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Original Article

# Clinical and laboratory presentation of von Willebrand disease: Experience from a single center in Saudi Arabia

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**الملخص**

**أهداف البحث:** لتقييم العرض السريري والنتائج المعملية بين المرضى الذين تم تشخيص إصابتهم بمرض فون ويلبراند في وحدة الرعاية الثالثة في السعودية.

**طريقة البحث:** تضمنت هذه الدراسة بأثر رجعي 189 مريضًا يعانون من مرض فون ويلبراند تمت متابعتهم في وحدتنا على مدار أربع سنوات ، وتم جمع البيانات السريرية والمخبرية وتحليلها باستخدام برنامج الحزمة الإحصائية للعلوم الاجتماعية.

**النتائج:** كان متوسط عمر مجموعة الدراسة 30 عامًا (المدى 11 شهرًا - 56 عامًا). كان هناك غلبة للإناث بنسبة 32.30٪ ذكور و 66.70٪ إناث. معظم المرضى (48٪) تعرضوا لأكثر من نوع واحد من النزيف بناءً على التوطين وتم تحديدهم على أنه نزيف من مواقع مختلفة ، معظمها من المفاصل والعضلات (23.90٪) ، يليها الغشاء المخاطي (14.60٪) ، والجهاز البولي التناسلي (7.70٪) ، كدمات (2.80٪) ، ونزيف معدي معوي (2.80٪). 48٪ من الأشخاص الذين يعانون من أكثر من نوع واحد من النزيف ، 105 (58.01٪) لديهم النوع الأول ، 29 (16.02٪) لديهم النوع الثاني ، و 47 (25.96٪) لديهم النوع الثالث. كان متوسط قيمة الهيموجلوبين 116 ± 25.60 جم / لتر ؛ كان الفيريتين 75.80 ± 166.80 ميكروغرام / لتر (متوسط 28.5) ؛ كان مستضد فون ويلبراند 0.40 ± 0.27 وحدة دولية / مل ، وفون ويلبراند: كان العامل المساعد ريستوسيتين 0.32 ± 0.20 وحدة دولية / ديسيلتر 49.20٪ من الأشخاص أظهروا لفترات طويلة ، وأظهر 50.80٪ وقت الثرومبوبلاستين الجزئي الطبيعي. أظهر التحليل المقارن لفصيلة الدم من النوع أو مع النوع غير أو أن فصيلة الدم مرتبطة بشكل كبير مع العامل الثامن (قيمة ب = 0.013) ، عامل فون ويلبراند: العامل المساعد للريستوسيتين (قيمة ب = 0.004 ) ، وعامل فون ويلبراند: المستضد (قيمة ب = 0.019)

**الاستنتاجات:** كان نزيف المفاصل والعضلات أكثر العروض السريرية شيوعا في مجموعتنا. على الرغم من أن مرض فون ويلبراند من النوع الأول كان الأكثر انتشارا في مجموعتنا ، فقد لاحظنا انتشارا أعلى نسبيا من النوع الثالث والذي قد يكون بسبب الاختلافات العرقية أو تحيز الإحالة. ومستضد عامل فون ويلبراند ، مع وجود فرق أكثر وضوحا لعامل مساعد ريستوسيتين.

**الكلمات المفتاحية:** مرض فون ويلبراند؛ عامل فون ويلبراند؛ فصيلة الدم؛ ملامح مرقئ؛ المملكة العربية السعودية

**Abstract**

**Objectives:** This study was aimed at assessing the clinical presentations and laboratory findings among patients diagnosed with vWD at a Saudi tertiary care unit.

**Methods:** This retrospective study included 189 patients with vWD who were followed up in our unit over 4 years. Clinical and laboratory data were collected and analyzed in SPSS.

**Results:** The median age of the study cohort was 30 years (range 11 months–56 years). The cohort had a female preponderance, with 32.30% males and 66.70% females. Bleeding from different sites was observed, mostly from the joints and muscles (23.90%), followed by the mucus membranes (14.60%), genitourinary areas (7.70%), ecchymoses (2.80%), and gastrointestinal areas (2.80%). A

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total of 48% of participants presented with more than one type of bleeding. A total of 105 (58.01%) participants had type 1; 29 (16.02%) had type 2; and 47 (25.96%) had type 3 vWD. Blood tests indicated the following mean value: hemoglobin, 116 ± 25.60 gm/L; ferritin, 75.80 ± 166.80 µg/L (median 28.5); vWAg, 0.40 ± 0.27IU/ml; and vWD:RCo, 0.32 ± 0.20IU/dL. The partial thromboplastin time was prolonged in 49.20% and normal in 50.80% of participants. Platelet function analysis values were prolonged in 92.90% and normal in 7.10% of participants. Comparative analysis of the O-type and non-O blood type showed that blood type O was significantly correlated with factor VIII (p-value = 0.013), vWF:RCo (p-value = 0.004), and vWF:Ag (p-value = 0.019).

**Conclusion:** Joint and muscle bleeds were the most common clinical presentations in our cohort. Although type 1 vWD was most prevalent in our cohort, we observed a comparatively higher prevalence of type 3, possibly because of ethnic differences or referral bias. We found a significant difference between O and non-O blood type regarding FVIII and vWF:Ag, and observed a more pronounced difference for vWD activity measuresd by vWF:RCo with blood type O being the systematic factor.

**Keywords:** ABO; Saudi Arabia; Blood group; Hemostatic profiles; vWD; vWF

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## Introduction

Von Willebrand factor (vWF) is one of the largest plasma proteins that circulates in the form of multimers; it is found in various sizes, including high-molecular-weight (HMW), intermediate-molecular-weight, and low-molecular-weight (LMW) vWF, in the plasma.[1,2] The hemostatic function of vWF is governed by its role in mediating the platelet adhesion to the sub-endothelial layer of injured blood vessels.[3,4] The multi-subunit proteins that constitute these multimers determine the functional properties of the complexes.[1]

von Willebrand disease (vWD) is the most common inherited bleeding disorder, with a reported prevalence ranging from 0.01% to 1.30%.[5] Genetic mutations that result in subunit dysfunction cause this disease. vWD can manifest as quantitative (types 1 and 3) or qualitative defects in the protein (type 2). The most common type is type 1, which is characterized by partial vWF deficiency and relatively milder bleeding manifestations.[6,7] Type 2 results from numerous structural and functional abnormalities in vWF, which are further subdivided according to multimer defects, and factor VIII (FVIII) carriage, adhesion, and aggregation.[8,9] Type 3, the most severe but rarest form of vWD, is characterized by a complete absence of vWF.[9,10]

vWD shows substantial clinical heterogeneity, thus making diagnosis challenging.[11,12] The diagnosis is made on the basis of multiple laboratory assays that evaluate the pleiotropic function of vWF.[13] The results of these assays, combined with a personal history of bleeding and family history, can lead to a confirmatory diagnosis.[9] Treatment is based on correcting the primary hemostasis defect due to inherited vWF deficiency and the secondary defect that results from an inability to bind and mediate FVIII function.[14]

A high incidence of coagulation factor disorders has been reported among young Saudi adults with at least one positive bleeding symptom, surveyed on the basis of semi-structured validated condensed MCMDM-1vWD in the Kingdom of Saudi Arabia (KSA). A total of 7.4% of participants were deficient in FVIII, 7.6% were deficient in FIX, 3.3% were deficient in FII, 26.1% were deficient in FV, 3.1% were deficient in FVII, and 1.8% were deficient in FX. Low vWF activity was found in 8% of participants.[15] vWD has been reported in 6.6% of patients presenting with abnormal menstrual bleeding to a Saudi tertiary care unit, thus indicating that vWD is a prevalent cause of abnormal uterine bleeding among Saudi women.[16] The present study evaluated the clinical presentation and laboratory findings among patients diagnosed with vWD at a Saudi tertiary care unit.

## Materials and Methods

### *Study design*

After ethical approval was obtained from KFSHRC under number (RAC KFSHRC-2111053), a retrospective study was conducted at our institute in Riyadh, KSA. a total of 189 Saudi patients who presented with a bleeding history, were diagnosed with vWD through laboratory and clinical data, and were treated at our tertiary care unit between 2016 and 2020 were included in the study.

Data on various blood tests were collected, including complete blood count (CBC), blood group, partial thromboplastin time (PTT), von Willebrand factor antigen (VwF:Ag), von Willebrand factor ristocetin cofactor activity (vWF:RCo), and FVIII assays. All coagulation tests were performed on a STA R Max® system (Diagnostica Stago, Marseille, France).

### *Statistical analysis*

Descriptive statistics were computed as baseline frequencies and percentages for categorical variables. Means, medians, standard deviations (SD), and minimum and maximum values were used for continuous variables. Student's t-test was used for continuous variables to assess significant differences in means. STATA v.13.0 (Stata Corp., College Station, TX, USA) was used for the analysis. A statistical significance threshold of $P = 0.05$ was used. No attempt at imputation was made for missing data.

## Results

The median age of the study cohort was 30 years (range 11 months−56 years); 62 (32.30%) were male, and 127 (66.70%) were female. Many patients [50 (48%)] of our cohort

**Table 1: Frequencies and percentages of categorical variables.**

| **Bleeding type (n = 189)** | **Frequency n (%)** |
|---|---|
| More than one | 50 (48.0) |
| Joint and muscle bleeding | 25 (23.9) |
| Mucous membrane bleeding | 14 (14.6) |
| Genitourinary bleeding | 8 (7.7) |
| Ecchymosis | 3 (2.8) |
| GIT bleeding | 3 (2.8) |
| **Bleeding nature** | n (%) |
| Spontaneous | 64 (68.1) |
| Post-trauma | 4 (4.2) |
| Post-surgery | 6 (6.3) |
| Combined | 20 (21.3) |
| **Family history** | n (%) |
| Yes | 37 (19.58) |
| No | 36 (19.04) |
| N/A | 116 (61.38) |
| **Blood group** | n (%) |
| A | 30 (15.87) |
| AB | 2 (1.06) |
| B | 31 (16.40) |
| O | 117 (61.91) |
| N/A | 9 (4.76) |
| **PLT** (140–450 × $10^9$/L) | n (%) |
| High | 26 (13.8) |
| Normal | 151 (80.3) |
| Low | 11 (5.8) |
| N/A | 1 (0.53) |
| **vWD type** | n (%) |
| Type 1 | 105 (58.01) |
| Type 2 | 29 (16.02) |
| Type 3 | 47 (25.96) |
| Unidentified | 8 (0.04) |

presented with multiple sites of bleeding. Bleeding from different sites was observed, mostly from joints and muscles [25 (23.90%)], followed by mucous membranes [14 (14.60%)], genitourinary areas (7.70%), gastrointestinal areas (2.80%), and ecchymoses (2.80%). The frequencies of these bleeding types among our cohort are described in Table 1.

The nature of bleeding was mostly spontaneous 64 (68.10%). A family history of bleeding was reported for 37 (19.58%) of the patients. The most frequent blood group was O [117 (61.91%)], which was followed by B [31 (16.40%)] and A [30 (15.87%)].

The mean hemoglobin (Hb) (116 ± 25.50 gm/L) and mean corpuscular volume (81.30 ± 8.50) were nearly within normal ranges. However, the mean ferritin levels (75.80 ± 166.80 ng/mL) were within the normal range (Table 2). Low ferritin (<30 ng/mL) was found in 11 male patients, with a mean of 15 ± 8.20 ng/mL (2.3–28), and in 64 female patients, with a mean of 13.90 ± 7.30 ng/mL (2.80–29.40). Iron deficiency anemia was reported in 5 male and 50 female patients (Table 3).

PTT was prolonged in 76 (40.4%) patients, whereas PFA 100 was prolonged in 104 (92.90%). The laboratory evaluation of vWD included vWF:Ag (0.40 ± 0.27 IU/ml), vWF:RCo (0.32 ± 0.20 IU/dL), FVIII (0.6 ± 0.43), and vWF:RCo/vWF:Ag ratio (1.70 ± 4.50). Type 1 disease was the most frequent (58.01%), and was followed by type 3 (25.96%) and type 2 (16.02%).

*Relationship between FVIII, vWF:RCo, or vWF:Ag and blood group*

Analysis of variance was performed for FVIII, vWF:RCo, and vWF:Ag with respect to blood types. The mean values for blood groups A, B, and O were similar, whereas those for AB differed, although the number of observations was very low. All variables showed significant differences in variance.. We found a significant difference in

**Table 2: Laboratory findings in vWD.**

| | Mean ± SD (range: minimum–maximum) | Median |
|---|---|---|
| **Hb (gm/L)** | **116 ± 25.5 (12.7–177)** | **116.0** |
| Hb (gm/L) male | 116 ± 30 (12.7–177) | 122 |
| Hb (gm/L) female | 115 ± 22 (13–177) | 118 |
| Mean corpuscular volume (fL) | 81.3 ± 8.5 (54–110) | 82.2 |
| **Ferritin (µg/L)** | **75.8 ± 166.8 (2.3–1528)** | **28.5** |
| Ferritin (µg/L) male | 66 ± 60 (2.3–261) | 40 |
| Ferritin (µg/L) female | 80 + 196 (2.8–1528) | 21 |
| **PTT** (28–40 s) | **Frequency** | |
| Prolonged | 91 (49.2) | |
| Normal | 94 (50.8) | |
| **PTT mix** | **Frequency** | |
| Corrected | 61 (67.03) | |
| Not corrected | 23 (25.27) | |
| **PFA-100 (77–133 s)** | | |
| Prolonged | 104 (92.9) | |
| Normal | 8 (7.1) | |
| vWAg (IU/ml) | 0.4 ± 0.27 (0.01–1.5) | 0.375 |
| vWF:RCo (IU/dL) | 0.32 ± 0.2 (0.01–1.66) | 0.32 |
| FVIII | 0.6 ± 0.43 (0.01–1.74) | |
| vWF:RCo/vWFAg ratio | 1.7 ± 4.5 (0.05–34) | |

**Table 3: Males and females with low Hb and ferritin.**

| Variable | Male (n, mean ± SD, range) | Female (n, mean ± SD, range) |
|---|---|---|
| Low ferritin <30 μg/L | 11 (14.6%), 15 ± 8.2, (2.3–28) | 64 (85.4%), 13.9 ± 7.3 (2.8–29.4) |
| Low Hb M ≤ 13 g/dL; F ≤ 12 g/dL | 30 (24.8%), 93.5 ± 26 (12.7–119) | 91 (75.2%), 107 ± 20.5 (13–129) |
| Low Hb and ferritin | 5 (9%), 15.9 ± 8.3 (2.3–24) | 50 (91%), 13.3 ± 7.7 (2.8–29.4) |

**Table 4: Analysis of variance between blood group O and non-blood group O regarding FVIII, vWF:RCo, and vWF:Ag.**

| Blood group | FVIII | vWF:RCo | vWF:Ag |
|---|---|---|---|
| Blood group O, n = 105 | 0.07 | 0.003 | 0.01 |
| Blood group non-O, n = 59 | 31.0 | 7.8 | 11.3 |
| P-value | 0.013 | 0.004 | 0.019 |

FVIII (p-value = 0.013) and vWF:Ag (p-value = 0.019) between O and non-O groups; a more pronounced difference was observed for vWF:RCo (p-value = 0.0004) (Table 4).

## Discussion

vWD is a hemostatic bleeding disorder with high clinical heterogeneity. The precise diagnosis of vWD is complicated, and no single screening tool has been identified for diagnosis. vWD is diagnosed on the basis of hemostasis profiles combined with personal and family history. vWD has been identified as a common pathological cause of menorrhagia. The reported prevalence of symptomatic and non-symptomatic vWD ranges from 0.01% to 1.3%.[17–19] However, the prevalence varies significantly across populations because of differing case definitions.[20] In KSA, national prevalence data are lacking. However, the data from some scale studies suggest that the prevalence is approximately 1.5%.[21] In our study, type 1 was the most frequent type of vWD. Type 1 is the most common vWD found in the developed world. The incidence of type 3 in our cohort was higher than expected. In developing countries such as India and Iran, type 3 vWD is most prevalent, possibly because of high consanguinity.[22,23] The rate of consanguineous marriages is also high in KSA,[24] thus leading to a higher than expected incidence rate of type 3 vWD among the Saudi population.

vWD can be diagnosed at any age. The levels of vWF increase with age.[25] An inverse relationship has been reported between bleeding symptoms and aging.[26] The prevalence of vWD is equal among males and females. However, the phenotype is usually more pronounced among women, because of menorrhagia and increased visibility of bruises.[27] Consequently, our sample had a female preponderance. Menorrhagia is one of the most common gynecological disorders among women, and in almost 50% of cases, the underlying pathological cause cannot be identified.[28] The prevalence of menorrhagia ranges from 14% to 48% in various adolescent populations.[29] vWD accounts for 5–20% of cases of menorrhagia.[30] In our cohort, we reported menorrhagia as part of mucous membrane bleeding; menorrhagia accounted for 14.6% of patients presenting with single symptom and a portion of the combined bleeding symptoms. Because one function of vWF is binding FVIII, vWD deficiency results in a phenotype of FVIII deficiency, which presents as joint and muscle bleeding. Approximately 24% of our patients had joint or muscle bleeding. Our findings contrast with those from with another study reporting oral mucosal bleeding as the most common site of the first bleed (70%), followed by muscle and joint bleeds (52%).[31]

Both hemophilia A and vWD are characterized by FVIII deficiency, mainly manifesting as recurrent, spontaneous joint and muscle bleeds.[32] Spontaneous bleeding (mucocutaneous, muscle and joint bleeding) is a common feature of bleeding in vWD.[33] Spontaneous bleeding episodes were found in 68.10% of our patients, as compared with 37% reported in an another study.[31]

Aberrations in normal platelet function, coagulation factor defects, and vWD contribute to most forms of symptomatic vWD.[29] vWD has been reported as a common cause of iron deficiency anemia among women, psychological stress, diminished quality of life, excessive days lost at work, and financial burden due to healthcare expenses.[34,35]

Patients with vWD have been reported to continue to experience bleeding symptoms even after diagnosis in many cases.[36] The precise prevalence of various symptoms depends on the type of bleeding disorder. Mucus membrane bleeding is the most frequently observed symptom. Excessive menstrual bleeding among women is also classified as mucus membrane bleeding and is commonly reported among patients with vWD.[37] This aspect might have contributed to our dataset's high frequency of this bleeding type. One study has reported that ecchymosis is a common clinical presentation in vWD, which was also a frequent symptom in our patients.[38] Spontaneous bleeding episodes were more frequent in our cohort than is usually reported for type 3 vWD,[39] possibly because of the relatively high prevalence of this type in our cohort. A family history of bleeding disorders is an important factor in the diagnosis of vWD[9]; however, more than half the patients in our cohort did not have a family history of bleeding disorders or were unaware of the presence of bleeding disorders in their family.

Orstavik et al. have reported that 66% of the variation in plasma vWF levels is attributable to genetic factors, of which

30% can be explained by the ABO blood group system.[40] The plasma levels of vWF have been reported to be lower in people with an O than a non-O blood type.[41,42] This finding is in concordance with those from a previous Saudi study wherein the highest number of cases had the O blood group, which was significantly correlated with vWD and low FVIII levels.[43] We found a significant correlation between blood type and the levels of FVIII, vWF:RCo, and vWF:Ag. The variance analysis of the O-type blood group with non-O-type revealed a more pronounced difference for vWD activity measuresd by vWF:RCo with blood type O being the systematic factor. Similarly, individuals with the AB blood group have the highest vWF levels,[44] in agreement with our finding that the fewest individuals had the AB blood type. Blood type has also been implicated as a major determinant of plasma FVIII levels.[45,46]

Screening of patients with vWD usually reveals normal platelet counts and prolonged PTT,[47] with the exception of type 2b, which is associated with thrombocytopenia. These findings were also observed in our participants. vWF:Ag, VWF:RCo, and FVIII assays are basic tests used to test for vWD.[48,49] vWF activity assays are also an important diagnostic marker for vWD.

The blood loss due to vWD can lead to hemoglobin and ferritin deficiencies, as supported by the reported findings among women with vWD, who are prone to excessive blood loss[50] and consequently iron deficiency anemia.[34,35] The hemoglobin and ferritin levels were significantly lower among patients with vWD type 3, and lower levels of these hematological markers were found among females. Menorrhagia, which is more common among females with than without vWD, is an important factor associated with low hemoglobin and ferritin levels.[50]

### *Limitations*

The retrospective study was conducted on a small cohort of patients with vWD from a single tertiary care center in the KSA.

## Conclusion

The present study evaluated the hemostatic profiles among Saudi patients with vWD and the trends in vWD marker assays. Type 1 was the most frequent vWD type found among our participants; however, the frequency of type 3 was slightly higher than expected. This finding is attributable to the high rates of consanguineous marriages among Saudis. Joint and muscle bleeds were the most common clinical presentations. Significant differences in FVIII and vWF:Ag were found between O and non-O blood types, and the difference was more pronounced for vWF:RCo.

### *Recommendation*

Future studies across regions in the KSA will aid in understanding of the patterns in hemostatic markers and improve the diagnosis and management of vWD.

**Abbreviations:** vWF, Von Willebrand factor; HMW, high-molecular-weight; LMW, low-molecular-weight; vWD, von Willebrand disease; FVIII, factor VIII; KSA, Kingdom of Saudi Arabia; MCMDM-1vWD, Molecular and Clinical Markers for the Diagnosis and Management of Type 1 VWD Bleeding; KFSHRC, King Faisal Specialist Hospital& Research Center; Hb, Hemoglobin; CBC, Complete blood count; PTT, Partial thromboplastin time; VwF:Ag, von Willebrand factor antigen; vWF:RCo, von Willebrand factor ristocetin cofactor activity; SD, Standard deviations; MCV, Mean corpuscular volume.

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## Conflict of interest

The authors have no conflict of interest to declare.

## Ethical approval

The study was approved by the Institutional Review Board of King Faisal Specialist Hospital and Research Centre, KSA, under approval # RAC KFSHRC (2111053), approval date is 2020.

## Consent

All authors consent to publication.

## Authors contributions

TO and MA designed and developed the study; both authors were responsible for the content and authenticity. MM, MS, AA, and RA oversaw data collection and data entry. HA and HK performed a final review of the data and analysis. All authors were responsible for the direction of the study team and the facilitation of the project plan. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

## Availability of data and materials

Furnished upon request.

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