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Bleeding symptoms in patients diagnosed as type 3 Von Willebrand Disease: results from 3WINTERS-IPS, an international and collaborative cross-sectional study

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Essentials

- Type 3 von Willebrand's disease is a rare bleeding disorders, with poorly characterized bleeding phenotype
- We conducted a multicenter, multinational observational study in patients previously diagnosed as type 3 VWD
- Analysis of 223 unrelated type 3 VWD patients disclosed a severe bleeding phenotype with intracranial bleeding, oral cavity, hemarthroses, and deep hematomas being at least five-fold more frequent in type 3 than in type 1 VWD and with clustering of bleeding symptoms within individual patients
- These findings represent the first systematic description of the clinical presentation of type 3 VWD

Abstract

Background: Type 3 von Willebrand's disease (VWD) patients present markedly reduced levels of von Willebrand factor and factor VIII. Because of its rarity, the bleeding phenotype of type 3 VWD is poorly described, as compared to type 1 VWD.

Aims: To evaluate the frequency and the severity of bleeding symptoms across age and sex groups in type 3 patients and to compare these with those observed in type 1 VWD patients; to investigate any possible clustering of bleeding symptoms within type 3 patients.

Methods: We compared the bleeding phenotype and computed the bleeding score (BS) using the MCMDM-1VWD bleeding questionnaire in patients enrolled in the 3WINTERS-IPS and MCMDM-1VWD studies.

Results: In 223 unrelated type 3 VWD patients, both the BS and the number of clinically relevant bleeding symptoms were increased in type 3 as compared to type 1 VWD patients (15. vs. 6.0 and 5 vs. 3). Intracranial bleeding, oral cavity, hemarthroses, and deep hematomas were at least five-fold over-represented in type 3 VWD. A more severe bleeding phenotype was evident in patients having VWF:Ag levels <20 IU/dL at diagnosis in the two merged cohorts. In type 3 patients, there was an apparent clustering of hemarthrosis with gastrointestinal bleeding and epistaxis, whereas bleeding after surgery or tooth extraction clusters with oral bleeding and menorrhagia.

Conclusions: In the largest cohort of type 3 VWD patients, we were able to describe a distinct clinical phenotype that is associated with the presence of a more severe hemostatic defect.

Keywords: von Willebrand Disease, Type 3; von Willebrand Disease, Type 1; epidemiology; Hemorrhage; Blood Coagulation Disorders

Introduction

Von Willebrand Disease (VWD) is an inherited disorder caused by a deficiency of the activity of von Willebrand factor (VWF), a multifunction plasma protein primarily binding to platelet GpIb and subendothelial collagen [1, 2]. The most prevalent form of VWD is type 1 VWD, having an autosomal dominant inheritance associated with a mild-to-moderate quantitative reduction of VWF. In contrast, autosomal recessive VWD, known as type 3 VWD (OMIN #277480), is characterized by a markedly severe deficiency of VWF, with nearly undetectable plasma levels of VWF antigen (VWF:Ag) and severely reduced factor VIII [3-7]. Patients having type 3 VWD do not respond to treatment with desmopressin, and substitution treatment with plasma or recombinant VWF concentrates is usually required [8-10]. Type 3 VWD is caused by homozygous or compound heterozygous mutations in the gene encoding VWF, with some genotypes associating with an increased risk of alloantibody development after substitution treatment [11, 12].

Several multicenter, collaborative studies have described the bleeding phenotype of type 1 VWD, confirming the highly heterogeneous variability of bleeding severity [13-16]. The clinical phenotype in type 3 patients is less well-characterized because of the rarity of these patients, with an estimated prevalence of around 1 case per million that may increase in countries with consanguineous offspring [17]. The clinical manifestations most frequently reported are disproportionate mucocutaneous bleeding, severe menorrhagia, and hemophilia-like symptoms, such as muscle hematomas and joint bleeding [17-19]. A more detailed description of the clinical phenotype of type 3 VWD patients would have relevant clinical implications, however, particularly taking into account the impact of bleeding symptoms in the patient's quality of life and the associated socio-economic burden [20, 21].

The type 3 Von Willebrand International RegistrieS Inhibitor Prospective Study (3WINTERS-IPS, registered at www.clinicaltrial.gov as NCT02460458) is a no-profit, investigator-initiated, multicenter, European-Iranian observational, retrospective and prospective study on patients with a diagnosis of type 3 VWD. The study was designed to assess the clinical phenotype of type 3 VWD, describe its laboratory pattern and genetic background, and assess the safety and efficacy of therapeutic products for the prevention and treatment of bleeding symptoms.

In this study, we aimed at evaluating the clinical presentation of type 3 VWD patients enrolled by the 3WINTERS-IPS. We specifically aimed at describing the frequency of the different bleeding symptoms and comparing them with those reported by type 1 VWD patients. We hypothesized that type 3 patients might have a different clinical presentation from type 1 VWD patients not only quantitatively,

but also qualitatively. We also wished to evaluate patterns of association between specific bleeding symptoms in type 3 patients.

Methods

Patient cohorts. The 3WINTERS-IPS enrolled patients from 22 Centers from 9 countries. We evaluated data originating from the first part of the study, having a cross-sectional design. Patients were eligible when having a documented bleeding history, VWF:Ag below 3 IU/dL, and an autosomal recessive inheritance based on phenotype analysis at the recruiting Centers [22, 23]. Clinical and laboratory data were obtained in an anonymized form from the MCMDM-1VWD study database, after having obtained consent from the MCMDM-1VWD study coordinator (I.P.).

Collection of the bleeding history. After signing an informed consent to participate in the study, all subjects were administered a bleeding questionnaire exploring the history of bleeding symptoms by a trained physician who queried patients in the local language. For this retrospective phase, the MCMDM-1VWD questionnaire was used to evaluate bleeding history, allowing an appropriate comparison between the two groups of patients [13]. Spontaneous bleeding symptoms (epistaxis, oral cavity bleeding, cutaneous bleeding, bleeding after minor wounds, hematomas, intracerebral bleeding, hemarthroses, menorrhagia) were collected from birth to the date of enrollment in the study. Bleedings after surgery, delivery, or tooth extraction were recorded only from the date of birth to the age of diagnosis since the appearance of these symptoms may have been influenced by medical treatment after diagnosis [13]. We calculated the Bleeding score (BS) according to the MCMDM-1VWD criteria and considering symptoms that occurred before the diagnosis of VWD.

Laboratory measurements. In all investigated patients, we collected twenty ml of citrated blood samples with clean venipuncture at the time of recruitment. Platelet-poor plasma was immediately aliquoted and stored at –80 ˚C for subsequent measurements. In the 3WINTERS-IPS, VWF:Ag was centrally measured in Hamburg (Dr. U. Budde) using a sensitive VWF:Ag enzyme-linked assay, whereas in the MCMDM-1VWD study VWF:Ag was measured in Vicenza using a commercial assay (VWF Assay, Stago, France). Both measurements had an interassay coefficient of variation below 6% and were carried out against the WHO Standard for VWF/FVIII and expressed as IU/dL. For safety reasons, a wash-out period was not mandatory in eligible patients; we did, however, exclude from phenotype analyses those patients having a VWF:Ag level ≥3 IU/dL at the time of sampling.

Statistical methods. We used median and interquartile ranges to describe quantitative values, and median and chi-square statistic to test for statistical differences of quantitative and qualitative variables, respectively. We used the ratio between the frequency of each bleeding symptoms in type 3 and type 1 VWD as a measure of association between a specific symptom and type 3 VWD; 95% CI were computed as for risk ratios [24]. When a symptom was not present (e.g., a central nervous system [CNS] bleeding in type 1 VWD), we imputed 0.5 instead of zero in that cell. If the lower 95% CI was higher than one, we assumed that the bleeding symptom was more frequently present in type 3 than in type 1 VWD. We compared only index cases, and affected family members enrolled in the MCMDM-1VWD study to type 3 patients. In both cohorts, individual bleeding symptoms (e.g., epistaxis or menorrhagia) were considered as significant when having a score >1 (hence requiring medical attention). For instance, epistaxis was regarded as clinically relevant when severe enough for the patient to seek medical advice. For each subject enrolled in either the MCMDM-1 VWD study or the 3WINTERS-IPS, we used two measures as a proxy for the clinical severity of the bleeding phenotype: the MCMDM-1 VWD BS, and the total number of relevant bleeding symptoms presented by the patient. While the BS is a well-known index of bleeding severity, it is nonetheless influenced by the most severe symptom ever suffered by a patient. On the other hand, counting the number of different bleeding symptoms sustained by an individual patient may also be a relevant indicator of the overall bleeding tendency of that patient. In a previous study, we demonstrated that the number of bleeding symptoms has a diagnostic capability similar to that of the BS for the diagnosis of mild VWD [25]. We used two different regression models to study the relation between VWF:Ag and the bleeding phenotype in the two merged cohorts. Linear regression was used to model VWF:Ag dependent variations of the BS, while Poisson regression was used to study the changes in the number of clinically relevant symptoms. In both models, we included ABO blood type, age, and sex as covariates and, since the relation between VWF:Ag and bleeding risk is known to be nonlinear, we used four-knots cubic splines for VWF:Ag values [26, 27]. The relation between VWF:Ag and the bleeding risk was then evaluated by plotting the partial residuals against VWF:Ag in the two models (i.e., linear or Poisson regression); the frequency of bleeding at VWF:Ag equal to 100 IU/dL was considered as the baseline risk. We finally used the chi-square statistics and its associated standardized residuals to evaluate if the observed distribution of each possible symptom pairs (e.g., epistaxis and surgery, epistaxis and menorrhagia, epistaxis and cutaneous bleeding) deviated from the expected one in the 3Winters-IPS cohort. We then used a circos plot to graphically depict the relation between bleeding symptoms in type 3 patients. In a circo plot, different symptoms are joined together by an arc whose bases are directly proportional to the number of individuals presenting the two signs together [28]. Hence, in a circo plot, the width of the strips is directly proportional to the number of patients having both symptoms

(symptom pairs). To reduce visual cluttering and to minimize the chances of model overfitting, we plotted only those relational pairs having a standardized residual corresponding to a $p<0.001$ in a chi-square statistics, therefore indicating a statistical association even after Bonferroni adjustment for ten pair comparisons. The R statistical package was used for data analysis [29], using the *circlize* package for circos plots [30].

Results

Patient cohorts. The 3WINTERS-IPS enrolled a total of 265 unrelated patients, of whom we analyzed in the present study 223 patients with an available bleeding history at recruitment (**Figure 1**). The median age at study inclusion was 29 years, whereas the median age at diagnosis was two years (interquartile range, 1-6); 129 were females. There were 106 patients of Iranian descent, while the remaining patients were from Europe. **Table 1** reports the clinical characteristics of patients enrolled in the 3Winters-IPS and the MCMDM-1VWD studies, respectively. The 3WINTERS-IPS and the MCMDM-1 VWD cohorts were similar as for sex distribution but differed significantly in terms of age of diagnosis and severity of clinical presentation. Both the median BS and the median number of clinically relevant bleeding symptoms were increased in type 3 patients. There were 18 (8.1%) type 3 patients that had a normal BS at diagnosis, as compared with 138 (33.1%) type 1 patients. The ABO composition was also noticeably different, with an excess of blood O group patients in the type 1 MCMDM-1 VWD cohort. Since the ABO blood group was similarly distributed in Iranian and non-Iranian patients in the 3WINTERS-IPS cohort ($p=0.48$, chi-square test), this difference most likely reflects an influence of the ABO blood group in the diagnostic process of type 1 VWD.

Bleeding symptoms in type 3 patients. **Figure 2** panel A shows that epistaxis was the most frequent clinically relevant bleeding symptom in type 3 patients, followed by menorrhagia in females. Males had a higher frequency of hemarthroses and hematomas than females (53.4% vs. 42.1% and 40.8% vs. 27.1%, respectively). Panel B shows the ratio between the frequency of bleeding symptoms in type 3 and type 1 patients, respectively. Surgical, post-extraction and post-partum bleeding, and menorrhagia were not specifically over-represented in type 3 VWD. In contrast, some bleeding symptoms (deep hematomas, hemarthroses, oral cavity, and CNS bleeding) were overrepresented (>five-fold) in type 3 VWD patients. When comparing the clinical presentation of type 3 vs. type 1 VWD, clearly increased bleeding scores were evident for all age-classes and even in pediatric cases (**Figure 3**).

Relation between VWF:Ag at diagnosis and bleeding phenotype. We restricted this analysis in all patients enrolled in the MCMDM-1 VWD and in the 3WINTERS-IPS patients having VWF:Ag <3 IU/dL at the time of sampling (n=178). Thus, we excluded from this analysis 45 3WINTERS-IPS patients, mainly because they did receive some form of replacement therapy in the days before sampling (**Figure 1**). As shown in **Figure 4,** VWF:Ag levels at diagnosis below 30 IU/dL were associated with a steep increase of bleeding severity both in terms of increased BS (Panel A) and the number of bleeding symptoms (Panel B). To further investigate the relation between bleeding phenotype and VWF:Ag levels, we evaluated differences in patients with type 1 or 3 VWD at three different VWF:Ag cut-offs (<10, 10-30, and >30 IU/dL) (**Table 2**). Patients with VWF:Ag below 30 IU/dL were younger, had a similar distribution of males and females, of O and non-O blood group, and were more symptomatic both in terms of BS and of the number of reported bleeding symptoms.

Bleeding patterns in type 3 VWD patients. Based on clinical experience with VWD patients, we hypothesized that some symptoms might cluster together. If this hypothesis was correct, then the observed distribution of symptoms would not be that expected by their frequency at large in all patients. For instance, if epistaxis clusters with cutaneous bleeding, we would expect the observed frequency of cutaneous bleeding to be higher in patients with epistaxis than in those without. **Figure 5, Panel A** shows the association between all symptoms pairs, expressed in terms of standardized residuals of the chi-square distribution (the darker the square, the higher the degree of the association, a standardized residual higher than five being statistically significant [31, 32]). Some symptoms pairs (cutaneous bleeding with epistaxis and post-surgical with post-extraction bleeding) were strongly associated together. Other significant associations were oral cavity bleeding with both post-surgical with post-extraction bleeding and epistaxis with both hemarthrosis and GI bleeding. The circo plot in **Figure 5, Panel B** expands these findings, showing two distinct patterns of clustering. The first comprises the association of hemarthrosis with GI bleeding and epistaxis and, to a lesser extent, with deep hematomas. The second cluster of association of oral cavity bleeding with post-surgical or post-extraction bleeding and with menorrhagia.

Discussion

Type 3 VWD is an autosomal recessive or co-dominant disorder with a reported prevalence ranging from 0.1 to 5.3 per million [33, 34]. Given its rarity, there are few systematic descriptions of the clinical phenotype of type 3 VWD patients, as is the case for type 1 VWD patients. The 3WINTERS-IPS is the first extensive, multicenter investigation of type 3 patients that systematically collects clinical and laboratory

phenotypic data, and therefore offers a unique opportunity for providing a full clinical picture of these rare disease patients.

This study shows that the bleeding phenotype in type 3 VWD patients is remarkably different from that of type 1 patients, not only in terms of disease severity (BS or number of bleeding symptoms) but also in terms of clinical presentation. Type 3 VWD patients had an increased BS since the pediatric age, and their median age at diagnosis (2 years) may be considered consistent with that of the clinically most severe bleeding disorders. The median BS in our cohort was 15, a figure that is remarkably similar to that reported in the more limited WiN cohort [15]. Epistaxis is the most prevalent clinical symptom, followed by hemarthrosis in males and menorrhagia in females. However, by comparing the prevalence of bleeding symptoms in patients with type 3 and type 1 VWD, we were able to demonstrate that some bleeding manifestations were typically associated with type 3 patients (Figure 1, panel B). Central nervous system bleeding, although rare in type 3 patients, was not reported in the previous MCMDM-1 VWD study, and we conservatively estimate that the prevalence of CNS bleeding is increased more than twenty-fold in type 3 than in type 1 patients.

Similarly, oral cavity bleeding, hemarthroses, and deep hematomas (especially muscle hematomas) were 7 to 10-fold more prevalent in type 3 patients. All these symptoms had a rate ratio significantly higher than one, therefore suggesting that they may be considered distinctive for type 3 rather than type 1 VWD. It is tempting to attribute this peculiar association not only to the more severely reduced VWF:Ag but also to the very low factor VIII levels, with a consequent clotting defect (rather than of primary hemostasis only) more resembling hemophilia. On the other hand, the prevalence of post-surgical or post-extraction bleeding was similar to that reported for type 1 VWD, possibly suggesting that the adoption of adequate treatments is sufficient to reduce bleeding severity despite the more severe factor defect.

Another significant study finding is the association between bleeding severity and factor levels measured at diagnosis. To adequately address this issue, we pooled clinical and retrospective laboratory data from the MCMDM-1 VWD type patients with those from type 3 patients, thus obtaining a spectrum of patients with a continuum of VWF:Ag ranging from 0.5 to 80 IU/dL and allowing the estimation of the relation between factor deficiency and clinical presentation. At this regard, a significant limitation of the present study is the lack of a specific metric unequivocally defining the bleeding severity, that is especially important when comparing bleeding disorders with different clinical phenotype, such as type 1 and type 3 VWD. For these latter patients, the use of a tool such as the Bleeding Score may prove inaccurate, because it may substantially underestimate the severity of a disease in an individual patient having

recurrent severe bleeding symptoms (e.g., two or more hemarthroses). Thus, the BS emphasizes the importance of a bleeding disorder as a determinant of the "severity" (e.g., amount of blood loss) of a single symptom.

On the other hand, accounting for the total number of bleeding symptoms gives more importance to disease as a risk factor for "bleeding tendency" in all body tissues. Although none of these two metrics is a perfect substitute for the actual patient bleeding rate, we were able to demonstrate that the severity of VWD is significantly increased when the VWF:Ag levels drop below 30 IU/dL. Interestingly, patients with a VWF:Ag below 5 IU/dL had a still sizeable increase of BS, but a lower risk of an increased number of bleeding symptoms. We hypothesize that VWD patients with a more marked reduction of VWF (such as type 3 patients) may require the adoption of more intensive treatments (e.g., blood products or concentrates, surgery) to appropriately manage bleeding symptoms than patients with milder forms of VWD, with a consequent steeper increase of the association between the laboratory and clinical phenotype.

Finally, we were able to show, for the first time, some non-random bleeding patterns in type 3 VWD. The first pattern includes the presence of hemarthroses with gastrointestinal bleeding, epistaxis in the same patient; other patients showed were the association of oral cavity bleeding, post-surgical, and post-extraction bleeding. It is worth noting that we observed an association between the presence of mucous bleeding and post-surgical or post-extraction bleeding, also in type 1 VWD patients [13]. While the factors resulting in a particular bleeding pattern are unpredictable at the patient's level, it is interesting to observe that some patients have a clinical picture resembling type 1 VWD, while others tend to present a more severe clinical presentation including hemarthroses and gastrointestinal bleeding, the latter symptom being possibly related to angiodysplasia [35].

Our study also has some weaknesses. First, as 41.5% of the enrolled patients were of Iranian origin, we cannot exclude that some genetic mutations may be recurrent in our study sample. Second, the MCMDM-1 VWD scoring system that was used in this retrospective study may be insensitive to describe severe bleeding disorders accurately [36].

These limitations notwithstanding, the present study represents the broadest available clinical description of type 3 VWD patients, confirming its clinical severity and elucidating its peculiar clinical phenotype.

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Conflict of interest disclosure

A Tosetto, Z Badiee, M Baghaipour, L Baronciani, J Battle, E Berntorp, I Bodó, U Budde, G Castaman, JCJ Eikenboom, P. Eshghi, C Ettorre, A Goodeve, J Goudemand, CRM Hay, H Hoorfar, M Karimi, B Keikhaei, R Lassila, FWG Leebeek, MF Lopez Fernandez, PM Mannucci, MG Mazzucconi, M Morfini, J Oldenburg, I Peake, R Parra Lòpez, F Peyvandi, R Schneppenheim, A Tiede, G Toogeh, M Trossaert, O Zekavat, EMK Zetterberg and AB Federici do not disclose any conflict of interest for this publication

Table 1. Clinical and laboratory characteristics of investigated subjects. For quantitative variables, median and interquartile values are reported; p values were calculated with the median test.

	3WINTERS-IPS (N=223)	MCMDM-1 VWD (N=417)	p value
Sex			0.964
Male	94 (42.2%)	175 (42.0%)	
Female	129 (57.8%)	242 (58.0%)	
Age at study inclusion, years	29.0 (16.0, 43.0)	35.0 (20.0, 48.0)	< 0.001
Number of symptoms at diagnosis	5.0 (4.0, 7.0)	3.0 (2.0, 5.0)	< 0.001
Bleeding Score	15.0 (8.0, 20.0)	6.0 (3.0, 10.0)	< 0.001
Bleeding Score class			< 0.001
≤3	18 (8.1%)	138 (33.1%)	
4-7	33 (14.8%)	121 (29.0%)	
8-15	70 (31.4%)	129 (30.9%)	
>15	102 (45.7%)	29 (7.0%)	
ABO blood group *			< 0.001
non-O	119 (54.6%)	160 (38.4%)	
O	99 (45.4%)	257 (61.6%)	
Median VWF:Ag (IU/dL) at diagnosis	0.0 (0.0, 2.0)	35.0 (20.2, 52.0)	< 0.001

* 5 patients were missing ABO group determination in the 3Winters-IPS cohort

Table 2. Characteristics of investigated subjects of the combined cohorts of MCMDM-1VWD and 3WINTERS-IPS stratified by VWF:Ag level. For quantitative variables, median and interquartile values are reported; p values were calculated with the median test.

	VWF:Ag <10 IU/dL (N=221)	**VWF:Ag 10-30 IU/dL (N=131)**	**VWF:Ag >30 IU/dL (N=240)**	**p value**
Sex				0.793
Male	96 (43.4%)	56 (42.7%)	97 (40.4%)	
Female	125 (56.6%)	75 (57.3%)	143 (59.6%)	
Median age at study inclusion, years	28.0 (16.0, 42.0)	34.0 (17.0, 48.0)	34.5 (20.8, 49.0)	<0.001
Median number of symptoms at diagnosis	5.0 (4.0, 7.0)	3.0 (2.0, 5.0)	3.0 (2.0, 5.0)	<0.001
Median Bleeding Score	13.0 (7.0, 18.0)	6.0 (3.0, 10.0)	5.0 (2.0, 10.0)	<0.001
ABO blood group*				0.002
non-O	113 (51.6%)	58 (44.3%)	85 (35.4%)	
O	106 (48.4%)	73 (55.7%)	155 (64.6%)	
Study				<0.001
3WINTERS-IPS	178 (80.5%)	0 (0.0%)	0 (0.0%)	
MCMDM-1VWD	43 (19.5%)	131 (100.0%)	240 (100.0%)	

* 2 missing values in the 3WINTERS-IPS (within the VWF:Ag <=10 IU/dL column)

Legends to Figures

Figure 1. CONSORT flow-chart of patients enrolled in the 3WINTERS-IPS

Figure 2. Panel A: frequency of clinically relevant bleeding symptoms in male and female patients with type 3 VWD; numbers above bars represent percent frequency. Panel B: frequency ratios of symptoms in type 3 vs. type 1 VWD. The horizontal dashed line represents the equivalence (similar frequency, rate ratio=1); 95% confidence intervals around the ratio are depicted. When the lower 95% CI is above the equivalence line, the symptom is more frequently present in type 3 than in type 1 VWD.

Figure 3. Distribution of bleeding score (BS) in the patients from the 3WINTERS-IPS (light gray boxes) and MCMDM-1 VWD cohorts (dark gray boxes) by age, showing that BS is higher in type 3 patients in all age categories. For both type 1 and type 3 patients, the BS reaches its highest values above age 50 and subsequently remains stable.

Figure 4. Relationship between bleeding severity and VWF:Ag in the two merged cohorts, showing that bleeding severity increases for VWF:Ag levels below 30 IU/dL. VWF:Ag was modeled using a four-knots cubic spline, with a linear model used for Panel A and a Poisson model for Panel B. Black lines: primary model; gray lines: 95% CI. Panel A: relation between bleeding score (BS) and VWF:Ag; Panel B: relation between risk of having one or more clinically relevant bleeding symptoms and VWF:Ag. In both panels, the ordinate (y-axis) expresses the absolute increase of BS or relative risk related to VWF:Ag in regression model also adjusted for age, sex, and ABO blood type.

Figure 5. Association between all symptoms pairs in investigated patients of the 3WINTERS-IPS cohort. **Panel A** shows the chi-square standardized residuals: the darker the square, the higher the degree of association between two symptoms. **Panel B**: Circo plot depicting the relation between bleeding symptoms in type 3 VWD patients. Only bleeding symptoms having a score >1 were considered; the width of the strips is directly proportional to the number of patients having both symptoms (symptom pairs). To reduce visual cluttering, we report only those relational pairs having chi-square $p<0.001$. For each symptom, the numeric scale indicates the total number of observed combination pairs, and the width of the connecting string represents the number of observed combinations. For instance, in the 223 investigated patients, cutaneous bleeding was present in 315 combinations of symptoms; in 54 patients, cutaneous bleeding was present together with epistaxis.

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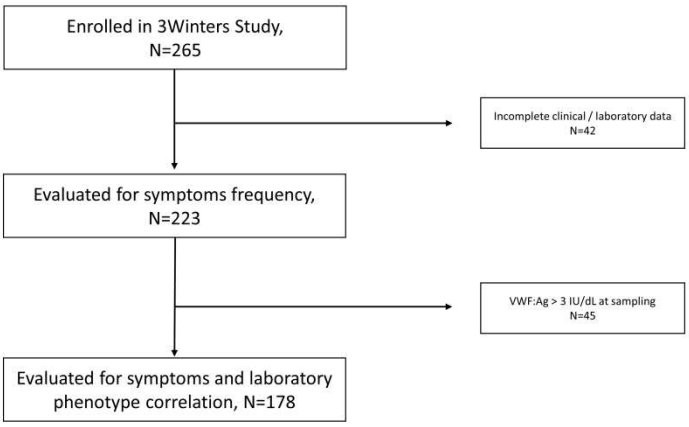

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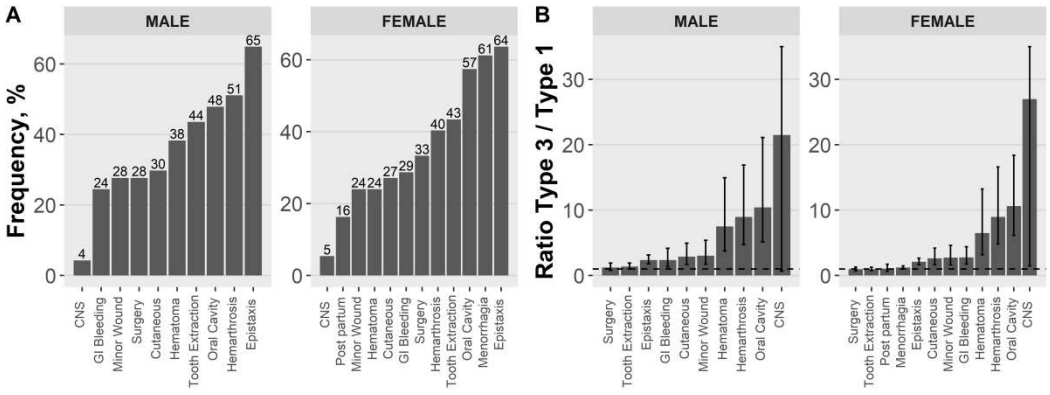

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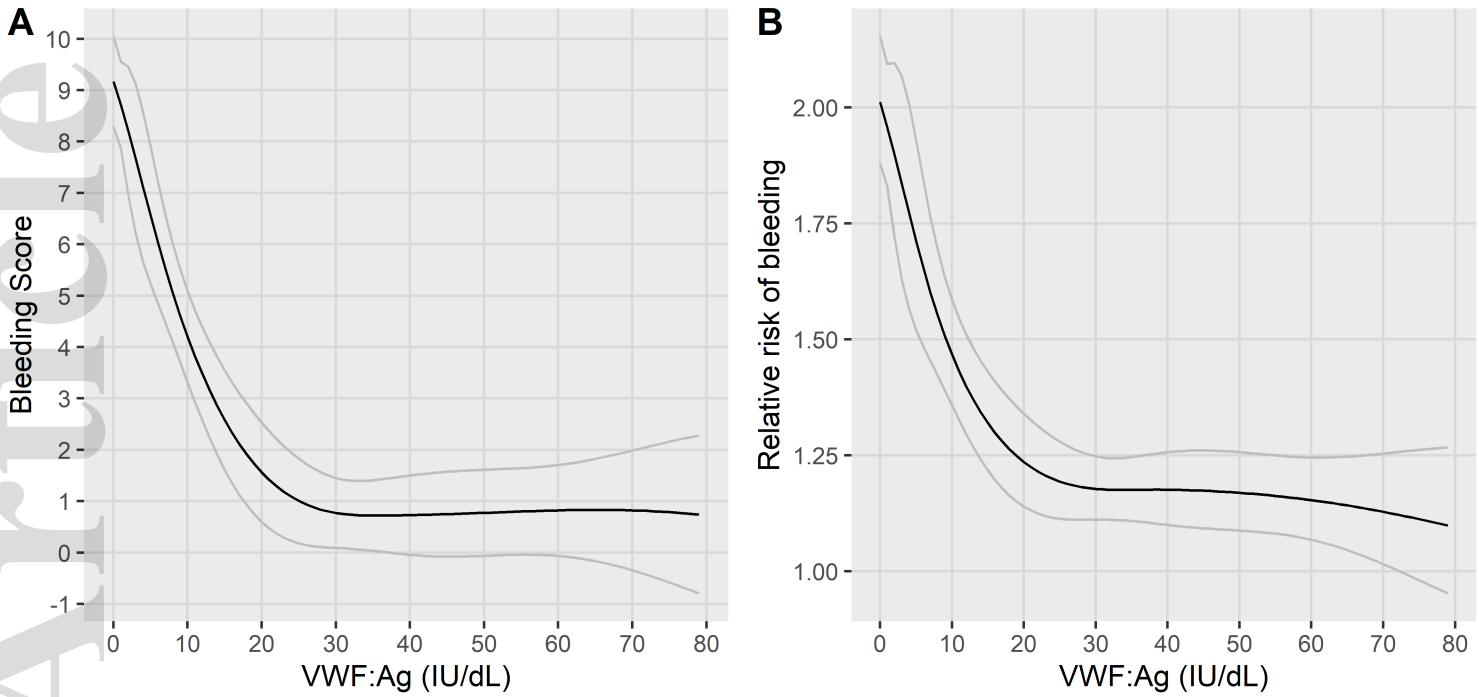

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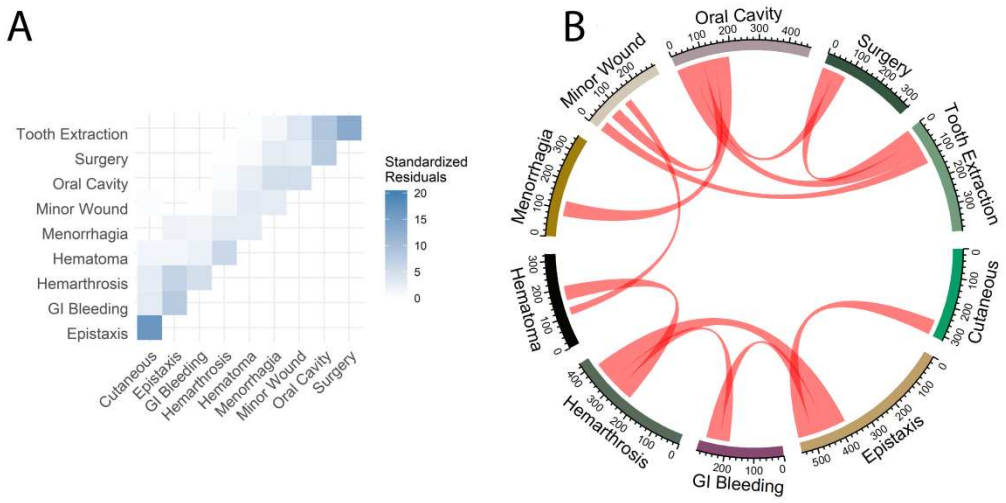

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