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ORIGINAL ARTICLE

Longitudinal bleeding assessment in von Willebrand disease utilizing an interim bleeding score

Michelle Lavin[1,2] | Pamela Christopherson[3] | Julie Grabell[4] | Thomas Abshire[3] | Veronica Flood[3] | Sandra L. Haberichter[3] | David Lillicrap[5] | James S. O'Donnell[1,2] | Robert R. Montgomery[3] | Paula D. James[4]

[1]National Coagulation Centre, St. James's Hospital, Dublin, Ireland

[2]Irish Centre for Vascular Biology, Royal College of Surgeons in Ireland, Dublin, Ireland

[3]Blood Research Institute, Versiti, Milwaukee, Wisconsin, USA

[4]Department of Medicine, Queen's University, Kingston, Ontario, Canada

[5]Department of Pathology & Molecular Medicine, Queen's University, Kingston, Ontario, Canada

Correspondence
Paula D. James, Department of Medicine, Queen's University, 94 Stuart Street, Rm 2015, K7L 3N6 Kingston, ON, Canada.
Email: jamesp@queensu.ca

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Abstract

Background: Assessment of bleeding phenotype is critically important in the diagnosis of von Willebrand disease (VWD). Despite advances in bleeding assessment tools (BATs), standardized tools to evaluate bleeding following diagnosis (interim bleeding) are lacking.

Objectives: We assessed the clinical utility of an interim bleeding protocol in a multicenter, international study involving patients with VWD.

Methods: The enrolment ISTH BAT formed the original bleeding score (0 BS). At follow-up, the International Society on Thrombosis and Haemostasis BAT was repeated but included only interval bleeding (Interim BS, 1 BS). Both scores were annualized (0 BS/yr, 1 BS/yr). BS were analyzed by VWD subtype, plasma VWF level, sex, and age.

Results: Interim BS discriminated by subtype, with significantly increased 0 BS and 1 BS in patients with type 3 VWD. In patients with type 1 VWD, a positive or negative 0 BS did not predict future bleeding, with similar 1 BS/yr (median 1.0 vs. 0.7, $p = .2$). Despite significantly higher 0 BS in females with type 1 VWD than males (median 7 vs. 5, $p = .0012$), 1 BS were not significantly different (median 4 vs. 4, $p = .16$). While 0 BS were lower in children than adults with type 1 VWD, interim BS were similar (median 5 vs. 3, $p = .5$; 1BS/yr, median 1 vs. 0.8, $p = .7$). Interestingly, in those with plasma von Willebrand factor:ristocetin cofactor levels >50 IU/dl, interim BS rates were similar to those 30–50 IU/dl (1 BS/yr 0.8 vs. 1.3, $p = .5$).

Conclusion: This study provides both a new approach to longitudinal bleeding assessment and insights into the evolution of bleeding in VWD.

KEYWORDS
hemorrhage, phenotype, symptom assessment, von Willebrand disease, von Willebrand factor

Michelle Lavin and Pamela Christopherson contributed equally to this work.

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1 | INTRODUCTION

Von Willebrand disease (VWD) is the most common inherited bleeding disorder worldwide, with an estimated 0.1%–1% of the population exhibiting reduced von Willebrand factor (VWF) levels.[1,2] VWD is a clinicopathological diagnosis, requiring documented quantitative or qualitative abnormalities of VWF and a bleeding phenotype.[3] Partial quantitative reductions in plasma VWF levels account for 70% of cases[4] and are classified as type 1 VWD. Type 2 VWD is diagnosed in those patients with qualitative abnormalities of circulating VWF and type 3 VWD refers to a complete absence of plasma VWF.[5] Determination of bleeding phenotype is challenging as both patient perception and physician assessment of bleeding symptoms are subjective in nature. In order to standardize the approach to phenotypic evaluation of patients referred for VWD workup, bleeding assessment tools (BAT) have been designed and validated.[6–10] The recently published American Society of Hematology (ASH) International Society on Thrombosis and Haemostasis (ISTH) National Hemophilia Foundation (NHF) World Hemophilia Foundation (WFH) VWD diagnosis guidelines highlights the important role of BATs in the screening and follow-up of VWD patients, including the need for more longitudinal data on bleeding symptoms.[11] Although BATs ensure a comprehensive evaluation of a bleeding history they have inherent limitations, particularly in younger patients who may have limited hemostatic challenges.[12] In addition, frequency of bleeding may not be accurately reflected as scores for individual domains are easily saturable. For example, severe epistaxis requiring transfusion will receive identical scores irrespective if it occurred once or on multiple occasions, a major limitation with many BATs. Although initially developed for assessment of patients at the time of presentation, some studies have also reported the use of retrospective BAT scores.[10,13–15] This approach poses distinct challenges as both the patient and physician are aware of the presence of an underlying bleeding disorder, potentially introducing recall or confirmation bias.

From the original BATs, such as the Vicenza Bleeding Questionnaire, further modifications and refinements (Molecular and Clinical Markers for the Diagnosis and Management of Type 1 [MCMDM-1] VWD score, Condensed MCMDM-1 VWD score) have reduced the time required to complete the questionnaire while improving sensitivity and specificity.[12] The ISTH BAT offers a comprehensive assessment of phenotype, administered in 20 min or less.[7] Clinical implementation of BATs has been facilitated by the validation of normal age- and sex-specific reference ranges.[6,16] While the majority of questionnaires are administered by health-care professionals, self-administered versions of the ISTH BAT have been developed with consistent bleeding score (BS) results observed.[17,18] Although few studies have directly compared BATs, recent evidence suggests that the ISTH BAT may be more sensitive to bleeding due to the incorporation of patient-reported symptoms.[19] Importantly, BAT scores have been shown to have prognostic benefits, with MCMDM-1 VWD scores >10 predictive of future bleeding episodes in VWD patients.[20]

ESSENTIALS

- Standardized methods to reassess bleeding in von Willebrand disease (VWD) are currently lacking.
- To address this issue we adapted the International Society on Thrombosis and Haemostasis bleeding assessment tool, developing an interim bleeding score (BS).
- The interim BS differed between VWD subtypes and provided insights into bleeding by sex and age.
- The optimal interval for reassessment of bleeding phenotype remains to be defined.

Despite these recent advances in phenotypic assessment at time of diagnosis, there is a clear and unmet clinical need for tools to prospectively and longitudinally monitor symptoms over time (interim bleeding) in patients with bleeding disorders. Development of a standardized approach to assessment of interim bleeding offers opportunities to overcome this clinical deficit, ensuring an easily communicable update of bleeding status for a given individual over time. The ideal interim BS would be both easy and quick to administer, capturing all bleeding events since last assessment. However, a clinically effective interim BS should also account for the differing time periods between assessments as longer intervals may allow increased BS to accrue. Importantly, examination of interim BS in larger patient cohorts has the potential to inform on evolution of bleeding phenotype in patients with VWD, offering novel insights into this condition.

To address these clinically relevant questions we undertook an international, multicenter study involving patients from the Zimmerman, Canadian, and Low Von Willebrand in Ireland (LoVIC) cohorts.[15,17,21–23] Through the adaption of a frequently used BAT, the ISTH BAT, we generated a novel approach to longitudinal bleeding assessment and prospectively determined the validity and clinical utility of this interim BS in a large cohort of patients with VWD.

2 | METHODS

2.1 | Subjects

All participants were recruited in three coordinated studies: the Zimmerman Program for the Molecular and Clinical Biology of VWD (ZPMCB-VWD) study, the LoVIC study, and Canadian VWD studies as previously described.[15,17,21–23] Local research ethics committee approval was obtained for all studies prior to recruitment and written, informed consent was obtained from all participants. A preexisting diagnosis of low VWF/VWD was required for study entry as determined by the study center. For the purposes of data interpretation, patients with partial quantitative reductions in plasma VWF levels (type 1 VWD and low VWF levels) were analyzed together as

type 1 VWD. Only index cases were included for the purposes of this study.

2.2 | Phenotypic evaluation

At the time of recruitment all participants completed an ISTH BAT questionnaire. The BAT was administered by a member of the research team (study coordinator, nurse, or physician) in each center. For each participant, the time frame covered by this questionnaire was recorded (all symptoms until diagnosis with VWD or all symptoms up to date of enrolment). In keeping with previously published data, a positive ISTH BAT score was defined as >3 for male, >5 for females, or >2 for children of either sex.[7,16] In an effort to minimize research burden on patients, follow-up testing (BAT and plasma VWF levels) were conducted opportunistically at routine clinical follow-up rather than imposing prespecified follow-up times on participants.

2.3 | Calculation of the interim and annualized BS

The recruitment BS was referred to as the original BS (0 BS) and included all historical events. The repeat ISTH BAT (interim BS or 1 BS) was administered opportunistically at routine clinical follow-up and the interval period recorded. Only bleeding events that had occurred since the 0 BS were included in the 1 BS and the use of prophylaxis was excluded. To account for influence of time elapsed between BATs the 0 BS and 1 BS were divided by the time period (years) covered by the questionnaire, resulting in annualized BS for both the original BS (0 BS/yr) and interim BS (1 BS/yr; Table 1).

2.4 | Laboratory assessments

Venous blood samples were collected in 3.2% sodium citrate, centrifuged, and plasma frozen at −80°C. All plasma VWF levels were performed as previously outlined at three centralized laboratories in Dublin (National Coagulation Reference Laboratory, St. James's Hospital), at Kingston General Hospital Core Laboratory, and Milwaukee (Versiti, Diagnostic Laboratories).[15,24] In Milwaukee, VWF:Ag (antigen) levels were performed by enzyme linked immunosorbent assay; in Dublin and Canada, a latex particle enhanced immunoturbidometric assay was used.[15,24] Plasma VWF:RCo (ristocetin cofactor) levels were assessed was by automated platelet agglutination.[15,24] Interlaboratory VWF quality control samples ensured consistency of plasma VWF testing. Repeated samples taken during the study were assessed using the same methodology.

2.5 | Statistical analysis

Continuous variables such as BS were expressed as medians with normally distributed laboratory data expressed using means. Plasma VWF levels below the lower limit of detection (<10 IU/dl) were recorded as 5 IU/dl for the purpose of analysis. Differences in BS between groups was tested using the Mann Whitney *U*-test, with a p value of $<.05$ considered statistically significant. BS were graphically represented using box and whisker graphs, where the box represents the 25th and 75th percentile, the whiskers the 5th and 95th percentile, and the outliers displayed as individual points. Statistical analyses were performed using Prism 7, Version 7.02 (GraphPad).

3 | RESULTS

3.1 | Patient cohort

Original and interim BS were performed on 305 subjects, 225 females (73.8%) and 80 males (26.3%). The majority of participants were aged ≥18 years of age (65.6%), with type 1 VWD predominating ($n = 232$, 76.1%; Table 2). The distribution by study center is outlined in Table 3.

3.2 | Original and interim BS are significantly increased in patients with type 3 VWD in comparison to other subtypes

We initially examined if BS discriminated between patients with different subtypes of VWD and found that 0 BS were significantly higher in patients with type 3 VWD (median 16) than patients with type 2 VWD (median 9, $p < .01$) and type 1 VWD (median 7,

TABLE 1 Outline of interim bleeding scores used and the method for their generation

Abbreviation	Bleeding scores (BS)	Description
0 BS	Original BS	Entire patient history up to time of diagnosis or enrolment
1 BS	Interim BS	Bleeding that occurred since 0 BS and follow up visit
0 BS/yr	Annualized original BS	Original bleeding score divided by years (timeframe covered by original questionnaire)
1 BS/yr	Annualized interim BS	Interim bleeding score divided by years (timeframe between questionnaires)

TABLE 2 Demographics of the study cohort

	Type 1 VWD	Type 2 VWD	Type 3 VWD
n	232	56	17
Sex			
Male (*n*)	46	22	12
Female (*n*)	186	34	5
Age (years)			
Pediatric (<18 years, *n*)	77	23	5
Adult (≥18 years, *n*)	155	33	12
Plasma VWF levels (IU/dl)			
VWF:Ag (mean, range)	37 (2–102)	35 (8–120)	1 (0.5–4)
VWF:RCo (mean, range)	34 (5–91)	15 (5–98)	5 (0–5)
Original ISTH BAT scores (0 BS)			
Median, range	7 (0–24)	9 (0–25)	16 (6–29)
Duration of follow up (years)			
Median, range	5 (1–33)	9 (0–25)	16 (6–29)

Abbreviations: Ag, antigen; BAT, bleeding assessment tools; ISTH, International Society on Thrombosis and Haemostasis; RCo, ristocetin cofactor; VWD, von Willebrand disease; VWF, von Willebrand factor.

TABLE 3 Number of participants by site and disease subtype

	Type 1 *n*, (%)			
VWD subtype	<30 IU/dl	>30 IU/dl	Type 2 *n*, (%)	Type 3 *n*, (%)
Zimmerman	41 (75%)	51 (29%)	47 (84%)	16 (94%)
Canadian	13 (25%)	49 (27%)	9 (16%)	1 (6%)
LoVIC	0	78 (44%)	0	0
Total (*n* = 305)	54	178	56	17

Abbreviations: LoVIC, Low Von Willebrand in Ireland; VWD, von Willebrand disease.

$p < .0001$; Figure 1A). All participants completed a pre-study questionnaire regarding prophylaxis use; of the 17 patients enrolled with type 3 VWD only one patient indicated that they were on prophylaxis. Therefore, these interim score findings must be interpreted in the context of type 3 VWD patients with limited use of prophylaxis. On assessment of bleeding over time, the 1 BS were significantly elevated in type 3 VWD patients compared to those with type 2 VWD (median 13 vs. 7, $p < .01$) or type 1 VWD (median 13 vs. 4, $p < .0001$; Figure 1B).

Of interest, no significant difference in 0 BS was observed between type 2 and type 1 VWD patients (median 9 vs. 7, $p = .10$; Figure 1A). We considered that this finding may be due to differing ages at presentation between the patients with type 2 and type 1 VWD, altering the preceding hemostatic challenges. However, the age at 0 BS was not significantly different (median 25 vs. 27, $p = .9$), nor was the 0 BS/yr (median 0.3 vs. 0.4, $p = .16$; Figure 1C). The limited number of patients with type 2 VWD ($n = 56$) and the wide spread of 0 BS in this group may have contributed to this finding. Over time, bleeding rates diverged between type 2 and type 1 VWD patients, with significantly increased 1 BS (median 7 vs. 4, $p < .01$; Figure 1B) and 1 BS/yr scores (median 1.4 vs. 0.9, $p < .05$; Figure 1D) seen in the type 2 patients. These data suggest that although similar BS were seen in both type 1 and type 2 VWD patients at diagnosis, patients with type 2 VWD will experience significantly more bleeding over time.

For a scoring system to be clinically useful, applying a standardized approach to the determination of interim scores should generate similar results across different sites. To assess geographical influences, if any, all bleeding scores were analyzed by disease subtype and clinical site (Figure S1 in supporting information). No significant differences were seen between centers for 0 BS, 1 BS, 0 BS/yr, or 1BS/yr for any disease subtype, except for 1 BS/yr in type 1 VWD patients between the Canadian and LoVIC cohorts (median 1.9 vs. 0.5, $p = .002$). This was due to the differences in the patient population (inclusion of those <30 IU/dl in the Canadian cohort) but also that the duration of follow-up was shorter in the Canadian type 1 VWD subgroup (median 3.3 years vs. 6.5 years, $p < .0001$). These data highlight not only the reproducibility of this approach to the assessment of interim bleeding but also the need to define the ideal interval assessment timeframe.

3.3 | In those patients whose plasma VWF:RCo levels normalize, interim bleeding scores are not significantly different to those with plasma VWF:RCo levels in the 30–50 IU/dl range

For each individual, the lowest recorded plasma VWF:RCo levels performed at the central laboratories were identified and patients segregated accordingly. On examination of the 0 BS a significant difference was seen between those with plasma VWF:RCo <30 IU/dl ($n = 110$) and >50 IU/dl ($n = 22$; median 9 vs. 6.5, $p = .047$) but not 30–50 IU/dl ($n = 173$; median 9 vs. 7, $p = .08$, Figure 2A). Although the similar 0 BS between patients with plasma VWF:RCo levels <30 IU/dl and 30–50 IU/dl was initially surprising, this resulted from the differing time periods covered by the 0 BS (median 19 years for VWF:RCo <30 IU/dl, 28 years for VWF:RCo 30–50 IU/dl). Using the 0 BS/yr to overcome this factor, a clear and highly significant difference became apparent between those patients with plasma VWF:RCo <30 IU/dl and 30–50 IU/dl (median 0.45 vs. 0.27, $p < .0001$; Figure 2C); underscoring the benefit of the annualized score. On subsequent follow-up, interim BS were significantly higher in those with plasma VWF:RCo levels <30 IU/dl compared to 30–50 IU/dl using either the 1 BS (median 6 vs. 4, $p = .0002$; Figure 2B) or 1 BS/yr (median 1.4 vs. 0.8, $p = .003$; Figure 2D) scores.

Comparing patients with plasma VWF:RCo levels in the 30–50 IU/dl or >50 IU/dl range, no significant difference in 0 BS (median 7 vs. 6.5, $p = .6$; Figure 2A), 1 BS (4 vs. 6, $p = .35$; Figure 2B), 0 BS/yr (0.27 vs. 0.25, $p > .9$; Figure 2C) or 1 BS/yr (0.8 vs. 1.3, $p = .5$;

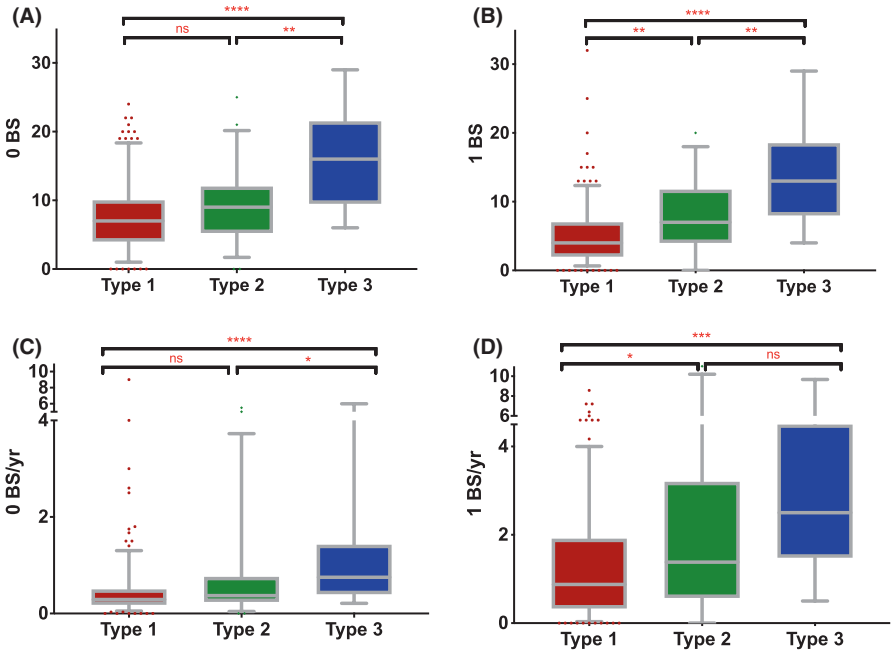

FIGURE 1 Interim bleeding scores can discriminate between subtypes of von Willebrand disease (VWD). Original bleeding score (0 BS; A), interim BS (1 BS; B), annualized original BS (0 BS/yr; C) and annualized interim BS (1 BS/yr; D) data for all patients by VWD subtype. 0 BS, 1 BS, 0 BS/yr, and 1 BS/yr scores were significantly increased in type 3 VWD patients ($n = 17$) compared to those with type 1 ($n = 232$) and type 2 VWD ($n = 56$). Data represented using box (25th and 75th percentile) and whisker (5th and 95th percentile) graphs, with outliers displayed as individual points.

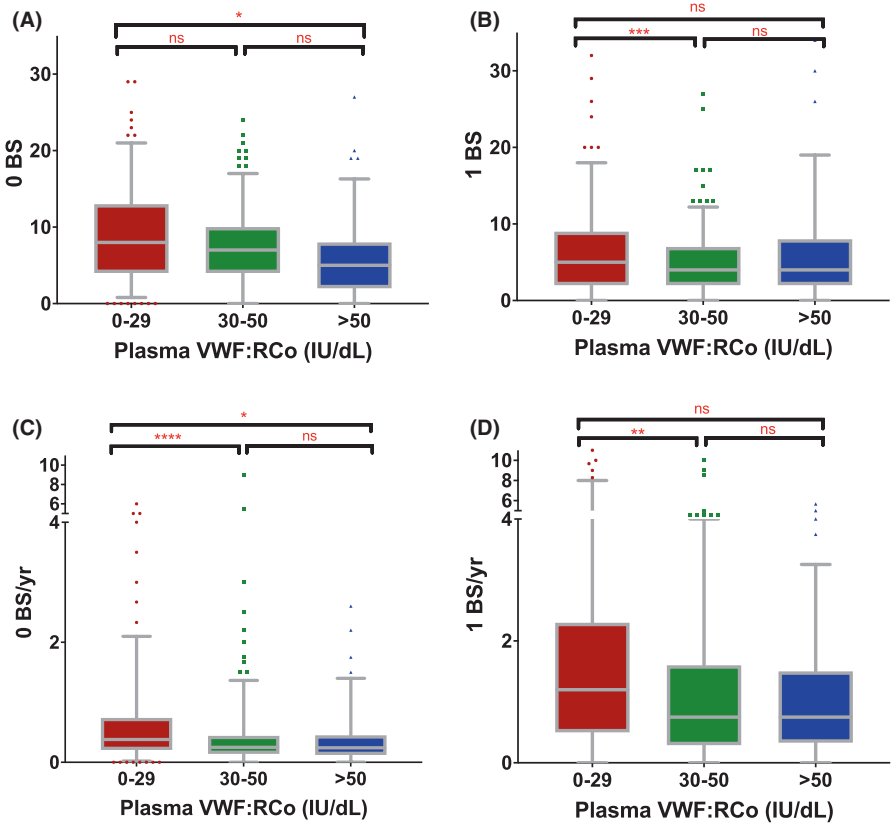

FIGURE 2 Interim bleeding scores were not significantly different between those patients with plasma von Willebrand factor ristocetin cofactor (VWF:RCo) levels 30–50 IU/dl or > 50 IU/dl. When bleeding scores (BS) were compared by plasma VWF:RCo levels, BS were similar between those patients with plasma VWF:RCo levels 30–50 IU/dl ($n = 173$) and > 50 IU/dl ($n = 22$) in the original bleeding score (0 BS; A; median 7 vs. 6.5, $p = .6$), interim BS (1 BS; B; 4 vs. 6, $p = .35$), annualized original BS (0 BS/yr; C; 0.27 vs. 0.25, $p > .9$), and annualized interim BS (1 BS/yr; D; 0.8 vs. 1.3, $p = .5$). Data represented using box (25th and 75th percentile) and whisker (5th and 95th percentile) graphs, with outliers displayed as individual points.

Figure 2D) was observed. Although plasma VWF levels may differ due to the inter- and intra-assay co-efficient of variation, these patients all had a pre-existing diagnosis of VWD from a specialist center and a marked increase in plasma VWF:RCo levels recorded centrally. This likely represented the well-described age-related increases in plasma VWF levels. These interim BS data suggest that, even with normalization of plasma VWF:RCo levels, patients continue to experience bleeding symptoms.

3.4 | Although original BS are higher in females, no significant difference in interim bleeding is seen between males and females with type 1 VWD

To investigate the influence of sex on interim bleeding we examined BS in the type 1 VWD subgroup (186 females, 46 males). Bleeding scores at enrolment were significantly higher in females than males with type 1 VWD (median 7 vs. 5, $p = .0014$; Figure 3A).

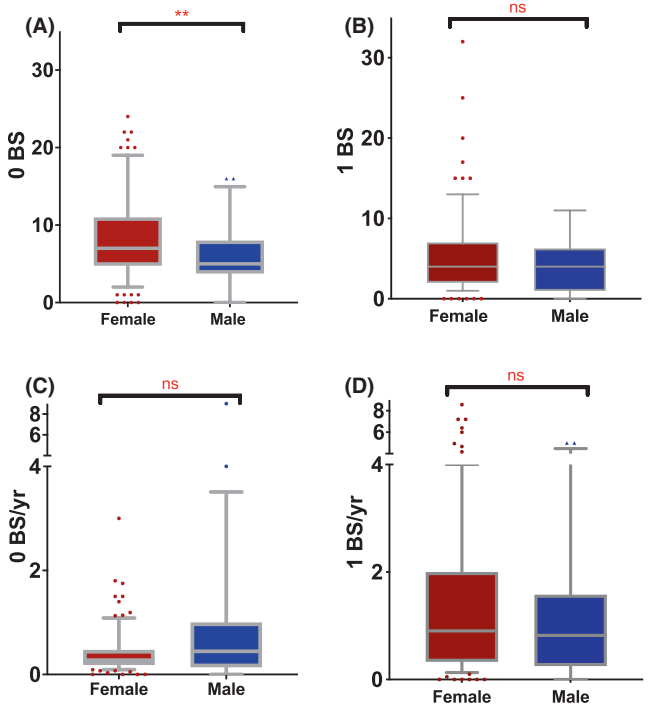

FIGURE 3 Although original bleeding scores (0 BS) were significantly higher in females than males with type 1 von Willebrand disease (VWD), over time interim bleeding scores were not significantly different. In a subset of 232 patients with type 1 VWD, BS were examined by sex. Only 0 BS were significantly elevated in females ($n = 186$) compared to males ($n = 46$; median 7 vs. 5, $p = .0014$, A); however, no significant difference was found between females and males by 1 BS (B, median 4 vs. 4, $p = .16$), 0 BS/yr (C, median 0.28 vs. 0.45, $p = .07$), or 1 BS/yr (D, 0.9 vs. 0.8, $p = .31$), suggesting bleeding over time is not impacted by sex. Data represented using box (25th and 75th percentile) and whiskers (5th and 95th percentile) graphs, with outliers displayed as individual points.

With follow-up, however, this difference no longer persisted with no significant difference evident in either the 1 BS (4 vs. 4, p = ns; Figure 3B), 0 BS/yr (0.28 vs. 0.45, $p = 0.7$; Figure 3C) or 1 BS/yr (0.9 vs. 0.8, p = ns; Figure 3D). Heavy menstrual bleeding was the most commonly reported bleeding symptom in women with VWD. Lower interim bleeding scores may reflect the impact of treatment received for heavy menstrual bleeding following diagnosis, resulting in similar bleeding rates over time in both men and women with type 1 VWD patients.

3.5 | Original bleeding phenotype does not predict 1 BS/yr in patients with type 1 VWD

For patients with mild to moderate reductions in plasma VWF levels, prediction of future bleeding risk is difficult. We examined the 232 patients with type 1 VWD to determine whether the 0 BS was predictive of future bleeding. Patients were segregated according to the outcome of their 0 BS score (positive +, $n = 182$ or negative –, $n = 50$) and interim scores compared. Plasma VWF levels were

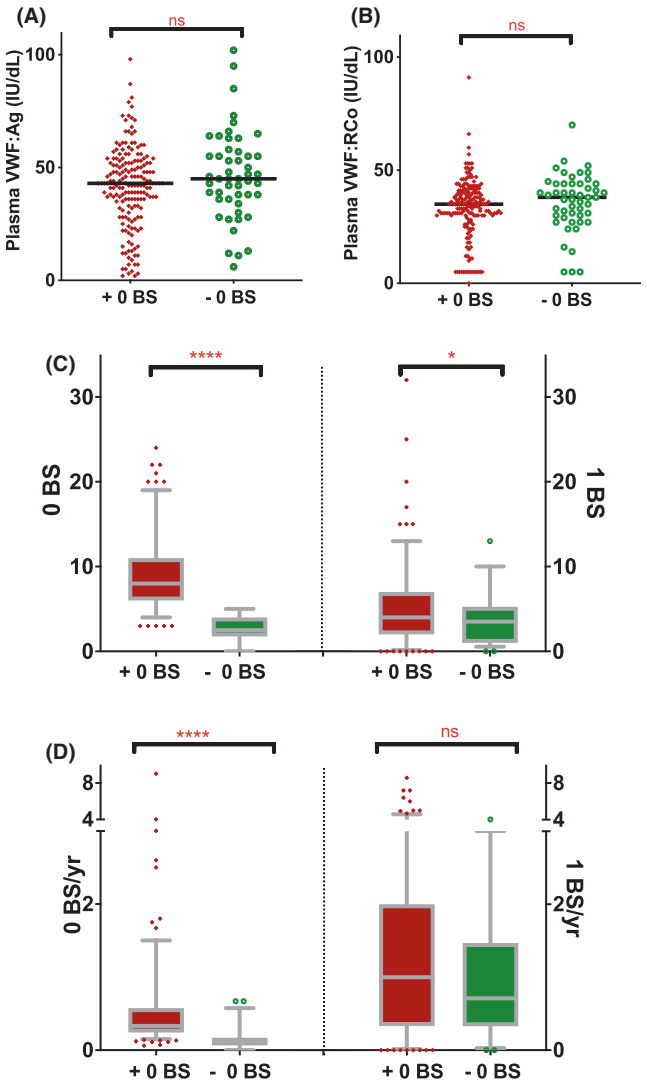

FIGURE 4 In patients with type 1 von Willebrand disease (VWD), interim bleeding scores were similar between those with a positive (+) or negative (−) original bleeding score (0 BS). The subset of patients with type 1 VWD ($n = 232$) were segregated according to the results of their 0 BS (+ 0 BS, $n = 182$ or −0 BS, $n = 50$) and interim bleeding assessed. Baseline plasma von Willebrand factor antigen (VWF:Ag; A, median 42 vs. 47 IU/dl, $p = .1$) and VWF ristocetin cofactor (VWF:RCo; B; median 32 vs. 40 IU/dl, $p = .1$) were similar between both groups. When +0 BS and −0 BS patients were compared, 1 BS were higher in those with a +0 BS (C; median 4 vs. 3.5, $p = .025$) but with annualization no significant difference in 1 BS/yr was seen (D; 1.0 vs. 0.7, $p = .2$), indicating similar degrees of interim bleeding. Data represented using box (25th and 75th percentile) and whisker (5th and 95th percentile) graphs, with outliers displayed as individual points.

not significantly different between both subgroups (median plasma VWF:Ag 42 vs. 47 IU/dl, p = .1; median plasma VWF:RCo 32 vs. 40 IU/dl, $p = .1$; Figure 4A,B).

As expected, the 0 BS (median 8 vs. 4, p=<.001; Figure 4C) and 0 BS/yr (median 0.3 vs. 0.1, p<.0001; Figure 4D) were significantly higher in those with a positive 0 BS. The 1 BS was also significantly higher in those with an initial positive 0 BS (median 4 vs.

3.5, $p = .025$; Figure 4C); however, when adjusted for the follow-up interval, no significant difference in 1 BS/yr was seen (1.0 vs. 0.7, $p = .2$; Figure 4D). These data raise the possibility that a negative 0 BS at initial evaluation may not preclude future bleeding in patients with type 1 VWD.

3.6 | Despite lower 0 BS scores in children with type 1 VWD, bleeding rates over time are not significantly different to adults

Bleeding assessment in children poses unique problems as both mild bleeding symptoms are common and hemostatic challenges limited. Particularly challenging are those children referred for assessment due to a family history of VWD but with limited bleeding phenotype. The ISTH BAT reference range differs accordingly, with a score of >2 considered abnormal in pediatric subjects (<18 years of age) compared to >3 for adult males and >5 for adult females.[16] As a result, children will often have lower bleeding scores than adults, a factor that may influence our analysis of interim BS when examined by disease subtype. To understand any differences in interim bleeding between adult ($n = 155$) and pediatric ($n = 77$) patients with type 1 VWD we compared interim bleeding between these subgroups.

The median 0 BS was significantly higher in adults than pediatric subjects (8 vs. 5, $p < .0001$; Figure 5A); however, the 0 BS/yr was significantly lower than in children (0.2 vs. 0.6, $p < .0001$, Figure 5C), related to the younger age at 0 BS for the pediatric subjects. In both groups, the median follow-up was similar (4 years and 6 years). Both the 1 BS (median 3 vs. 5, $p = .5$, Figure 5B) and 1 BS/yr (median 0.8 and 1, $p = .7$, Figure 5D) were not significantly different between adults and children. Although BS in children were lower than adults at diagnosis, our data demonstrate that children with type 1 VWD will experience interim bleeding symptoms at a rate similar to adults.

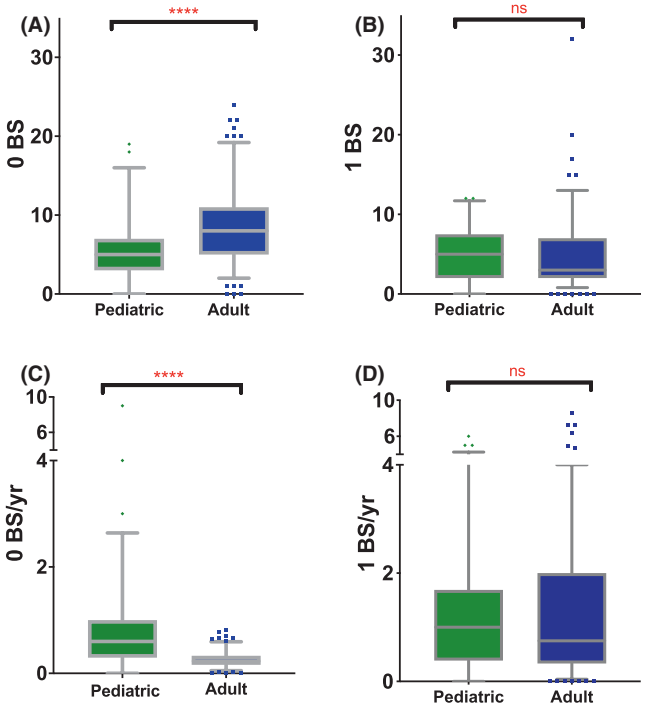

FIGURE 5 Children with type 1 von Willebrand disease (VWD) experience interim bleeding at a similar rate to adults. Patients with type 1 VWD were subdivided by age (adults, ≥18 years old, $n = 155$ or pediatric, $n = 77$). Only original bleeding scores (0 BS) were significantly lower in pediatric than adult subjects (A, median 5 vs. 8, $p < .0001$), with no significant difference in 1 BS (A, median 5 vs. 3, $p = .5$) or 1 BS/yr (B, median 1 and 0.8, $p = .7$). The paradoxically elevated 0 BS/yr in pediatric subjects (B, median 0.6 vs. 0.2, $p < .0001$) related to the short time period covered by the 0 BS, increasing the 0 BS/yr. Data represented using box (25th and 75th percentile) and whiskers (5th and 95th percentile) graphs, with outliers displayed as individual points.

4 | DISCUSSION

Determination of bleeding phenotype is the cornerstone of clinical assessment for patients with a suspected bleeding disorder. The introduction and evolution of BATs has offered a standardized and validated approach to the assessment of bleeding in patients with possible VWD. Nonetheless, areas of clinical uncertainty remain, including the prediction of future bleeding risk in patients with VWD and the assessment of children and young adults with reduced plasma VWF levels but minimal hemostatic challenges. An interim score offers the potential to monitor the evolution of bleeding over time and may help to guide clinical management strategies in such individuals. The interim score also reduces the saturability of BS, a major limitation of current BATs.

In the development of an interim score we adapted the current ISTH BAT, an instrument familiar to many physicians, to minimize the clinical burden of a novel questionnaire. Through the creation of an annualized bleeding score, the impact of differing time intervals between questionnaires on BS has been minimized. In contrast to hemophilia, in which the annualized bleeding rate (ABR) is simply the number of bleeds experienced during the reporting period annualized ([bleeds/months reporting] multiplied by 12), the annualized bleeding score we propose takes into account the totality of bleeding burden in patients with VWD through utilization of and scoring via the ISTH BAT.

Both the interim and annualized BS are important to consider as shortened timeframes covered by assessments may falsely elevate the BS/yr. This issue was highlighted in our analysis of pediatric subjects with type 1 VWD. Despite significantly lower 0 BS scores compared to adults, the 0 BS/yr results were significantly higher. This finding was due to the younger age at time of 0 BS administration in pediatric subjects; both the time period covered by 0 BS and the denominator of the 0 BS/yr are reduced, resulting in a misleadingly elevated 0 BS/yr. As yet, the optimal interval between questionnaire administration for both adults and children has not been defined; however, utilization of a standardized approach to interim BS assessments offers the opportunity to investigate and develop this further. The consistency of results

between study centers suggests that this approach is reproducible; however, there remains a need to identify the optimal timeframe for interval assessment. Mild bleeding symptoms in the general population are both common and physiological; therefore, establishment of the normal 1 BS and 1 BS/yr scores will be important in defining a threshold at which bleeding becomes excessive. Nonetheless, this study highlights important insights into the evolution of bleeding over time in patients with VWD. Recall and confirmation bias may influence the use of all BATs, particularly with retrospective assessment. To determine reference ranges for the interim BS, further studies will be required with longer term, prospective recording of bleeding symptoms and calculation of interim bleeding scores.

The potential role of BATs in prediction of future bleeding was highlighted in the paper by Federici et al., in which markedly elevated BS (MCMDM-1 VWD >10) in patients with VWD were demonstrated to be the single most significant determinant of future bleeding.[20] For many patients with VWD the increase in BS will be more modest and counseling regarding future bleeding risk remains challenging. Utilizing the interim score in our cohort of patients with type 1 VWD we demonstrated that the 0 BS did not predict the rates of future bleeding, with similar 1 BS/yr observed between those with a positive or negative 0 BS. The predictive benefit of BATs therefore may depend not only on the BAT used, but also the baseline severity of bleeding in the population studied.

In our study we have demonstrated the ability of the interim BS to discriminate between subtypes of VWD, with significantly higher 0 BS and 1 BS in type 3 VWD patients than other subtypes. Of interest, when time elapsed between BATs was accounted for, the 1 BS/yr was similar in type 2 and type 3 VWD, although this may be related to the wide spread of values seen for the patients with type 2 VWD and the limited patient numbers. When examined by lowest recorded plasma VWF:RCo, the 0 BS/yr and 1 BS/yr levels were significantly higher in those patients with plasma VWF:RCo levels <30 IU/dl compared to those 30–50 IU/dl. This study included patients with plasma VWF levels >50 IU/dl, historically classified as type 1 VWD or low VWF but with normalization of plasma VWF levels by the time of inclusion. A key question in the clinical management of patients is the impact of age-related alterations in plasma VWF levels. Importantly, no significant difference in bleeding over time was seen between those patients with plasma VWF:RCo in the 30–50 IU/dl and >50 IU/dl range, suggesting that even in patients with normalization of plasma VWF levels, bleeding symptoms may persist. The contribution of additional non-VWF hemostatic modifiers to bleeding in this cohort continues to be investigated. The plasma VWF threshold required to prevent bleeding and the influence of age, if any, on this threshold remains unclear.

Females may have higher BS than men, related to excessive gynecological bleeding, and reflected by the sex-specific normal reference ranges used for the ISTH BAT (positive BS >3 for males, >5 for females). We observed significantly increased 0 BS in females with type 1 VWD compared to males. However, despite the differences in 0 BS, the bleeding over time (as assessed by the 1 BS) was not significantly different between males and females. Similarly, in children the absence of multiple hemostatic challenges result in lower BS (positive ISTH BAT >2) and the assessment of children with limited bleeding symptoms but a positive family history remains challenging. Unsurprisingly, 0 BS were significantly lower in children than adults but again the bleeding scores over time did not significantly differ from that of adults. Even in those patients with a negative 0 BS and reduced plasma VWF levels, the same rates of bleeding over time were experienced as those with a positive 0 BS. Cumulatively these data suggest that, in patients with type 1 VWD, an initial low or normal bleeding score may not preclude future bleeding.

Implementation of the interim BS has provided a structured and reproducible approach to longitudinal assessment of bleeding in a large cohort of patients with VWD managed through specialist coagulation centers. Moreover, the insights gained into evolution of bleeding may assist in counseling of patients with VWD regarding their future bleeding risk. These data clearly highlight the need for annualization of the BS to control for the inter-individual differences in time intervals between questionnaires. However, in children a cautious approach to interpretation of initial annualized data is required, given that the young age of children at first assessment may markedly increase the 0 BS/yr. The novel approach outlined herein offers a framework for longitudinal phenotypic assessment in patients with VWD. Future prospective studies will be required to validate the use of the interim bleeding score and to determine the ideal interval timeframe for administration of the BAT and to understand the influence of age and gender on the interim bleeding score.

AUTHOR CONTRIBUTIONS

P.D.J. designed the questionnaire protocol; J.G., M.L., P.D.J., J.S.O'D., V.F., and R.R.M., administered the questionnaires; P.C., M.L., and P.D.J. analyzed the data. All authors (M.L., P.C., J.G., T.A., V.F., S.H., D.L., J.S.O'D., R.R.M., and P.D.J.) were involved in writing and reviewing the manuscript.

CONFLICTS OF INTEREST

M.L. has served as consultant for Sobi and CSL Behring, received speaking fees from Pfizer, and received indirect funding from Takeda for development of educational materials. T.A. has served on a Data Safety Monitoring Board for NovoNordisk and advisory boards for Takeda and CSL Behring. J.S.O'D. has served as a member of the speaker's bureau for Baxter, Bayer, Novo Nordisk, Boehringer Ingelheim, Leo Pharma, and Octapharma; has served on advisory boards for Baxter, Bayer, Octapharma, CSL Behring, Daiichi Sankyo, Boehringer Ingelheim, and Pfizer; and has received research grant funding awards from Baxter, Bayer, Pfizer, and Novo Nordisk. D.L. receives research funding from Bayer, BioMarin, Bioverativ, CSL Behring, and Octapharma. R.R.M. has served on advisory boards for Shire, CSL Behring, Bioverativ, Bayer, NovoNordisk, and Octapharma. P.D.J. has received honoraria and research funding from CSL Behring, Octapharma, Shire/Takeda, and Bayer. P.C., V.F., S.H., and J.G. have no conflicts to disclose.

ORCID

Michelle Lavin https://orcid.org/0000-0003-2999-4216
Pamela Christopherson https://orcid.org/0000-0001-6758-9815
Julie Grabell https://orcid.org/0000-0002-8739-7842
Thomas Abshire https://orcid.org/0000-0002-2386-7358
Veronica Flood https://orcid.org/0000-0001-8998-6838
Sandra L. Haberichter https://orcid.org/0000-0002-5545-8014
David Lillicrap https://orcid.org/0000-0003-2410-6312
James S. O'Donnell https://orcid.org/0000-0003-0309-3313
Robert R. Montgomery https://orcid.org/0000-0003-2285-4077
Paula D. James https://orcid.org/0000-0003-4649-9014

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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