptoms (4 versus 3), and higher percentage of patients with clinically relevant symptoms (score > 2).

The ISTH-BAT showed excellent discrimination power between IPFD and HC ($0.9 < \text{area under the curve [AUC]} < 1$), moderate ($0.7 < \text{AUC} < 0.9$) between IPFD and VWD-1 and between IPFD and inherited thrombocytopenia (IT), while it was inaccurate ($\text{AUC} \leq 0.7$) in discriminating IT from HC.

Conclusions: The ISTH-BAT allows to efficiently discriminate IPFD from HC, while it has lower accuracy in distinguishing IPFD from VWD-1. Therefore, the ISTH-BAT appears useful for identifying subjects requiring laboratory evaluation for a suspected IPFD once VWD is preliminarily excluded.

KEYWORDS

bleeding assessment tool, inherited platelet disorders, bleeding diathesis, platelets, bleeding disorders

1 | INTRODUCTION

An accurate assessment of the presence and severity of bleeding symptoms is critical in the clinical evaluation of patients referred for a possible bleeding disorder, especially those with mild bleeding diatheses.¹ In particular, a well established mucocutaneous bleeding history is crucial for the decision to embark in complex and expensive laboratory studies.² The high frequency of bleeding manifestations in the normal population and the wide interindividual variability in the subjective appraisal of symptoms makes the identification of a real bleeding tendency rather difficult. A number of structured bleeding history questionnaires, called bleeding assessment tools (BATs), have been developed to standardize the collection of the bleeding history in order to improve diagnostic accuracy and sensitivity, more precisely describe symptom severity, inform treatment, and possibly predict the future bleeding risk.³ In particular, several BATs have been developed for type 1 von Willebrand disease (VWD-1), like the Vicenza BAT,⁴ the Molecular and Clinical Markers for the Diagnosis and Management of type 1 VWD (MCMDM-1 VWD) bleeding questionnaire,⁵ or the Pediatric Bleeding Questionnaire (PBQ),⁶ and revealed to be able to distinguish between affected and unaffected subjects with good specificity and sensitivity.^{4,6-8} More recently, a prospective study in VWD patients demonstrated that the ISTH-BAT bleeding score (BS) is a predictor of bleeding outcomes helping to identify patients requiring intensive treatment.⁹

The ISTH-BAT combines a standardized questionnaire designed to capture also recurrent minor but not trivial bleeds, and a well-defined interpretation grid allowing the computation of a final BS. It was developed as a consensus tool to record bleeding symptoms in patients with any suspected bleeding disorder¹⁰ and it has been recently proposed by an International Working Group as the main tool to discriminate bleedings deserving investigation from not relevant hemorrhages.¹¹

Essentials

- The ISTH-BAT has been validated for VWD-1 but not sufficiently for inherited platelet disorders.
- We tested the utility of the ISTH-BAT in patients with inherited platelet disorders in comparison with VWD-1 and controls.
- The ISTH-BAT clearly distinguished inherited platelet function disorders (IPFD) from controls.
- Patients with a bleeding score >6 and preliminarily excluded VWD-1 have 99% probability of having an IPFD.

Inherited platelet disorders are a heterogeneous group of bleeding diseases of variable clinical severity associated with a reduction of platelet number (inherited thrombocytopenias, IT) and/or function (inherited platelet function disorders, IPFDs).

A study applying the ISTH-BAT to a small cohort of adult patients with suspected IPFD supported its use for documenting lifelong bleeding history, but not for predicting defective platelet function. However, the study excluded patients with Glanzmann thrombasthenia (GT), Bernard-Soulier syndrome (BSS), MYH9-related disease (MYH9-RD), or Hermansky-Pudlak syndrome (HPS), therefore, it did not provide information on a significant fraction of disorders.¹²

On the other hand, another study conducted in a low-income country including 261 subjects with suspected IPFD showed that the ISTH-BAT is useful in documenting bleeding symptoms and is predictive of a platelet defect on light transmission aggregometry (LTA).¹³

An additional small study enrolling only BSS and GT cases showed that the ISTH-BAT discriminates patients from normal controls with good sensitivity and specificity.¹⁴

Finally, recently the ISTH-BAT was applied to a wide group of subjects referred for a suspected bleeding disorder, 54 of whom had a confirmed and 64 a possible IPFD, and the presence of a platelet function disorder was associated with a higher BS.¹⁵

Although altogether these studies enrolled a substantial number of patients, none of them was sufficiently large to draw conclusions on the utility of the ISTH-BAT for IPFD and no one systematically compared a well-defined population of individuals with inherited platelet disorders with VWD patients and healthy subjects.

The aim of the present study was to test the utility of the ISTH-BAT in a large cohort of patients with an established diagnosis of inherited platelet disorder in comparison with two parallel cohorts, one of VWD-1 patients and one of healthy controls (HC). In particular, we aimed to assess if the ISTH-BAT may be useful to discriminate between: (1) inherited platelet disorders and HC, (2) inherited platelet disorders and VWD-1, and (3) different inherited platelet disorders.

2 | METHODS

2.1 | Inclusion criteria

This study was promoted by the Platelet Physiology SSC of the ISTH. The Institutional Review Board of the coordinating center approved the study (CEAS Umbria, Italy, n.2473/15), each center complied with local ethical rules, and all subjects or their legal representatives signed a written informed consent. Enrolled subjects had to be living and available for direct history taking.

The study included only patients with a diagnosis of inherited platelet disorder confirmed according to well-defined laboratory and/or molecular genetic criteria^{2,16,17} (Tables S1 and S2 in supporting information). Both adult and pediatric (≤ 16 years old) subjects were enrolled.

Participating centers were asked to enroll for each patient an age- (± 5 years) and sex-matched HC and an unequivocally diagnosed VWD-1 patient.¹⁸ HC were defined as subjects in ostensible good health, never referred for hemostasis evaluation for hemorrhagic symptoms, with normal platelet count and, whenever available, LTA (for example, a subject used as control for platelet function testing).

2.2 | Assessment of the bleeding history

A physician or another adequately trained health professional administered the questionnaire. All hemorrhagic symptoms and related treatments occurred until diagnosis had to be considered. The BS was calculated either manually, using the interpretation grid, or automatically using the web-based version (<https://bh.rockefeller.edu/ISTH-BATR/>).

Bleeding history was assessed in parallel also using the World Health Organization (WHO) bleeding assessment scale,¹⁹ as described.¹⁶

2.3 | Statistical analysis

Based on previous data on the prevalence of hemorrhagic symptoms in VWD-1, patients with IPFD or IT and HC,^{7,12,20} we expected that a significant difference in the BS would be shown by enrolling at least 300 subjects per group ($\beta = .8$, $\alpha = .05$).

Data are reported as medians and 25th to 75th percentiles (interquartile range [IQR]) when continuous, and as counts and percentages when categorical. Correlation between BS and other variables were assessed using the Pearson correlation coefficient (ρ).

Kappa statistics were used to test interrater reliability.²¹ Receiver operating characteristic (ROC) curves were calculated to establish a diagnostic prediction rule to discriminate between different groups and area under curve (AUC), sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV) were assessed for the analyzed populations. Cut-off values using the Youden index for the most relevant comparisons were also calculated. The R software (R Foundation for Statistical Computing, www.R-project.org) was used for all analyses. A two-sided $P < .05$ was considered as statistically significant.

3 | RESULTS

3.1 | Participants' characteristics

The study included 1098 subjects (age 1-93 years; median 39; IQR 25-52; 58.4% females) enrolled by 44 centers across 17 countries (Figure S1 in supporting information): 482 with inherited platelet disorders (43.9%; 196 IPFD and 286 IT), 303 with VWD-1 (27.6%) and 313 HC (28.5%) (Figure S2 in supporting information). Baseline characteristics are reported in Table S3 in supporting information. Among inherited platelet disorders, 28 different forms (17 IPFD and 11 IT) were represented (Table S4 in supporting information).

Among IPFD the most widely represented were GT (40.3%), δ -granule defect (10.7%), primary secretion defect (10.2%), and biallelic BSS (bBSS) (9.7%), while among IT MYH9-RD (40.5%), ANKRD26-related thrombocytopenia (RT) (21.8%), and monoallelic BSS (mBSS) (19.4%). Thrombocytopenia of IT patients was on average mild (median $57.5 \times 10^9/L$; IQR 28-85).

3.2 | Bleeding scores

The average BS assessed by the ISTH-BAT was clearly increased in IPFD (median 9, IQR 6-14), moderately increased in VWD-1 (median 5, IQR 2-8), and only minimally altered in IT (median 2, IQR 0-3) as compared with HC (median 0, IQR 0-1; $P < .05$ for all comparisons; Figure 1A; Table S5 in supporting information). Some disorders, such as gray platelet syndrome (GPS), GT, primary secretion defect (PSD), Quebec platelet disorder (QPD), P2Y₁₂-defect, Paris-Trousseau

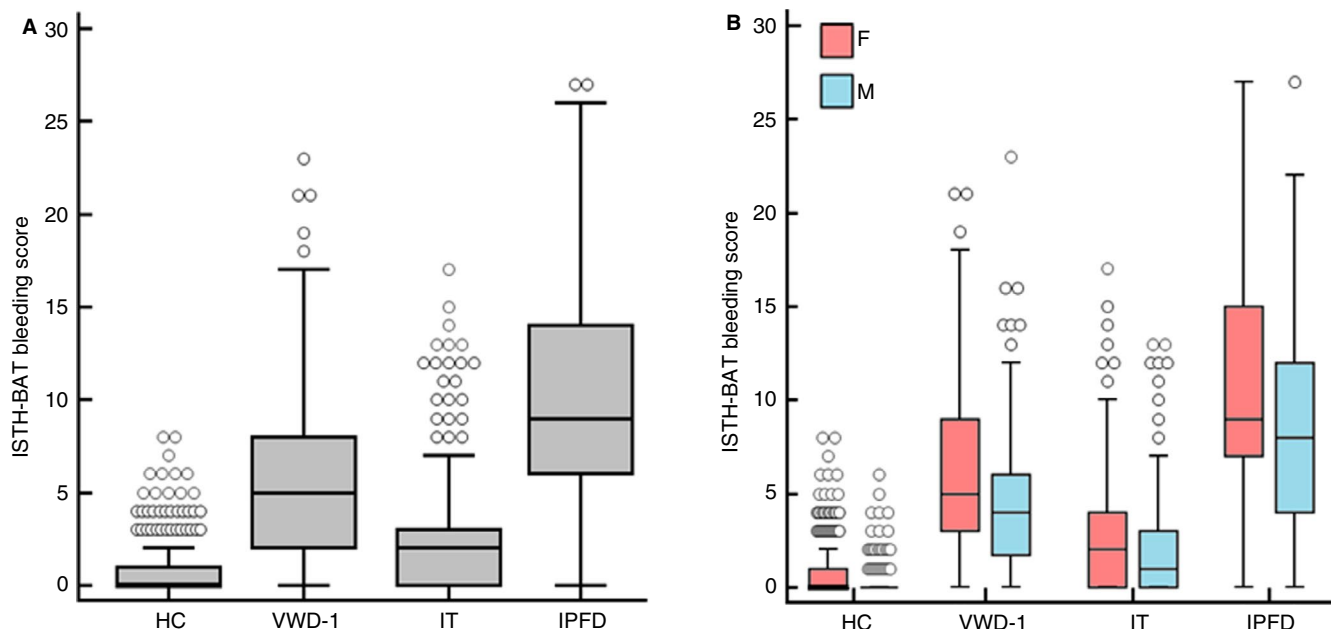


FIGURE 1 ISTH-BAT bleeding score distribution in the global population of the different groups (A) and by sex (B). Data are reported as box and whisker plots; isolated points represent outliers (outside 95% CIs). All comparisons are statistically significant ($P < .05$)

syndrome, showed a bleeding score higher than the average of the IPFD group (Table S4).

Given that approximately 50% of IPFD were GT and bBSS, notoriously severe forms,^{22,23} we recalculated the BS of IPFD group excluding these disorders and it was still significantly higher than VWD-1 (8; IQR 4-12, $P < .0001$). The BS was significantly higher in females than males in all groups ($P < .01$), due to the contribution of menorrhagia and post-partum hemorrhage, especially in VWD-1 and IPFD (Figure 1B; Table S5). The BS correlated positively with age in the VWD-1 group ($\rho = 0.2$; $P = .0003$) and negatively with platelet count in the IT group ($\rho = -0.19$, $P = .0009$).

In IPFD the median number of hemorrhagic symptoms was 4 (IQR 2-6), in VWD-1 3 (IQR 1-4), in IT 1 (IQR 0-2), and in HC 0 (IQR 0-1; $P < .05$ for all comparisons; Figure 2A). The mean score

of the individual symptoms was also calculated. Epistaxis and oral cavity bleeding had the highest score in IPFD, cutaneous bleeding and menorrhagia in IT, and epistaxis and menorrhagia in VWD-1. Postsurgical bleeding was significantly more severe in IPFD than in all the other groups, confirming previous results¹⁶ (Figure S3 in supporting information).

In IPFD 75% of patients had at least one symptom requiring medical treatment (score > 2), in VWD-1 51.5%, in IT 20.6%, and in HC 6.7% (Figure 2B). The most frequent symptom in the IPFD group was epistaxis, followed by cutaneous and oral cavity bleeding; in IT cutaneous bleeding, followed by epistaxis and oral cavity bleeding; in VWD-1 cutaneous bleeding, followed by menorrhagia and epistaxis; and in HC oral cavity bleeding, followed by menorrhagia and epistaxis (Figure S4, Table S6 in supporting

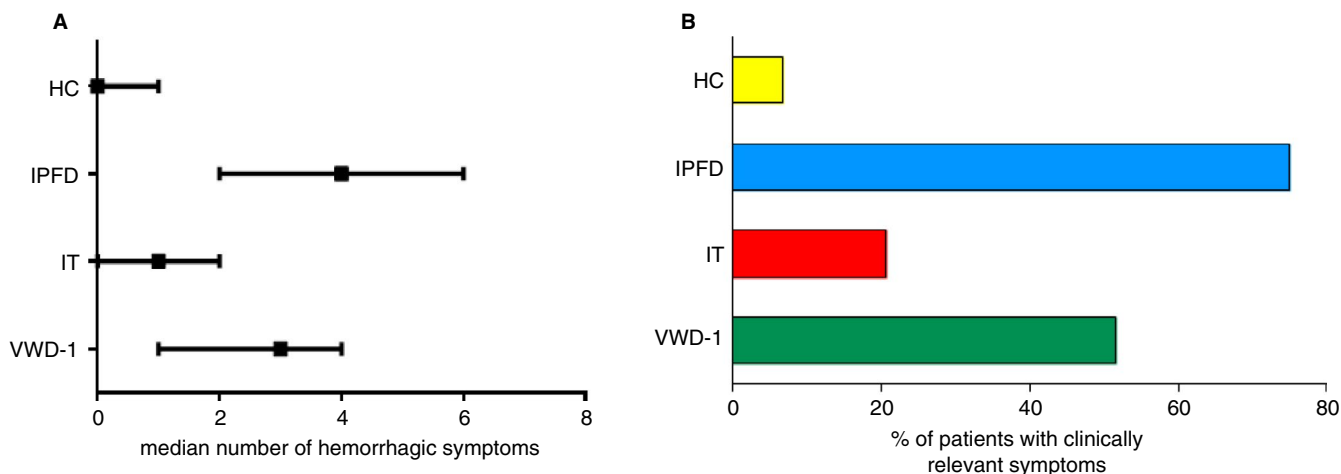


FIGURE 2 (A) Median number (IQR) of hemorrhagic symptoms and (B) percentage of clinically relevant symptoms in the different study populations. All comparisons are statistically significant ($P < .001$)

information). The frequency of symptoms and percentage requiring medical treatment in specific disorders are shown in Table S7 in supporting information.

The average BS assessed by the WHO bleeding scale (min 0, max 4) was clearly abnormal in IPFD (median 3, IQR 2-3), mildly abnormal in VWD-1 (1, IQR 1-2) and in IT (1, IQR 0-2), and normal in HC (0, IQR 0-0; Table S5). Disorders with the highest WHO-BS were GT (3, IQR 3-3), bBSS (3, IQR 2-3), QPD (3, IQR 3-3), and cPLA₂ deficiency (3).

3.3 | Sensitivity, specificity, positive and negative predictive values

The ISTH-BAT showed high accuracy ($0.9 < \text{AUC} < 1$) in discriminating IPFD from HC; moderate accuracy ($0.7 < \text{AUC} < 0.9$) in discriminating VWD-1 from HC, IT and IPFD from VWD-1, and IPFD from IT; while it was inaccurate ($0.5 < \text{AUC} \leq 0.7$) in discriminating between IT and HC (Table S8A in supporting information). The best cut-off discriminating IPFD from HC was >3 (>4 for females and >3 for males), IPFD from VWD-1 was >7 (>7 for females and >5 for males), and IPFD from IT was >5 (>6 for females and >3 for males; Table 1; Table S8A). Of note, a BS >6 had a PPV of 98.0% and a NPV of 85.0% to discriminate IPFD from HC (Table S9 in supporting information). Inter-rater agreement analysis showed that a BS >6 is highly likely to be associated with an IPFD (Cohen's kappa = 0.7922, $P < .0001$).

The WHO-BS showed high accuracy in discriminating IPFD from HC; moderate in discriminating VWD-1 from HC, IPFD from IT, and IT from HC; while it was inaccurate ($0.5 < \text{AUC} \leq 0.7$) in distinguishing IPFD and IT from VWD-1 (Table S8B). The best cut-off discriminating IPFD from HC was >1 , with a PPV of 78% and a NPV of 94% (Table S8B).

The comparison of the AUCs revealed that the ISTH-BAT is more sensitive than the WHO-BS in discriminating IPFD and VWD-1 from HC, IPFD from IT, and VWD-1 from IT, while the

WHO-BS was better in discriminating IT from HC (Table S8C). Moreover, for some specific disorders the two scores gave poorly comparable results, eg, PSD had a median WHO-BS of 1 and a median ISTH-BAT BS of 7.5, Paris-Trousseau syndrome a WHO-BS of 1 and an ISTH-BAT BS of 14.5, thrombocytopenia with absent radius (TAR) a WHO-BS of 1.5 and an ISTH-BAT BS of 10.5.

4 | PEDIATRIC POPULATION

Pediatric subjects were 12% of total (22.4% of IPFD, 10.8% of IT, 10.5% of VWD-1, and 7.9% of HC; Table S10 in supporting information). WHO and ISTH-BAT BS distribution in the four groups did not differ from the adult population, the only difference being that females and males had identical BS (Table S11 in supporting information).

The ISTH-BAT showed high accuracy in discriminating pediatric IPFD from HC and from IT, moderate in discriminating VWD-1 from HC and IPFD, while it was inaccurate in discriminating IT from VWD-1 and HC. The best cut-off discriminating IPFD from VWD-1 was >7 , while that discriminating IPFD from IT was >3 (Table 1; Table S12 in supporting information).

5 | DISCUSSION

Our study, representing the largest systematic investigation of the diagnostic utility of the ISTH-BAT in patients with inherited platelet disorders, shows that this tool has an excellent discrimination power between IPFD and HC, with a NPV of 85% and a PPV of 98%. Thus, for the populations analyzed in this study, if a subject with a mucocutaneous bleeding diathesis has an ISTH-BAT BS >6 (in our study these were 71% of IPFD patients) and preliminary laboratory screening has excluded VWD and blood clotting defects² he/she has $\geq 99\%$ probability of being affected by an IPFD.

TABLE 1 Sensitivity, specificity, and positive and negative predictive values of the ISTH-BAT BS

	Sex	Best cut-off	AUC (p)	Sensitivity	Specificity	PPV (95% CI)	NPV (95% CI)
IPFD vs HC	F	>4	0.962 (<0.0001)	84.87	94.68	91.0	90.8
	M	>3	0.936 (<0.0001)	82.89	96.00	92.6	90.2
VWD-1 vs HC	F	>1	0.891 (<0.0001)	87.29	76.06	77.8	86.1
	M	>0	0.876 (<0.0001)	86.40	76.80	78.8	85.0
IPFD vs IT	F	>6	0.881 (<0.0001)	75.63	89.37	84.1	83.1
	M	>3	0.846 (<0.0001)	82.89	78.95	69.2	89.0
IT vs VWD-1	F	≤ 3	0.753 (<0.0001)	73.12	69.61	68.0	74.6
	M	≤ 2	0.716 (<0.0001)	67.67	68.80	69.8	66.7
IPFD vs VWD-1	F	>7	0.722 (<0.0001)	72.27	67.96	59.7	78.8
	M	>5	0.737 (<0.0001)	72.37	72.00	61.1	81.1
IT vs HC	F	>1	0.691 (<0.0001)	57.50	76.06	67.2	67.8
	M	>0	0.694 (<0.0001)	57.89	76.80	72.6	63.2

Abbreviations: AUC, area under curve; CI, confidence intervals; 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.

Our study also shows that the bleeding history of patients with IPFD is significantly more severe than that of patients with VWD-1 and much more than that of patients with IT. Also, the median number of hemorrhagic symptoms was highest for IPFD (4), followed by VWD-1 (3) and lowest in IT (1) and HC (0). Moreover, the percentage of patients with clinically relevant symptoms (score >2) was significantly higher in IPFD than in all the other groups, including VWD-1.

Many forms of IT are associated with platelet function defects and their ISTH-BAT BS was high, similar to IPFD with normal platelet count. In this case the application of the ISTH-BAT may not support the hypothesis of an IT because the bleeding tendency is too severe. Therefore, in the presence of thrombocytopenia and a high ISTH-BAT an inherited disorder should not be excluded, leading to misdiagnosis of acquired thrombocytopenia, and a careful assessment of the medical history and blood cell morphology should always be made.²⁴

Four previous studies have shown that the ISTH-BAT is useful to discriminate IPFD from HC,¹²⁻¹⁵ but none of them included a group of patients with VWD-1 which is, the most frequent mucocutaneous bleeding disorder and/or IT. Moreover, all the studies included small cohorts of patients and/or patients without a well-defined diagnosis. Our study enrolled 1098 well-characterized subjects, including VWD-1, IPFD, IT, and HC, from 17 different countries worldwide, thus providing a thorough global representation.

Despite the preponderance of patients with GT among IPFD and with MYH9-RD among IT, the enrolled population was representative of a wide range of disorders and included also very rare forms, thus providing information on the whole spectrum of these heterogeneous diseases.^{2,11,22-26}

The BS was more severely altered in some specific conditions, like the CalDAG-GEFI-related disorder, GPS, and GT among IPFD, and the TAR and X-linked thrombocytopenia among IT, although for some of these the observation requires confirmation given the low number of cases.

Some bleeding symptoms were more frequently associated with specific patient groups, such as epistaxis for IPFD, cutaneous bleeding for IT, and menorrhagia for VWD-1.

The ISTH-BAT had a higher discriminative power as compared with the WHO-BS in differentiating IPFD from IT and IPFD from HC, probably because the WHO-BS is a global score based on not-structured history-taking while the ISTH-BAT BS derives from the sum of the scores of well-defined individual symptom items each one progressively graduated.

Strengths of our study are the large study population, very stringent inclusion criteria, the enrollment of pediatric cases, the systematic comparison with another BS and the worldwide representation. Limitations are (1) the lack of a population of subjects with mucocutaneous bleeding symptoms but without a definite diagnosis, thus the sensitivity of the ISTH-BAT in differentiating IPFD from HC in bleeding of unknown cause^{11,20} will require a prospective validation in a large international collaborative study; (2) the enrollment of subjects in specialized hemostasis centers, which may have led to a selection of the more symptomatic cases—however, VWD-1 and HC were enrolled by the same centers making the comparison between groups reliable; (3)

the inability to provide information on the predictive value of an increased BS for subsequent bleeding—however a prospective arm of the study is ongoing to assess its prognostic capability; (4) the lack of correlative data between altered BS and the presence of a defect at diagnostic laboratory tests—however, an ad hoc designed substudy (BAT-LAB) is ongoing and will provide this information.

In conclusion, the application of the ISTH-BAT allows us to clearly discriminate IPFD from HC and, potentially also from IT, while it has limited accuracy in distinguishing IPFD from VWD-1. On the other hand, the guidance on the diagnosis of IPFD by the ISTH advises to exclude VWD before embarking in complex diagnostic tests for patients with a mucocutaneous bleeding history.² Our study shows that a patient with a BS >6 for whom preliminary investigations have excluded VWD or a blood clotting defect has 99% probability of being affected by an IPFD.

AUTHOR CONTRIBUTIONS

PG, PN, HD, AF, PH, DM, and AM conceived and designed the study; PG, PN, EF, MCA, LB, MB, CS, AG, ARC, AT, EDC, PF, AP, FM, CF, AC, GP, MK, KJ, TS, GC, EG, MF, PZ, YH, KM, AD, CH, CZ, MA, GF, MGM, GT, PJ, FF, AR, NB, MN, JC, GV, BZ, MF, MC, ML, LB, BC, PG, CP, IE, and MCMK collected cases and provided study materials; SO, EF, LB, and GG assembled and analyzed data; SO, EF, LB, and PG wrote the manuscript. All authors revised and gave final approval of the manuscript.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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REFERENCES

- Rodeghiero F, Tosetto A, Castaman G. How to estimate bleeding risk in mild bleeding disorders. *J Thromb Haemost.* 2007;5(Suppl 1):157-166.
- Gresele P. Subcommittee on platelet physiology of the international society on thrombosis and hemostasis. Diagnosis of inherited platelet function disorders: guidance from the SSC of the ISTH. *J Thromb Haemost.* 2015;13:314-322.
- Rydz N, James PD. The evolution and value of bleeding assessment tools. *J Thromb Haemost.* 2012;10:2223-2229.
- Rodeghiero F, Castaman G, Tosetto A, et al. The discriminant power of bleeding history for the diagnosis of type 1 von Willebrand disease: an international, multicenter study. *J Thromb Haemost.* 2005;3:2619-2626.
- Tosetto A, Rodeghiero F, Castaman G, et al. A quantitative analysis of bleeding symptoms in type 1 von Willebrand disease: results from a multicenter European study (MCMDM-1 VWD). *J Thromb Haemost.* 2006;4:766-773.
- Bowman M, Riddel J, Rand ML, Tosetto A, Silva M, James PD. Evaluation of the diagnostic utility for von Willebrand disease of a pediatric bleeding questionnaire. *J Thromb Haemost.* 2009;7:1418-1421.
- Bowman M, Mundell G, Grabell J, et al. Generation and validation of the Condensed MCMDM-1VWD Bleeding Questionnaire for von Willebrand disease. *J Thromb Haemost.* 2008;6:2062-2066.
- Biss TT, Blanchette VS, Clark DS, Wakefield CD, James PD, Rand ML. Use of a quantitative pediatric bleeding questionnaire to assess mucocutaneous bleeding symptoms in children with a platelet function disorder. *J Thromb Haemost.* 2010;8:1416-1419.
- Federici AB, Bucciarelli P, Castaman G, et al. The bleeding score predicts clinical outcomes and replacement therapy in adults with von Willebrand disease. *Blood.* 2014;123:4037-4044.
- Rodeghiero F, Tosetto A, Abshire T, et al. ISTH/SSC joint VWF and Perinatal/Pediatric Hemostasis Subcommittees Working Group. ISTH/SSC bleeding assessment tool: a standardized questionnaire and a proposal for a new bleeding score for inherited bleeding disorders. *J Thromb Haemost.* 2010;8:2063-2065.
- Rodeghiero F, Pabinger I, Ragni M, et al. Fundamentals for a systematic approach to mild and moderate inherited bleeding disorders: a EHA consensus report. *Hemasphere.* 2019;3:e286.
- Lowe GC, Lordkipanidze M, Watson SP, UK GAPP study group. Utility of the ISTH bleeding assessment tool in predicting platelet defects in participants with suspected inherited platelet function disorders. *J Thromb Haemost.* 2013;11:1663-1668.
- Rashid A, Moiz B, Karim F, Shaikh MS, Mansoori H, Raheem A. Use of ISTH bleeding assessment tool to predict inherited platelet dysfunction in resource constrained settings. *Scand J Clin Lab Invest.* 2016;76:373-378.
- Kaur H, Borhany M, Azzam H, Costa-Lima C, Ozelo M, Othman M. The utility of International Society on Thrombosis and Haemostasis-Bleeding Assessment Tool and other bleeding questionnaires in assessing the bleeding phenotype in two platelet function defects. *Blood Coagul Fibrinolysis.* 2016;27:589-593.
- Adler M, Kaufmann J, Alberio L, Nagler M. Diagnostic utility of the ISTH bleeding assessment tool in patients with suspected platelet function disorders. *J Thromb Haemost.* 2019;17:1104-1112.
- Orsini S, Noris P, Bury L, et al. European Hematology Association - Scientific Working Group (EHA-SWG) on thrombocytopenias and platelet function disorders. Bleeding risk of surgery and its prevention in patients with inherited platelet disorders. *Haematologica.* 2017;102(7):1192-1203.
- Noris P, Schlegel N, Klersy C, et al., European Hematology Association - Scientific Working Group on Thrombocytopenias and Platelet Function Disorders. Analysis of 339 pregnancies in 181 women with 13 different forms of inherited thrombocytopenia. *Haematologica.* 2014;99(8):1387-1394.
- Sadler JE, Rodeghiero F, Factor ISSovW. Provisional criteria for the diagnosis of VWD type 1. *J Thromb Haemost.* 2005;3:775-777.
- Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. *Cancer.* 1981;47:207-214.
- Quiroga T, Goycoolea M, Panes O, et al. High prevalence of bleeders of unknown cause among patients with inherited mucocutaneous bleeding. A prospective study of 280 patients and 299 controls. *Haematologica.* 2007;92:357-365.
- Cohen J. A coefficient of agreement for nominal scales. *Educ Psychol Measur.* 1960;20:37-46.
- Gresele P, Bury L, Falcinelli E. Inherited platelet function disorders: algorithms for phenotypic and genetic investigation. *Semin Thromb Hemost.* 2016;42:292-305.
- Gresele P, Falcinelli E, Bury L. Inherited platelet function disorders. Diagnostic approach and management. *Hamostaseologie.* 2016;36:265-278.
- Balduini CL, Cattaneo M, Fabris F, et al.; Italian Gruppo di Studio delle Piastrine. Inherited thrombocytopenias: a proposed diagnostic algorithm from the Italian Gruppo di Studio delle Piastrine. *Haematologica.* 2003;88:582-592.
- Gresele P, Bury L, Mezzasoma AM, Falcinelli E. Platelet function assays in diagnosis: an update. *Expert Rev Hematol.* 2019;12:29-46.
- Gresele P, Falcinelli E, Bury L. Laboratory diagnosis of clinically relevant platelet function disorders. *Int J Lab Hematol.* 2018;40(Suppl 1):34-45.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.
 Supinfo

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APPENDIX

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