



ORIGINAL ARTICLE

Bleeding assessment tools to predict von Willebrand disease: Utility of individual bleeding symptoms

Jordan Spradbrow¹  | Sasha Letourneau¹ | Julie Grabell BA¹ | Yupu Liang PhD² | James Riddel RN, MS³ | Wilma Hopman MSc⁴ | Victor S. Blanchette MB BChir^{5,6} | Margaret L. Rand PhD^{7,8} | Barry S. Collier MD⁹ | Andrew D. Paterson MD¹⁰ | Paula D. James MD¹ 

¹Department of Medicine, Queen's University, Kingston, ON, Canada

²Research Bioinformatics, Rockefeller University, New York, NY, USA

³Division of Hematology/Oncology, University of California, San Francisco, CA, USA

⁴Clinical Research Centre, Kingston General Hospital, Kingston, ON, Canada

⁵Department of Pediatrics, University of Toronto, Toronto, ON, Canada

⁶Division of Haematology/Oncology, The Hospital for Sick Children, Toronto, ON, Canada

⁷Departments of Laboratory Medicine & Pathobiology, Biochemistry and Paediatrics, University of Toronto, Toronto, ON, Canada

⁸SickKids, Division of Haematology/Oncology and Translational Medicine, Research Institute, Hospital for Sick Children, Toronto, ON, Canada

⁹Allen and Frances Adler Laboratory of Blood and Vascular Biology, Rockefeller University, New York, NY, USA

¹⁰Program in Genetics and Genome Biology, The Hospital for Sick Children, Toronto, ON, Canada

Correspondence

Paula James, Department of Medicine, Queen's University, Room 2015 Etherington Hall, 94 Stuart Street, Kingston, ON K7L 3N6, Canada.

Email: jamesp@queensu.ca

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Abstract

Background: Bleeding assessment is part of the diagnostic workup of von Willebrand disease (VWD). Bleeding assessment tools (BATs) have standardized obtaining this information but have been criticized because they are time consuming.

Objective: To use our legacy data to determine which questions from BATs are the strongest predictors of a VWD diagnosis.

Patients/Methods: Bleeding score data from 3 different BATs were used. Patients aged <12 years were excluded. Questions on BATs relate to different bleeding symptoms, and each symptom is scored by severity. Scores for each symptom were sorted based on whether they indicated clinically significant bleeding, and nonsignificant scores were set as the reference category. Multivariable logistic regression was used to determine the symptoms that were the strongest predictors of a laboratory-confirmed VWD diagnosis.

Results: A total of 927 participants were included; 144 (16%) were patients with VWD, and 783 (84%) were healthy controls. The top 3 symptoms for which a clinically significant positive response increased the likelihood of VWD were hemarthrosis (odds ratio [OR], 19.2; 95% confidence interval [CI], 3.7-100.4), postsurgical bleeding (OR, 15.2; 95% CI, 5.9-38.9), and menorrhagia (OR, 10.3; 95% CI, 4.9-21.9). With each increase in number of bleeding symptom categories with clinically significant scores, subjects had a stepwise increase in odds of a VWD diagnosis.

Conclusions: Our results suggest that most of the bleeding symptoms on BATs are significant predictors of VWD, and there is value in assessing multiple bleeding symptoms when eliciting a bleeding history. Certain bleeding symptoms are more useful predictors than others. Future BAT revisions may consider adding a relative weighting to each symptom.

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KEYWORDS

hemorrhage, hemostasis, surveys and questionnaires, symptom assessment, von Willebrand disease

Essentials

- We determined which bleeding symptoms from bleeding assessment tools (BATs) best predict von Willebrand disease (VWD).
- Many symptoms were strongly related to a VWD diagnosis, notably joint bleeding, postsurgical bleeding, and heavy period bleeding.
- Some symptoms were better predictors of VWD than others; therefore, adding relative weightings to each bleeding symptom may improve future BATs.
- There is value in assessing multiple bleeding symptoms when eliciting a bleeding history.

1 | INTRODUCTION

The diagnosis of bleeding disorders such as von Willebrand disease (VWD) can be a challenge for physicians. Mild bleeding events are common in individuals without bleeding disorders and the reporting and interpretation of hemorrhagic events is subjective. As a result, there has been significant focus over the past decade on the development of bleeding assessment tools (BATs) to aid in the quantification of bleeding symptoms and standardize bleeding histories.¹ BATs are questionnaires that score a range of bleeding symptoms based on their severity and generate an overall quantitative bleeding score. The Vicenza Bleeding Questionnaire (BQ), was developed in 2005, followed by the MCMDM-1VWD BQ in 2006, and subsequently its condensed form in 2008; the latter reduced the administration time from 40 to 10 minutes.^{1,2} In 2009, the Pediatric Bleeding Questionnaire (PBQ) added consideration of pediatric-specific bleeding symptoms to the existing Condensed MCMDM-1VWD BQ.³ Most recently, in 2010, Rodeghiero et al⁴ published the ISTH-BAT, designed for both pediatric and adult subjects, with the goal of achieving greater accuracy by considering both the frequency and severity of bleeding episodes. Administration time is approximately 20 minutes.

Bleeding assessment tools are an important part of the diagnostic workup of VWD because they can help prioritize laboratory testing as well as standardize communication of bleeding histories among clinicians. However, BATs have been criticized for being time consuming and for their limited utility outside of research settings.⁵ In response, efforts have been made to make BATs more accessible to patients through development of a self-administered BAT and to expand their use beyond VWD to other bleeding disorders.^{1,6,7} Several recent reviews discuss their value and limitations.^{1,5,6,8-10} The study and optimization of BATs clearly remains an active and evolving field of research.

Since BATs have been available for more than a decade, significant amounts of data have been collected from their use. In this study, we used our legacy data to determine which questions from BATs are the strongest predictors of a VWD diagnosis. We believe that the identification of these questions may serve to streamline BATs in future revisions and optimize their clinical utility.

2 | PATIENTS AND METHODS**2.1 | Legacy data**

The legacy data contain bleeding scores, demographic data, and VWD-relevant laboratory data collected from 1167 Canadian subjects for prior use in 9 studies ranging over 10 years.^{2,6,11-16} We chose to exclude subjects who were <12 years of age, and thus a total of 927 patients were included. We chose to exclude the younger patients because their presenting symptoms differ and they have not had the opportunity to experience some of the hemorrhagic challenges (eg, menarche) assessed by BATs. Data were collected via expert administration prior to a laboratory-defined VWD diagnosis using the Condensed MCMDM-1VWD BQ (n = 730), ISTH-BAT (n = 56), PBQ (n = 141). Questions on the BATs relate to different bleeding symptoms (eg, epistaxis and cutaneous bleeding), and each symptom is scored on the basis of its severity. Both the PBQ and ISTH-BAT contain an Other Bleeding symptom category (which includes umbilical stump bleeding, cephalohematoma, cheek hematoma during breast/bottle feeding, postcircumcision and postvenipuncture bleeding). Given that these symptoms are specific to infants, we did not include this category in our analysis. Table 1, adapted from Bowman and James,⁸ displays a comparison of the 3 BATs and bleeding symptom categories.

2.2 | Laboratory definition of VWD and controls

VWD diagnoses were made on the basis of laboratory definitions commonly used in both clinical and research settings.^{2,17} For type 1 VWD this includes von Willebrand factor antigen (VWF:Ag) and/or von Willebrand ristocetin cofactor (VWF:RCo) between 0.05 and 0.50 U/mL on at least 2 occasions; RCo:Ag ratio > 0.60; and a normal pattern of VWF multimers. For type 2A, abnormal laboratory investigations include VWF:Ag and/or VWF:RCo between 0.05 and 0.50 U/mL on at least 2 occasions and an appropriately abnormal multimer pattern. Type 2M is diagnosed on the basis of VWF:Ag and/or VWF:RCo between 0.05 and 0.50 U/mL on at least 2 occasions; RCo:Ag ratio < 0.60; and a normal multimer pattern. Type 2B VWD is diagnosed based on the same criteria as type 2A VWD with the

TABLE 1 Comparison of the three bleeding assessment tools used for analysis

Symptom	Score -1	0	1	2*	3	4
Epistaxis	-	No or trivial	>5 or more than 10	Consultation only	Packing or Cauterization or antifibrinolytics	Blood transfusion or replacement therapy or desmopressin
	-	No or trivial	>5 or more than 10	Consultation only	Packing or Cauterization	Blood transfusion or replacement therapy
	-	No or trivial	>5 year or more than 10	Consultation only	Packing or Cauterization or antifibrinolytics	Blood transfusion (use of hemostatic blood components and rFVIIa) or desmopressin
Cutaneous	-	No or trivial (< 1cm)	> 1cm and no trauma	Consultation only	-	-
	-	No or trivial	> 1cm and no trauma	Consultation only	-	-
	-	No or trivial	For bruises 5 or more (> 1cm) in exposed areas	Consultation only	Extensive	Spontaneous hematoma requiring transfusion
Minor Wounds	-	No or trivial (<5)	>5 or more than 5*	Consultation only or suture-strips	Surgical hemostasis or antifibrinolytics	Spontaneous or replacement therapy or desmopressin
	-	No or trivial	>5 or more than 5*	Consultation only	Surgical hemostasis	Blood transfusion or replacement therapy or desmopressin
	-	No or trivial	>5yr or more than 10*	Consultation only	Surgical hemostasis	Blood transfusion or replacement therapy or desmopressin
Oral Cavity	-	No	Reported or at least one	Consultation only	Surgical hemostasis or antifibrinolytics	Blood transfusion or replacement therapy or desmopressin
	-	No	Referred to at least one	Consultation only	Surgical hemostasis or antifibrinolytics	Blood transfusion or replacement therapy or desmopressin
	-	No or trivial	Referred to at least one	Consultation only	Surgical hemostasis or antifibrinolytics	Blood transfusion or replacement therapy or desmopressin
Gastrointestinal	-	No	Identified Cause	Consultation or spontaneous	Surgical hemostasis, antifibrinolytics, blood transfusion, replacement therapy or desmopressin	-
	-	No	Associated with ulcer, portal hypertension, hemorrhoids, angiodysplasia	Spontaneous	Surgical hemostasis, antifibrinolytics, blood transfusion, replacement therapy or desmopressin	-
	-	No or trivial	Associated with ulcer, portal hypertension, hemorrhoids, angiodysplasia	Consultation only	Surgical hemostasis, antifibrinolytic	Blood transfusion, replacement therapy, or desmopressin
Teeth Extraction	-	None done or no bleeding in one extraction	Reported, no consultation	Consultation only	Resuturing, repacking, antifibrinolytics	Blood transfusion, replacement therapy or desmopressin
	-	None done or no bleeding in one extraction	Reported, no consultation	Consultation only	Resuturing or packing	Blood transfusion, replacement therapy or desmopressin
	-	No or trivial	Reported in <25% of all procedures, no intervention	Reported in >25% of all procedures, no intervention	Resuturing or packing	Blood transfusion, replacement therapy or desmopressin
Surgery	-	None done or no bleeding in one surgery	Reported, no consultation	Consultation only	Surgical hemostasis or antifibrinolytic	Blood transfusion, replacement therapy or desmopressin
	-	None done or no bleeding in one surgery	Reported, no consultation	Consultation only	Surgical hemostasis or antifibrinolytic	Blood transfusion, replacement therapy or desmopressin
	-	No or trivial	Reported in <25% of all procedures, no intervention	Reported in >25% of all procedures, no intervention	Surgical hemostasis or antifibrinolytic	Blood transfusion, replacement therapy or desmopressin
Menorrhagia	-	No	Reported or consultation only	Antifibrinolytics or pill use	D&C, iron therapy	Blood transfusion or replacement therapy or desmopressin or hysterectomy
	-	No	Consultation only	Antifibrinolytics or pill use	D&C, iron therapy, endometrial ablation	Blood transfusion or replacement therapy or desmopressin or hysterectomy
	-	No or trivial	Consultation only or changing pads more frequently than every 2 hours or clot or flooding or PBAC score > 100	Time off work/school > 2 year or requiring antifibrinolytics, hormonal or iron therapy	Requiring combined treatment with antifibrinolytics and hormonal therapy or present since menarche and > 12 mo	Acute menorrhagia requiring hospital admission and emergency treatment or requiring transfusion, replacement therapy, desmopressin, D&C, endometrial ablation, hysterectomy
Postpartum	-	None done or no bleeding in 1 delivery	Reported, or consultation only	D&C, iron therapy, antifibrinolytics	Blood transfusion, replacement therapy or desmopressin	Hysterectomy
	-	None done or no bleeding in 1 delivery	Consultation only	D&C, iron therapy, antifibrinolytics	Blood transfusion, replacement therapy or desmopressin	Hysterectomy
	-	No or trivial or no deliveries	Consultation only or use of oxytocin or foctha > 6 weeks	Iron therapy or antifibrinolytics	Blood transfusion, replacement therapy or desmopressin or requiring examination under anesthesia and/or the use of uterine balloon/package to compress uterine vessels	Any procedure requiring critical care or surgical intervention (e.g. hysterectomy, internal iliac artery ligation, uterine artery embolization, uterine brace)
Hemarthrosis	-	Never	Posttrauma, no therapy	Spontaneous, no therapy	Spontaneous or traumatic requiring desmopressin, or replacement therapy	Spontaneous or traumatic requiring surgical intervention, or blood transfusion
	-	Never	Posttrauma, no therapy	Spontaneous, no therapy	Spontaneous or traumatic requiring desmopressin, or replacement therapy	Spontaneous or traumatic requiring surgical intervention, or blood transfusion
	-	Never	Posttrauma, no therapy	Spontaneous, no therapy	Spontaneous or traumatic requiring desmopressin, or replacement therapy	Spontaneous or traumatic requiring surgical intervention, or blood transfusion
Central Nervous System	-	Never	-	-	Subdural, any intervention	Spontaneous or traumatic requiring surgical intervention, or blood transfusion
	-	Never	-	-	Intracerebral, any intervention	Intracerebral, any intervention
	-	Never	-	-	Subdural, any intervention	Intracerebral, any intervention

The white row is for the Pediatric Bleeding Questionnaire, the medium gray row is for the Condensed MCMDM-1VWD Bleeding Questionnaire, and the dark gray row is for the ISTH-BAT. Scores were considered clinically significant if they were of 2 or greater, as outlined in bold.

* Consultation only: the patient sought medical evaluation and was either referred to a specialist or offered detailed laboratory investigation. D&C, dilation and curettage; PBAC, Pictorial Blood Loss Assessment Chart; rFVIIa, recombinant factor VIIa.

additional requirement for a heightened ristocetin-induced platelet aggregation response. For simplicity, all patients with type 2 VWD were combined into 1 group for analysis. Type 3 VWD is diagnosed on the basis of VWF:Ag and/or VWF:RCo < 0.05 U/mL and factor VIII < 0.10 U/mL.

Most controls were recruited from waiting rooms of primary or tertiary outpatient clinics after answering “no” to screening questions that included whether they had been diagnosed with a bleeding disorder or experienced a problem with bleeding or bruising. Other studies recruited healthy subjects from local advertisements.

2.3 | Statistical analysis

Analysis of the association between different bleeding symptoms and VWD diagnosis was performed using multivariable logistic regression with backward elimination.¹⁸ Bleeding symptom scores were categorized as significant or nonsignificant to indicate absence or presence of clinically relevant bleeding (defined as when medical attention was sought or bleeding was spontaneous, which equated to a score of ≥ 2). Scores considered nonsignificant/trivial were set as the reference category. VWD diagnosis was used as the dependent variable. No adjustments were made for multiple comparisons, and $P < 0.05$ was used as the threshold for statistical significance. Sex and age (10-year increments) were included in the model to control for age- and sex-specific bleeding categories (eg, menorrhagia or postpartum hemorrhage). Analyses were performed using all subjects, patients diagnosed with type 1 VWD, and by age and sex. An additional multivariable logistic regression analysis was performed to assess the predictive value of having a progressive increase in the number of bleeding symptom categories with scores ≥ 2 (ie, clinically significant). Three significant categories was selected as the maximum as there was <5% representation in groups with higher levels of categories. The reference category was composed of those with no categories with significant scores. Independent variables ranged from having 1 significant score to have ≥ 3 significant scores. The Hosmer-Lemeshow test was used to calculate goodness of fit, and the Cox and Snell R square was used to assess the amount of variation explained by the model. Continuous variables were summarized with medians and range, and categorical data with counts and percentages. All analyses were performed using IBM SPSS Statistics for Windows, Version 25.0. (IBM Corp., Armonk, NY)

3 | RESULTS

A total of 927 individuals were included in the analysis, of whom 783 were healthy controls. Sixteen percent (144/927) of the subjects were patients with VWD, with more than two-thirds having type 1 VWD (99/144). The mean age was 40 years (range, 12-90 years), with 15% ($n = 139$) of the subjects aged <18 years. Approximately two-thirds of the participants were women (613/927). The frequency of subjects with clinically significant scores in each of the bleeding

symptom categories as well as abnormal total bleeding scores is reported in Table 2. Please see Table 3 for relevant laboratory values. VWD patients most commonly had clinically significant scores in menorrhagia (85% of women; 88/104) and epistaxis (42%; 60/144). Clinically significant scores in muscle hematoma (8%; 12/144) and central nervous system (CNS) bleeding (1%; 2/144) were found to be least common.

The number of categories of bleeding symptoms reported by the individual had a major impact on odds ratio (OR) for a VWD diagnosis (Table 4), with each increase in the number of bleeding symptom categories with clinically significant scores associated with a stepwise increase in the OR for a VWD diagnosis. For example, compared to patients with only 1 significant category, those with 2 categories with significant scores had a 5-fold higher OR for a VWD diagnosis.

Figure 1 displays the results of the multivariable logistic regression for all subjects. The top 3 symptoms for which having clinically significant bleeding scores increased the odds of VWD were hemarthrosis (OR, 19.2; 95% confidence interval [CI], 3.7-100.4), postsurgical bleeding (OR, 15.2; 95% CI, 5.9-38.9), and menorrhagia (OR, 10.3; 95% CI, 4.9-21.9). Muscle hematoma and CNS bleeding were the only symptoms found not to significantly increase the OR for a VWD diagnosis in the multivariable model, possibly due to the small sample of individuals reporting these symptoms. While hemarthrosis and postsurgical bleeding are among the most powerful predictors, their clinical value is limited by the relatively small percentage of patients who experience these symptoms; similarly, menorrhagia affects only women.

When we limited the analysis to adult subjects in the multivariable logistic regression model, our results were similar to our analysis of all ages. Postsurgical bleeding (OR, 19.8; 95% CI, 6.8-57.2), menorrhagia (OR, 19.0; 95% CI, 7.1-51.0), and hemarthrosis (OR, 16.8; 95% CI, 3.2-89.4), were the top 3 symptoms significantly associated with increasing odds of VWD diagnosis. Muscle hematoma and CNS bleeding were not found to significantly increase the odds of a VWD diagnosis. Constraints in sample size prevented exploration of a pediatric-only model. When only women were included in the model, bleeding after tooth extraction (OR, 14.7; 95% CI, 5.1-42.1), oral cavity bleeding (OR, 12.3; 95% CI, 3.3-28.6), and menorrhagia (OR, 12.2; 95% CI, 5.7-26.2) most significantly increased the OR for having a VWD diagnosis. Gastrointestinal (GI) bleeding, bleeding from minor wounds, CNS bleeding, and muscle hematoma did not significantly increase the OR for a VWD diagnosis.

Multivariable logistic regression was repeated with a type 1 VWD diagnosis as the dependent variable (Figure 2). Significant bleeding scores in the categories of postsurgical bleeding (OR, 16.7; 95% CI, 6.1-45.7), menorrhagia (OR, 10.4; 95% CI, 4.9-22.2), and bleeding after tooth extraction (OR, 10.0; 95% CI, 3.9-25.6) increased the odds of type 1 VWD the most. Clinically significant bleeding scores in CNS bleeding, GI bleeding, and muscle hematoma did not increase the odds of having a type 1 VWD diagnosis.

TABLE 2 Legacy data patient demographics and total bleeding scores

	All VWD patients n = 144	Type 1 VWD n = 99	Type 2 VWD n = 19	Type 3 VWD n = 26	Normal controls n = 783
Female sex, n(%)	104 (71)	78 (79)	10 (53)	16 (57)	509 (66)
Mean age, y (range)	35 (12-85)	33 (12-85)	37 (12-71)	39 (16-72)	41 (12-90)
Age < 18 y, n(%)	27 (18)	21 (21)	2 (28)	1 (4)	112 (14)
Median total BS (range) ^a					
PBQ	6 (0-20)	5 (1-18)	7 (0-17)	13 (10-20)	0 (-2 to 5)
Condensed MCMDM-1 VWD	9 (-1 to 30)	7 (-1 to 21)	15 (6-22)	14 (4-30)	-1 (-3 to 8)
ISTH	11 (3-22)	11 (3-22)	0 (0-6)
Subjects with an abnormal total BS, n (%)					
PBQ	25 (86)	19 (86)	2 (67)	4 (100)	14 (12)
Condensed MCMDM-1 VWD	88 (89)	50 (82)	16 (100)	22 (100)	20 (3)
ISTH	13 (81)	13 (81)	1 (3)
Subjects with clinically significant scores, n (%)					
Epistaxis	60 (42)	30 (30)	9 (47)	21 (81)	65 (8)
Cutaneous bleeding	39 (27)	25 (25)	11 (58)	3 (15)	14 (2)
Bleeding from minor wounds	43 (30)	18 (18)	12 (63)	13 (46)	11 (1)
Oral bleeding	36 (25)	21 (21)	5 (26)	10 (35)	19 (2)
Bleeding after tooth extraction	47 (32)	31 (31)	6 (32)	9 (35)	14 (2)
GI bleeding	18 (13)	8 (8)	3 (16)	7 (27)	7 (1)
Postsurgical bleeding ^b	38 (37)	21 (42)	11 (84)	5 (46)	17 (4)
Menorrhagia ^c	88 (85)	62 (79)	10 (53)	16 (100)	132 (26)
Postpartum hemorrhage ^c	25 (24)	19 (24)	5 (50)	1 (6)	27 (5)
Muscle hematoma	12 (8)	1 (1)	2 (11)	9 (32)	1 (0.1)
Hemarthrosis	23 (16)	5 (5)	4 (21)	14 (50)	3 (0.5)
CNS bleeding	2 (1)	0 (0)	1 (5)	1 (4)	2 (0.3)

^aFor PBQ, abnormal score ≥ 2 ; For condensed MCMDM-1, abnormal score ≥ 4 ; For ISTH-BAT, abnormal score ≥ 4 for male adults, ≥ 3 for male children and ≥ 6 for female adults and ≥ 3 for female children.

^bDenominator is the number of subjects who have ever had surgery.

^cDenominator is number of women.

BS, bleeding score; CNS, central nervous system; GI, gastrointestinal; PBQ, Pediatric Bleeding Questionnaire; VWD, von Willebrand disease.

4 | DISCUSSION

The goal of our study was to use our legacy data to determine which bleeding symptoms assessed by presently circulating BATs are most predictive of a laboratory-defined VWD diagnosis. As noted in a recent publication by Rimmer and Houston,¹⁹ the Vicenza BQ and its subsequent revisions were developed using expert opinion, often without rigorous methodology for identifying the most discriminatory bleeding symptoms for inclusion. This fact suggests that such a high volume of questions on BATs may be unnecessary. Our findings indicate that most of the bleeding symptoms assessed by existing BATs are indeed significant predictors of VWD diagnosis, which confirms that a comprehensive bleeding history is necessary to understand a patient's phenotype. In our analysis of all 927 subjects,

hemarthrosis was found to be the most significant predictor of VWD. This finding was not surprising because of its prevalence within our case population, specifically in patients with type 3 VWD, and rarity in the general population. Postsurgical bleeding and menorrhagia were the second and third most predictive, which was similarly found in our model of patients with type 1 VWD. Findings from our analysis of patients with type 1 VWD may be of greatest clinical relevance, as BATs are thought to be efficacious in primary care settings (where first presentations of type 1 VWD commonly occur) where they can aid in decisions regarding VWF testing.²⁰ Both postsurgical bleeding and menorrhagia have been found in previous studies to best discriminate normal from abnormal bleeding, in addition to bleeding after tooth extraction, found to be significant in our type 1 model.^{21,22} Significant scores in CNS bleeding and muscle hematoma

TABLE 3 Relevant laboratory values

	Type 1 VWD N = 99	Type 2 VWD N = 19	Type 3 VWD N = 26
Blood type O+, n (%)	40 (40)	8 (42)	10 (38)
Median VWF:Ag, U/mL (range)	0.38 (0.07-0.62)	0.55 (0.11-1.61)	0.05 (0-0.09)
Median VWF:RCo, U/mL (range)	0.33 (0-0.49)	0.28 (0-0.71)	0.06 (0-0.15)
Median FVIII:C, U/mL (range)	0.70 (0.24-2.20)	0.49 (0.21-1.09)	0.05 (0-0.09)

FVIII:C, chromogenic factor VIII; VWF:Ag, von Willebrand factor antigen; VWF:Rco, von Willebrand ristocetin cofactor; VWD, von Willebrand disease.

TABLE 4 Odds of VWD diagnosis with stepwise increase in number of bleeding symptoms reported by each subject

Number of bleeding symptom categories with clinically significant scores ^a	Odds ratio	95% confidence interval	
		Lower limit	Upper limit
1 (n = 227)	9.3	4.2	20.8
2 (n = 76)	43.2	18.7	99.7
≥3 (n = 86)	645.9	253.6	1770.6

^aReference Category is 0 significant scores (n = 538). Clinically significant scores defined as those with a score of ≥ 2. VWD, von Willebrand disease.

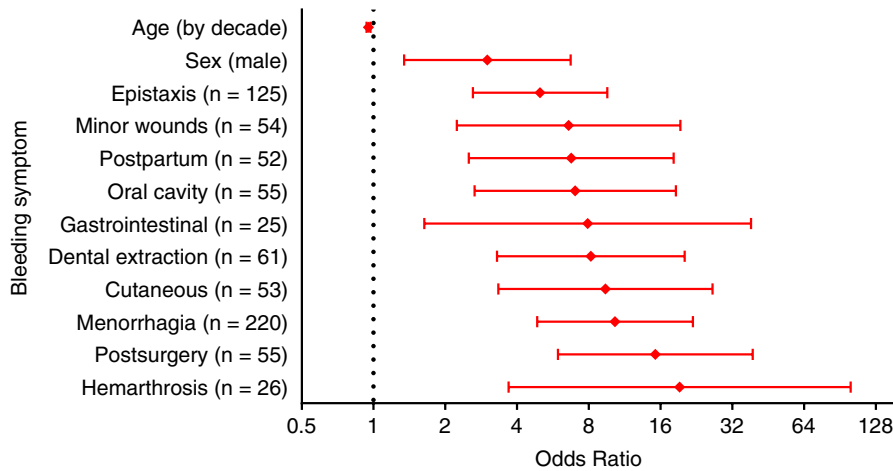


FIGURE 1 Association between bleeding symptoms and VWD diagnosis using multivariable logistic regression with backward elimination. The number of subjects with clinically significant scores in each category is listed in parentheses. For each bleeding symptom, the graph reports the odds ratio and its 95% confidence interval. Significance was set at $P < 0.05$. Having clinically significant bleeding scores for the symptoms of CNS bleeding and muscle hematoma did not significantly increase the odds of a VWD diagnosis. The Hosmer and Lemeshow test of the goodness of fit suggests the model is a good fit to the data as $P = 0.13$. The Cox and Snell R^2 was 0.378. The unit for age is increasing decades of years. Female sex was set as the reference category. Please note that the x-axis is not to scale. CNS, central nervous system; VWD, von Willebrand disease

were found not to significantly increase the odds of a VWD diagnosis, which was not surprising given their low frequency in both the case and control populations.

We found that the odds of a VWD diagnosis were higher when subjects had significant scores in an increasing number of bleeding symptom categories. In an analysis of patients with type 1 VWD and healthy controls, Rodeghiero et al²³ found that having >2 hemorrhagic symptoms, regardless of severity, was the minimum criterion useful to generate a discriminatory bleeding history (specificity,

99.5%; sensitivity, 64.3%). Our finding suggests that, although most of the bleeding symptoms on BATs were found to be significant predictors, there is value in assessing multiple bleeding symptoms when eliciting a bleeding history.

We also found that being of male sex increased the odds of diagnosis in all analyses. It is likely that bleeding symptoms in men are more of a red flag to both clinicians and patients than in women, leading to faster presentation and diagnosis. It is suggested that 15% of women with heavy menstrual bleeding have an underlying inherited

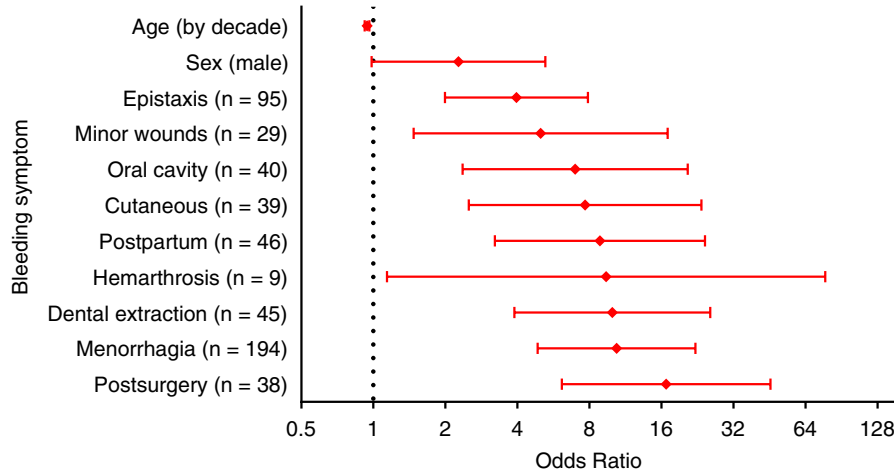


FIGURE 2 Association between bleeding symptoms and type 1 VWD using multivariable logistic regression with backward elimination. The number of subjects with clinically significant scores in each category is listed in parentheses. Having clinically significant scores for the symptoms of CNS bleeding, GI bleeding, and muscle hematoma did not significantly increase the odds of a type 1 VWD diagnosis. The Hosmer and Lemeshow test of the goodness of fit suggests the model is a good fit to the data as $P = 0.43$. The Cox and Snell R^2 was 0.278. The unit for age is increasing decades of years. Female sex was set as the reference category. Please note that the x-axis is not to scale. CNS, central nervous system; GI, gastrointestinal; VWD, von Willebrand disease

bleeding disorder, most commonly VWD, but remain undiagnosed, given barriers such as lack of understanding regarding the difference between normal and abnormal bleeding and social stigma.²⁴ Menorrhagia was one of the most predictive symptoms of VWD in all regression models, highlighting the importance of screening women with unexplained menorrhagia for underlying bleeding disorders.

Our study has several limitations. First, the frequency of significant scores for some of the symptoms (namely, muscle hematoma and CNS bleeding) was low, which may mean our analysis of these symptoms was underpowered. It is possible that no significant association with VWD was found for CNS bleeding and muscle hematoma due to a lack of statistical power. However, the clinical importance of these symptoms is undisputable, as they are relatively rare in the general population and raise a red flag for further hemostatic evaluation. Second, our findings may not be generalizable to all clinical scenarios, as the distribution of patients with VWD in our study is more heavily weighted to type 3 VWD than what is typically seen in practice. This may explain our finding that hemarthrosis was the most significant predictor of VWD in our “all subjects” analysis. Therefore, in the design of future BATs, our results from analysis of only patients with type 1 VWD may be most useful to highlight important symptoms experienced by patients presenting for the first time with bleeding, where a diagnosis of type 1 VWD is more likely. An additional limitation is the lack of replication in the development of our prediction model, which we were unable to perform given our limited case population. Finally, it is critical to highlight that we excluded patients from our study that were aged <12 years, which is an important caveat for interpretation of our results. Given the age restriction, our results predictably shift away from some of the symptoms that are more common triggers for evaluation of a possible mild bleeding disorder in children (eg, recurrent epistaxis, excessive bruising) and toward symptoms seen only in an older age cohort (eg, menorrhagia, postpartum hemorrhage). Our findings relate exclusively to a population of adolescents and adults.

Our study found that most of the bleeding symptoms assessed by BATs are statistically significant predictors of a laboratory-confirmed VWD diagnosis; however, certain bleeding symptoms may have greater predictive value than others. A recent study by Garcia et al²⁵ proposed similar conclusions. The authors investigated which ISTH-BAT bleeding symptom subscores contributed the most to the total bleeding score of the ISTH-BAT in patients with type 1 VWD. The authors found that all ISTH-BAT bleeding symptoms were correlated with a diagnosis of type 1 VWD, but some contributed more significantly than others.²⁵ Future BAT revisions may benefit from the addition of relative weighting for each bleeding symptom to accommodate for this observed variability in contribution of each bleeding symptom to a VWD diagnosis. Our data also suggest that such weightings may be optimized by adjusting them for patient demographics, as the symptoms most predictive of VWD changed when our analysis was divided by age and sex.

Recent research has focused on expanding the use of BATs from tertiary to primary care settings, as well as into the hands of patients in the form of a self-BAT.^{6,8} When used outside of the tertiary care setting, there is an understandable tendency to want to reduce the length.^{2,5} We found that nearly all bleeding symptoms evaluated on BATs held their own significance or were rare symptoms that were clinically important. Therefore, removing symptoms to shorten BAT length may compromise efficacy. Our finding of a significant increase in the odds of VWD with a stepwise increase in number of significant bleeding symptom scores further supports evaluation of multiple bleeding symptoms, as represented on BATs.

In conclusion, BATs serve as an important tool to elicit a comprehensive and objective bleeding history to identify patients who may benefit from further hemostatic testing. However, despite their strengths, there may be room for further optimization of these scores, such as the addition of a weighting system to incorporate the differential value of bleeding symptoms in predicting VWD.

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RELATIONSHIP DISCLOSURE

The authors report nothing to disclose.

AUTHOR CONTRIBUTION

Study initiation and coordination: JS, JG, and PJ; preparation of legacy data: JS, SL, and JG; analysis and interpretation of results: JS and PJ; statistical analysis: JS and WH; lead author of initial manuscript: JS; revisions of draft manuscripts: JS, YL, JR, WH, VSB, MLR, BSC, ADP, and PJ; and review and approval of the final manuscript: JS, YL, JR, WH, VSB, MLR, BSC, ADP, and PJ.

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SUPPORTING INFORMATION

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

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