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ORIGINAL ARTICLE

Predictors of diagnostic delays and loss to follow-up in women with von Willebrand disease: a single-center retrospective cohort study

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Abstract

Background: Women with von Willebrand disease (VWD) often face diagnostic delays, leading to increased bleeds, stress, and healthcare use. The factors influencing these delays and their effects on gynecologic outcomes are not well understood.

Objectives: This study aimed to 1) identify the prevalence and predictors of diagnostic delays and loss to follow-up in women with VWD and 2) determine how these delays affect severe gynecologic bleeding, emergency visits, transfusions, and hysterectomies.

Methods: We conducted a single-center retrospective cohort study and included women aged ≥18 years diagnosed with VWD. Delayed diagnosis was defined as ≥3 bleeding events prior to VWD diagnosis, excluding easy bruising due to its subjectivity. Loss to follow-up was defined as ≥5 years since the last hematology visit. We used logistic regression for analysis.

Results: Among 178 diagnosed women (median age, 27 years), 71 (40%) experienced ≥3 bleeding events before diagnosis. The median time from the first bleeding event to VWD diagnosis was 14.2 years. Severe bleeding events significantly predicted diagnostic delays (adjusted odds ratio, 3.1; 95% CI, 1.5-6.2). Fifty-four (30%) women were lost to follow-up, with remote era of initial bleed and VWD type identified as significant predictors. Delays were associated with increased risks of hysterectomies (odds ratio, 2.7; 95% CI, 1.2-6.3) and other gynecologic procedures.

Conclusion: Delayed diagnosis and loss to follow-up in VWD are common even in a specialized Hemophilia Treatment Centre. Such delays lead to more severe bleeding and increased gynecologic interventions. Prompt diagnosis is paramount for better patient outcomes and reduced healthcare utilization.

KEYWORDS
blood coagulation disorders, diagnosis, heavy menstrual bleeding, quality of care, von Willebrand disease

Jaclyn Shelton and Michelle Millions are co-first authors.

Essentials

- Diagnostic delay of von Willebrand disease is common, disproportionately affecting women.
- A cohort study was conducted to identify predictors of delay in 178 women with von Willebrand disease and their impact on outcomes.
- Delayed diagnosis after ≥3 bleeds occurred in 40%, which is associated with severe bleeding and remote era.
- Delays were associated with a higher risk of hysterectomy and other gynecologic procedures.

1 | INTRODUCTION

Von Willebrand disease (VWD) is the most common inherited bleeding disorder, with prevalence between 1/100 and 1/10,000 [1–4]. It is caused by either a deficiency or defect in von Willebrand factor (VWF) protein, resulting in increased risk of excessive mucocutaneous bleeding and bleeding associated with surgery and trauma. Women are disproportionately affected by VWD due to high prevalence of gynecologic bleeding, including heavy menstrual bleeding (HMB) and postpartum hemorrhage (PPH). HMB is often the first presenting symptom in VWD and can be associated with iron deficiency anemia (IDA), psychological stress, and impaired quality of life [5–7]. Women with VWD also have higher rates of surgical interventions for HMB. A retrospective study from the United Kingdom reported that women with VWD were more than twice as likely to have a hysterectomy than women without VWD [8].

Diagnostic delay is common among patients with VWD and it disproportionately affects women [9,10]. A recent Dutch cross-sectional study of 1092 patients reported a significantly longer diagnostic delay of autosomal inherited bleeding disorder in women than men, despite a similar age of bleeding symptom onset, with delays of 11.6 and 7.7 years, respectively [9]. Diagnostic delays may lead to preventable bleeding events during surgeries and deliveries, unnecessary blood transfusions, and increased health resource utilization. For this reason, the American College of Obstetricians and Gynecologists recommends that all adolescents with HMB should undergo screening for an underlying bleeding disorder [11]. While the frequency and sex-specific differences in diagnostic delays are reported, patient- and disease-related factors associated with diagnostic delays and the impact of diagnostic delays on women's health outcomes and resource utilization remain unclear. Further, there are limited data on time to diagnosis in publicly funded universal healthcare systems such as Canada. In addition to diagnostic delays, we hypothesize that women with VWD are also more likely to experience loss to follow-up, possibly related to the perception of a "milder" disease phenotype compared with hemophilia and sexism [12]. While comprehensive care standards published by the Association of Hemophilia Clinic Directors of Canada stipulated the frequency of clinic assessments for persons with hemophilia, there are no Canadian standards for the frequency of follow-up in VWD [13]. We have previously shown a high rate of loss to follow-up (41%) in young adults with mild hemophilia compared with that in young adults with moderate–severe hemophilia (41% vs 11%) [14]. However, the attrition rate has not been previously examined in VWD.

In this retrospective cohort study, we aim to 1) examine the prevalence and predictors of diagnostic delays and loss to follow-up in women with VWD and 2) assess the impact of diagnostic delays on the rates of severe gynecologic bleeding, emergency department (ED) visits, red cell transfusions, persistent IDA, hysterectomy, and other invasive gynecologic procedures.

2 | METHODS

2.1 | Study design

This single-center retrospective cohort study included all women aged ≥18 years with a diagnosis of inherited VWD followed by the Northern Alberta Hemophilia Treatment Centre (HTC) between January 2000 and July 2023. Alberta is a large province with a geographic area of 661,848 km^2, and its population of 4.7 million is served by 2 adult HTCs. VWD was defined based on the ASH ISTH NHF WFH 2021 guidelines [15]. Type 1 VWD was identified based on an VWF antigen and/or VWF activity of <0.30 IU/mL, or VWF levels of <0.50 IU/mL in patients with significant bleeding phenotype. Type 2 VWD was identified based on a combination of genetic testing, VWF multimer analysis, and ristocetin-induced platelet aggregation. Patients with acquired von Willebrand syndrome, platelet-type VWD, or other concomitant bleeding disorders were excluded. Research ethics approval was obtained through the University of Alberta Research Ethics Board.

2.2 | Data collection

Data were abstracted from electronic medical records with a cutoff date of August 2023. Demographic data included age, urban or rural residence, any family history of VWD, and pre-existing family history at the time of patient referral. Rural status was ascertained based on the second digit of the residential postal code. Disease characteristics included VWD type, International Society on Thrombosis and Haemostasis Bleeding Assessment Tool (ISTH-BAT) bleeding score, baseline coagulation parameters prior to diagnosis (international normalized ratio [INR], activated partial thromboplastin time [aPTT], and fibrinogen), lowest and most recent VWF activity, factor VIII activity, ABO blood group, date of the first bleeding event, and number of bleeding events prior to VWD diagnosis.

2.3 | Definitions of outcome measures

Time to diagnosis was defined as the first documented bleeding event to the time of VWD diagnosis, with delayed diagnosis defined as ≥3 bleeding events prior to diagnosis. Loss to follow-up was defined as ≥5 years since the last hematology visit (in-person or virtual) at the time of data collection. A bleeding event was defined as any of the 14 bleeding categories listed in the ISTH-BAT, except for cutaneous bruising due to its subjectivity and suboptimal documentation in medical records. We used the exact date of the first bleeding event (if known) and imputed the first bleeding date as age 13 for women with documented "lifelong HMB since menarche", since this is the average age of menarche in Canada [16]. The number of bleeding events prior to diagnosis included distinct ISTH-BAT bleeding categories, with each episode of PPH or surgery-related bleed recorded as separate events (ie, the number of bleeding events in a patient with a history of HMB and 3 episodes of PPH prior to VWD diagnosis is classified as 4 bleeding events). A severe bleeding event is defined as a bleeding event requiring ED visit, hospitalization, red cell transfusions, or surgical hemostasis.

We collected outcome measures including all bleeding events, severe bleeding events, ED visits and hospitalizations related to bleeding complications, red cell transfusions, invasive procedures for HMB such as dilatation and curettage (D&C), endometrial ablation, and hysterectomy. Hysterectomies performed for other indications (eg, endometriosis, malignancy, and fibroids without HMB) were not counted. We specifically focused on the rates of gynecologic bleeding including HMB, antepartum hemorrhage, PPH, and hemorrhagic ovarian cysts. Outcomes were stratified by timing prior to or after VWD diagnosis. HMB was defined as bleeding lasting >7 days, changing protection more than every 2 hours, flooding, or passage of large clots, or as labeled by the hematologist [17]. PPH was defined as a blood loss of ≥500 mL for vaginal delivery or ≥1000 mL for Caesarian delivery within the first 24 hours of birth (primary PPH), heavy lochia necessitating medical review after the first 24 hours, or prolonged lochia lasting over 6 weeks postpartum (secondary PPH) [17,18]. Severe PPH was defined as PPH requiring blood transfusions, hysterectomy, or other procedures to control bleeding (including uterine packing/suturing, Bakri balloon, ligation, or embolization of pelvic vessels) [19,20]. IDA was ascertained by serum ferritin levels of <30 mg/L and hemoglobin levels of <120 g/L. Persistent IDA was defined as an ongoing IDA lasting 2 years or longer.

2.4 | Statistical analysis

Descriptive analysis was performed using median and IQR for continuous variables and frequencies (percentages) for categorical variables. Student's *t*-test or Mann–Whitney's *U* test was used to assess for differences in continuous variables, while the chi-squared test or Fisher's exact test was used to assess for differences in categorical variables, as appropriate. Univariate and multivariable logistic regression was used to examine predictors of diagnostic delays and predictors of loss to follow-up. Logistic regression models were used to examine the association between delayed diagnosis and gynecologic outcomes and health resource utilization (ED visits, red cell transfusions, and gynecologic procedures). Variables with a *P* value of <.20 on univariate analysis were included in the multivariable logistic regression model. A 2-sided *P* value of <.05 was considered statistically significant. Statistical analyses were performed using R statistical software.

3 | RESULTS

We identified 210 women with VWD followed by our HTC between 2000 and 2023: 32 were excluded due to other diagnoses based on chart review (9 platelet-type VWD, 3 acquired von Willebrand syndrome, 20 with a historic diagnosis of VWD but not meeting the ASH ISTH NHF WFH 2021 diagnostic guidelines). Overall, 178 women with VWD were included: 144 (81%) type 1, 29 (16%) type 2, and 5 (3%) type 3. The median age of VWD diagnosis was 27 years (IQR, 18-37), with 18 (10%) women diagnosed under the age of 12 years, 28 (16%) diagnosed between 12 and 18 years, 56 (31%) between 19 and 30 years, 40 (22%) between 31 and 40 years, and 31 (17%) diagnosed over the age of 40 years. Of the 157 women with available timing of the first bleeding event, the median time from the first bleeding event to VWD diagnosis was 14.2 years (IQR, 5.7-25.2). Baseline characteristics are shown in Table 1 and the Supplementary Table.

3.1 | Predictors of delayed diagnosis

Seventy-one (40%) women presented with ≥3 bleeding events prior to diagnosis, and 19 (11%) women presented with ≥5 bleeding events prior to diagnosis. Alarmingly, 76 (43%) women experienced at least 1 severe bleeding event prior to hematology referral. Compared with women who experienced <3 bleeding events prior to diagnosis, those who experienced ≥3 bleeding events prior to diagnosis were significantly older at diagnosis (median 30 vs 21 years, $P < .001$), had a higher ISTH-BAT bleeding score (median 8 vs 5, $P < .001$), had their first bleeding event prior to 1990 (51% vs 25%, $P = .003$), and were more likely to have experienced a severe bleed prior to diagnosis (65% vs 33%, $P < .001$; Table 2). There were no significant differences in urban/rural residence, VWD type, baseline VWF activity, abnormal INR/aPTT prior to diagnosis, or blood type between patients with <3 or ≥3 bleeding events prior to diagnosis (Table 2).

On univariate logistic regression, remote era at the initial bleeding event (pre-1980: odds ratio [OR], 3.9; 95% CI, 1.1-16.7; 1981-1990: OR, 5.7; 95% CI, 1.5-24.9; $P = .003$) and severe bleeding event (OR, 3.8; 95% CI, 2.0-7.4; $P < .001$) were associated with higher odds of delayed diagnosis after ≥3 bleeding events, whereas a known family history of VWD prior to hematology referral was protective (OR, 0.5; 95% CI, 0.25-0.98; $P = 0.048$). Type 3 VWD trended toward lower odds of delayed diagnosis (OR, 0.3; 95% CI, 0.02-2.2), albeit nonsignificant ($P = .62$). On multivariable regression, only severe bleeding

TABLE 1 Characteristics of the cohort, stratified by number of bleeding events prior to diagnosis.

Characteristics	<3 bleeding events prior to diagnosis (*n* = 92)	≥3 bleeding events prior to diagnosis (*n* = 71)
Median age at diagnosis, IQR	21 (13-32)	30 (24-41)
Rural residence, *n* (%)	17 (18)	15 (21)
First bleeding event, *n* (%)		
2011-2021	12 (13)	4 (6)
2001-2010	26 (28)	15 (21)
1991-2000	23 (25)	16 (23)
1981-1990	10 (11)	19 (27)
1980 or earlier	13 (14)	17 (24)
Missing	8 (9)	0
VWD type, *n* (%)		
Type 1	74 (80)	58 (82)
Type 2	14 (15)	12 (17)
Type 3	4 (4)	1 (1)
Baseline VWF activity, median IU/mL (IQR)	0.34 (0.24-0.42)	0.35 (0.22-0.42)
Blood type O, *n* (%)	54/74 (73)	47/60 (78)
ISTH-BAT score, median (IQR)	5 (3-8) *n* = 63 available	8 (7-10) *n* = 49 available
Known family history of VWD (prior to hematology referral), *n* (%)	37 (40)	18 (25)
Abnormal coagulation parameters (INR > 1.2, aPTT > 38 s) prior to diagnosis, *n* (%)	8/43 (19)	8/36 (22)
Severe bleeding event prior to hematology referral (ED visit, hospitalization, transfusions, or surgical hemostasis)	30 (33)	46 (65)

aPTT, activated partial thromboplastin time; ED, emergency department; INR, international normalized ratio; ISTH-BAT, International Society on Thrombosis and Haemostasis Bleeding Assessment Tool; N/A, not applicable; VWD, von Willebrand disease; VWF, von Willebrand factor.

prior to referral (adjusted odds ratio [aOR], 3.1; 95% CI, 1.5-6.2; *P* = .002) was associated with delayed diagnosis after ≥3 bleeding events. Remote era at the initial bleeding event trended toward higher odds of delayed diagnosis (aOR, 3.2 [95% CI, 0.8-14.4] for pre-1980; aOR, 3.4 [95% CI, 0.8-15.7] for 1981-1990) but not statistically significant (*P* = .09).

3.2 | Predictors of loss to follow-up

A total of 54 (30%) women were lost to follow-up for ≥5 years, with the median time from the last follow-up of 9 years (IQR, 6-11). The median age of the last follow-up was 34 years (26-50 years). Of those lost to follow-up, 20/54 (37%) were nonmenstruating (aged >50 years and/or posthysterectomy) at the time of the last follow-up, whereas 9 (17%) were lost in young adulthood (aged 19-25). Baseline median VWF antigen and activity was 0.43 IU/mL (IQR, 0.32-0.47) and 0.36 IU/mL (IQR, 0.26-0.43) in those lost to follow-up compared with 0.35 IU/mL (IQR, 0.26-0.43) and 0.32 IU/mL (IQR, 0.20-0.41) in those with ongoing follow-up, whereas the most recent VWF levels were comparable (0.45-0.46 IU/mL) in both groups. On logistic regression analysis, type 2 VWD (OR, 0.2; 95% CI, 0.1-0.6, compared with type 1 VWD, *P* = .01) was associated with lower odds of loss to follow-up, whereas a higher baseline VWF activity trended toward higher odds of loss to follow-up (OR, 9.8 per 1 IU/mL increase; 95% CI, 1.0-106.2; *P* = .05). Compared with patients who presented with initial bleeding events in 2011-2021, those with initial bleeding pre-1980 (OR, 9.0; 95% CI, 1.5-173.1; *P* = .04) and between 2001 and 2010 (OR, 7.8; 95% CI, 1.4–147.9; *P* = .049) also experienced higher odds of loss to follow-up. Age at diagnosis, age at last follow-up, rural residence, ISTH-BAT bleeding score, prior hysterectomy status, and most recent VWF and FVIII activities were not associated with loss to follow-up.

3.3 | Impact of diagnostic delays on outcomes

Gynecologic procedures were commonly performed for women with HMB, including hysterectomies (30; 18%), endometrial ablation (16; 10%), and D&C (16; 10%). Of the 30 women who underwent hysterectomies for HMB, 11 (37%) did so prior to VWD diagnosis. Women who experienced ≥3 bleeding events prior to diagnosis had significantly higher odds of undergoing hysterectomy (OR, 2.7; 95% CI, 1.2-6.3; *P* = .02) and D&C (OR, 3.2; 95% CI, 1.1-10.6; *P* = .04) for HMB (Table 3). They also trended toward higher odds of severe HMB

TABLE 2 Factors associated with delayed diagnosis of von Willebrand disease after presenting with ≥3 bleeding events.

Characteristics	OR of delayed diagnosis (95% CI)	*P* value
Median age at diagnosis, IQR	1.05 (1.03-1.08)	<.001
Rural residence, *n* (%)	1.2 (0.5-2.6)	.64
First bleeding event, *n* (%)		.003
2011-2021	1	
2001-2010	1.7 (0.5-7.1)	
1991-2000	2.1 (0.6-8.5)	
1981-1990	5.7 (1.5-24.9)	
1980 or earlier	3.9 (1.1-16.7)	
Missing	N/A	
VWD type, *n* (%)		.62
Type 1	1	
Type 2	1.1 (0.5-2.5)	
Type 3	0.3 (0.02-2.2)	
Baseline VWF activity, median IU/mL (IQR)	1.6 (0.2-14.0)	.69
Blood type O, *n* (%)	1.4 (0.6-3.5)	.47
ISTH-BAT score, median (IQR)	1.3 (1.2-1.6)	<.001
Known family history of VWD (prior to hematology referral), *n* (%)	0.50 (0.25-0.98)	.048
Abnormal coagulation parameters (INR > 1.2, aPTT > 38 s) prior to diagnosis, *n* (%)	1.3 (0.4-3.8)	.69
Severe bleeding event prior to hematology referral (ED visit, hospitalization, transfusions, or surgical hemostasis)	3.8 (2.0-7.4)	<.001

aPTT, activated partial thromboplastin time; ED, emergency department; INR, international normalized ratio; ISTH-BAT, International Society on Thrombosis and Haemostasis Bleeding Assessment Tool; N/A, not applicable; OR, odds ratio; VWD, von Willebrand disease; VWF, von Willebrand factor.

(OR, 1.9; 95% CI, 0.98-3.6; *P* = .06), severe antepartum hemorrhage (OR, 2.4; 95% CI, 0.7-9.5; *P* = .18) and persistent IDA for >2 years (OR, 2.5; 95% CI, 0.8-8.6; *P* = .11), albeit not statistically significant. There were no significant differences in the rates of ED visits or red cell transfusions for HMB, severe PPH, and severe hemorrhagic ovarian cysts between women with and without delayed diagnosis.

Women with delayed diagnosis also experienced a significantly higher incidence of ED visits for bleeding complications, both prior to VWD diagnosis (incidence rate ratio [IRR], 2.3; 95% CI, 1.1-5.0) and after VWD diagnosis (IRR, 2.0; 95% CI, 1.2-3.2). Even following VWD diagnosis and management by the bleeding disorders clinic, acute healthcare utilizations persisted in women who experienced delayed diagnosis and in those without. For instance, among women who experienced <3 bleeding events prior to diagnosis, the incidence of ED visits for bleeding complications was 1.0 (95% CI, 0.5-1.8) per 100 person-years prior to diagnosis and was 2.9 (95% CI, 2.0-4.2) per 100 person-years after VWD diagnosis.

4 | DISCUSSION

In this large single-center cohort study of 178 women with VWD followed by a specialized HTC, we demonstrated a high prevalence of delayed diagnosis and loss to follow-up. This study, to the best of our knowledge, is the first to examine the predictors of diagnostic delays and to demonstrate the adverse impact of delayed diagnosis on gynecologic outcomes and healthcare resource utilization. Women who experienced ≥3 bleeding events prior to diagnosis have approximately 3-fold higher odds of undergoing hysterectomy and D&C for HMB control than those with <3 bleeds prior to diagnosis.

Our findings of marked diagnostic delays in women with VWD at a median of 14.2 years from the first bleeding event (median age of diagnosis, 27 years) are consistent with the existing literature from other jurisdictions. The United States Centre for Disease Control data showed a comparable delay from the symptom onset to VWD diagnosis of 16 years [21]. However, about 50% of girls and women with VWD in the Centre for Disease Control data were diagnosed by age 12, whereas only 26% of our cohort was diagnosed by age 18. This difference may have been affected by the exclusion of girls under age 18 with VWD in our cohort. Compared with our cohort, the median age of diagnosis was also younger (16 years) in a recent European Haemophilia Consortium (EHC) survey of 709 women with bleeding disorders from mostly Western European countries [22]. Interestingly, in contrast to the EHC patient survey, which showed a gradient in earlier diagnosis across VWD types 1, 2, and 3 (median age, 25 years vs 19 years vs 1 year), our study failed to demonstrate the impact of type 2 VWD or baseline VWF levels on timely diagnosis [15]. What is more alarming is that a quarter of our cohort who experienced delayed diagnosis had a pre-existing family history of VWD prior to hematology referral. This is in stark contrast to the findings from the EHC survey, in which patients with a family history were diagnosed much earlier than those without (age 1 vs 17 years) [22]. This calls for improved family screening and coordination of care between general pediatrics, pediatrics, and adult HTCs. This would also require better collaboration between hematology, patient organizations, and primary care professionals to increase awareness. Finally, our observed association between delayed VWD diagnosis and severe bleeding events prior to diagnosis is likely confounded by differential observation time. Those with delayed diagnosis were exposed to a longer period without adequate treatment, in which they are susceptible to PPH and postoperative bleeding.

Timely diagnosis of VWD in girls and women likely depends on a myriad of factors including 1) universal access to a primary care physician; 2) early recognition of normal vs abnormal bleeding, including awareness of what constitutes HMB among both patients, parents, and physicians; 3) timely referral to hematology; and 4) access to specialized coagulation laboratories and HTCs. While our study was not designed to delineate the relative contribution of these

TABLE 3 Association between diagnostic delays and gynecologic outcomes.

Outcome	<3 bleeding events prior to diagnosis (*n* = 92)	≥3 bleeding events prior to diagnosis (*n* = 71)	OR or IRR (95% CI)	*P* value
Severe HMB, *n* (%)				
Any	50 (54)	49 (69)	1.9 (0.98-3.6)	.06
Hysterectomy	11 (12)	19 (27)	2.7 (1.2-6.3)	.02
D&C	5 (5)	11 (15)	3.2 (1.1-10.6)	.04
Endometrial ablation	6 (7)	10 (14)	2.3 (0.8-7.2)	.12
ED visit	15 (16)	14 (20)	1.3 (0.6-2.8)	.57
Red cell transfusion	9 (10)	4 (6)	0.6 (0.1-1.8)	.34
Severe PPH, *n* (%)	6 (6)	6 (8)	1.3 (0.4-4.4)	.64
Severe antepartum hemorrhage, *n* (%)	4 (4)	7 (10)	2.4 (0.7-9.5)	.18
Severe hemorrhagic ovarian cysts, *n* (%)	7 (8)	3 (4)	0.5 (0.1-2.0)	.38
Persistent IDA > 2 y, *n* (%)	5 (5)	9 (13)	2.5 (0.8-8.6)	.11
Incidence of ED visits for bleeding prior to VWD diagnosis, per 100 person-y (95% CI)	1.0 (0.5-1.8)	2.3 (1.6-3.3)	2.3 (1.1-5.0)	.02
Incidence of ED visits for bleeding after VWD diagnosis, per 100 person-y (95% CI)	2.9 (2.0-4.2)	5.8 (4.2-7.7)	2.0 (1.2-3.2)	.004
Incidence of hospitalizations for bleeding prior to diagnosis, per 100 person-y (95% CI)	0.6 (0.2-1.2)	0.4 (0.2-1.0)	0.8 (0.2-3.0)	.72
Incidence of hospitalizations for bleeding after diagnosis, per 100 person-y (95% CI)	1.3 (0.7-2.2)	0.7 (0.2-1.5)	0.5 (0.1-1.5)	.21

D&C, dilatation and curettage; ED, emergency department; HMB, heavy menstrual bleeding; IDA, iron deficiency anemia; IRR, incidence rate ratio; OR, odds ratio; PPH, postpartum hemorrhage.

factors in our diagnostic delays, a number of studies in the literature highlighted gaps in these domains. First, despite the Canadian universal healthcare system, between 14.5% and 16.8% of Canadians and 14.9% and 19.5% of Albertans report not having a regular healthcare provider in the 2015 and 2019 Canadian Community Health Survey [23]. Second, even though HMB is the most common and burdensome symptom of VWD, underrecognition and underreporting of HMB are well recognized among both patients and clinicians [12,24–26]. Third, while the ASH ISTH NHF WFH 2021 guidelines recommended the use of VWF platelet-binding activity assay (eg, VWF:GPIbM and VWF:GPIbR) over ristocetin cofactor activity for the diagnosis of VWD, availability of a specialized assay remains a major challenge even in specialized coagulation laboratories affiliated with HTCs [15]. For instance, we do not have access to VWF platelet-binding assay in our HTC, thereby limiting diagnostic accuracy. In response to these barriers to delayed diagnosis, a recent modified Delphi survey in the United Kingdom and the Republic of Ireland developed a set of consensus recommendations to define higher standards of care for both men and women with VWD [27].

While a small number of prior studies examined the time to diagnosis, there are no data on the loss to follow-up in VWD. Our study highlighted that nearly a third of women with VWD followed by our HTC were lost to follow-up for ≥5 years, with a bimodal pattern (37% nonmenstruating at the last follow-up due to postmenopausal age or posthysterectomy status, another 17% in young adulthood years). Reassuringly, those with type 2 VWD and lower baseline VWF activities have lower likelihood of loss to follow-up. As patients with an initial bleeding event prior to 1980 (ie, postmenopausal at the time of data collection) have the highest odds of loss to follow-up, we hypothesize that the observed loss to follow-up rates could be contributed by an age-related increase and potential normalization of VWF levels, absence of bleeding symptoms for decades in the postmenopausal state, and/or patient relocation out-of-province. Given the lack of updated VWF/FVIII levels and bleeding symptoms in those who were lost to follow-up, we were unable to ascertain this, although our data showed that the most recent VWF levels remained low (0.4-0.5 IU/mL) prior to loss to follow-up. Despite the reduced risk of gynecologic or obstetric bleeding in aging women, the risk of traumatic or perioperative bleeding and/or the impact of VWD on aging (such as cardiovascular health and need for antithrombotic therapy) in this subgroup remains an ongoing concern. Hence, we felt that both the young adult population and postmenopausal population are vulnerable subgroups at the risk of "falling through the cracks," requiring special attention.

Our study reports the alarming finding that women with diagnostic delays had significantly higher rates of hysterectomies and D&C for HMB, ED visits for bleeding, and a nonsignificant trend toward prolonged IDA. Delayed diagnosis often reflects a quality-of-care

problem upstream of hematology referral, calling for improvement in routine VWD screening and IDA management in women with HMB in primary care and gynecology clinics. While our study is not designed to assess the yield of basic hemostasis testing among women with HMB, our data demonstrates the potential impact of timely diagnosis in avoiding unnecessary surgical procedures, especially as over a third of hysterectomies occurred prior to VWD diagnosis. Earlier diagnosis of VWD did not completely circumvent the need for hysterectomy for HMB control, as 19 women underwent hysterectomy after their VWD diagnosis. Our observations are in keeping with a US claims-based study that reported increased rates of hysterectomy or endometrial ablation after VWD diagnosis compared with those before diagnosis [28]. This may be explained by the low rates of VWF prophylaxis in our cohort, suboptimal control of HMB with medical management demonstrated in another Canadian HTC, and/or patients' preference [29,30]. Given the challenges in VWD diagnosis, updated education of frontline healthcare providers is paramount, addressing changes in diagnostic criteria over the years, accessibility to specialized assays, and preanalytical variables such as estrogen- and stress-related increases in VWF in women with HMB [31,32]. Counterintuitively, acute care utilization for bleeding-related presentations persisted even after diagnosis and management by HTCs. We hypothesize that this may be related to the level of engagement with the HTC, lower rates of patients with VWD on home infusion program with factor concentrates (compared with the hemophilia population), and/or the need for source identification and control (eg, ED presentation with severe abdominal pain from ruptured hemorrhagic ovarian cysts and delayed postpartum hemorrhage from retained products).

Our study has a number of limitations. First, given that our study cohort is composed of known VWD cases followed by our specialized HTC, we likely missed undiagnosed cases, thereby underestimating the true time to diagnosis in the general population. However, our numbers are consistent with the registry data. The province of Alberta has about 12% of the Canadian population, served by 2 adult HTCs of comparable size. Our cohort of 178 women consists of approximately 6% of the 2743 Canadian women over age 18 who were registered as VWD in the Canadian Bleeding Disorders Registry [33]. Second, given its retrospective nature, the study has missing or imprecise data on the time of the first bleeding event. For patients who moved from a different jurisdiction, we used the date of the first recorded bleeding event, which often underestimates the time from bleeding to diagnosis. Third, our sample size may be underpowered to identify statistically significant associations between diagnostic delays and healthcare utilization and health outcomes. Fourth, we do not have access to sociocultural predictors of diagnostic delays or loss to follow-up, such as race/ethnicity, socioeconomic status, education attainment, and access to a primary care physician at the time of symptom onset. Fifth, the study is subject to selection bias, information bias, and unadjusted confounding given its retrospective design. Finally, generalizability is limited due to our study setting of a single Canadian province, with approximately 23% of immigrant population [34]. Given Canada's universal public healthcare system, we postulate that diagnostic delays and inequities in healthcare access may be similar or worse in settings with either limited healthcare resources or private healthcare systems.

5 | CONCLUSION

Women with VWD experience prolonged diagnostic delays and high rates of loss to follow-up. Delayed diagnosis occurred even in women with a known family history, type 2 VWD, and those with severe bleeding events. Alarmingly, delayed diagnosis was associated with higher rates of surgical interventions for HMB and acute care utilization. A high index of suspicion is paramount to ensure a prompt diagnosis of VWD, as this may prevent severe gynecologic bleeding complications and their need for invasive surgical management. In addition to ongoing educational efforts to facilitate earlier recognition of abnormal bleeding in girls and women, parents, and clinicians, infrastructural changes are required to improve timely access to primary care and specialized bleeding disorders programs. Finally, the lack of published guidance on the frequency of follow-ups for women with VWD, in contrast to specific recommendations on the frequency of comprehensive assessments in people with hemophilia, highlights sexism in the management of bleeding disorders. Future guidelines and institutional protocols need to be developed to optimize the frequency and quality of follow-up in women with VWD, in order to reduce loss to follow-ups, reduce unnecessary acute care utilization, and improve women's quality of life.

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AUTHOR CONTRIBUTIONS

J.S. and M.M. conceived the study idea, designed the study, performed data collection and interpretation, and wrote the first draft of the manuscript. R.K. critically revised the manuscript. H.(L).S. conceived the study idea, designed the study, assisted with data collection, performed data analysis and interpretation, and critically revised the manuscript. All authors reviewed and approved the current version.

RELATIONSHIP DISCLOSURE

H.(L).S. received honoraria from Pfizer, Sanofi/Sobi, and Shire/Takeda. R.K., M.M., and J.S. have no competing interests to disclose.

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SUPPLEMENTARY MATERIAL

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