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Clinical Spectrum, Subtype Distribution, and Treatment Outcomes in von Willebrand Disease: A Prospective Study from a Hemophilia Treatment Center in Pakistan

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Abstract

Introduction: von Willebrand Disease (VWD) is the most common inherited bleeding disorder, exhibiting diverse clinical manifestations depending on subtype and severity. This study aimed to assess the distribution of VWD subtypes, evaluate the correlation between Bleeding Assessment Tool (BAT) scores and clinical symptoms, and examine treatment outcomes and quality-of-life (QoL) improvements at a Hemophilia Treatment Center (HTC).

Methods: We conducted a prospective observational study of 147 VWD patients. Data were collected using the World Bleeding Disorders Registry (WBDR) on demographics, subtype classification, BAT scores, bleeding symptoms, and clinical outcomes. Annual bleeding rate (ABR) was calculated to quantify bleeding frequency. Treatment response and QoL changes were evaluated after twelve months. Statistical analysis included ANOVA and Kruskal–Wallis tests to assess differences in bleeding severity and disease burden.

Results: Among 147 VWD patients (mean age 14.5 ± 10.9 years), type 3 was the most common (80.9%), followed by type 2 (12.2%) and type 1 (6.8%). Gum bleeding (80.7%) was the leading symptom, followed by heavy menstrual bleeding (63%) and hemarthrosis (35%). BAT scores (>12) occurred in 93.3% of type 3 and 16.7% of type 2 patients, with type 3 showing the highest ABR (>30/year in 91.6%). Joint scores were significantly higher in type 3 versus type 1 ($p = .002$) and type 2 ($p = .004$), and mean hemoglobin was lowest in type 3 (6.2 g/dL, $p = .001$). Treatment varied on the types. After management, ABR decreased across all subtypes; in type 3, >30 bleeds/year reduced from 91.6% to 57.1%, with improved joint scores, hemoglobin levels, and psychological well-being.

Conclusion: Type 3 von Willebrand disease is associated with the highest clinical burden, characterized by frequent and severe bleeding requiring intensive management. In this cohort, individualized treatment was associated with reduced bleeding frequency, improved hemoglobin levels, and better patient-reported quality of life. These findings underscore the importance of comprehensive care approaches, including attention to psychological well-being, particularly in patients with severe disease.

Keywords

von willebrand disease, type 1, type 2, type 3, inherited bleeding disorder, bleeding assessment tool, hemophilia treatment center, annual bleeding rate, heavy menstrual bleeding, quality of life

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Introduction

von Willebrand Disease (VWD) is the most common inherited bleeding disorder, affecting up to 1% of the general population. It results from quantitative or qualitative defects in von Willebrand factor (VWF), a multimeric

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glycoprotein essential for platelet adhesion and stabilization of coagulation factor VIII. Clinical manifestations range from mild mucocutaneous bleeding to severe hemorrhagic events, depending on the subtype and severity of the deficiency.[1]

VWD is classified into three primary types. Type 1, the most common form, involves a partial quantitative deficiency of VWF and accounts for 70%–80% of symptomatic cases, a subset of these patients exhibit increased VWF clearance (type 1C), which may require distinct clinical consideration. Type 2 is characterized by qualitative defects and includes subtypes 2A, 2B, 2 M, and 2N. Type 3 VWD, the rarest and most severe form, is inherited in an autosomal recessive pattern and typically presents in infancy with spontaneous mucocutaneous and joint bleeding.[2] In regions with high rates of consanguineous marriages—such as Pakistan, where approximately 60% of marriages are consanguineous—the prevalence of recessive disorders like type 3 VWD is notably higher.[3]

Diagnosis of VWD requires both clinical evaluation and specialized laboratory testing, including measurement of VWF antigen (VWF: Ag), ristocetin cofactor activity (VWF: RCo), and factor VIII (FVIII) activity levels.[4] The International Society on Thrombosis and Haemostasis (ISTH) Bleeding Assessment Tool (BAT) is a validated instrument that quantifies bleeding severity and supports diagnosis and monitoring.[5] Higher BAT scores correlate with increased bleeding frequency and severity.

Management strategies are tailored according to disease type and severity. Desmopressin (DDAVP) effectively increases VWF and FVIII levels in most patients with type 1 VWD, whereas responses in type 2 are variable. In type 3 disease, where DDAVP is ineffective, plasma-derived VWF concentrates remain the mainstay of treatment in many low- and middle-income countries owing to the limited availability and high cost of recombinant products, which are largely confined to high-income settings. Consequently, plasma-derived concentrates continue to be the most accessible and commonly used therapy in developing countries.[4,5] Despite therapy, breakthrough bleeding is still common in severe cases. VWD can substantially impair quality of life (QoL), particularly in moderate to severe forms. Studies demonstrate a strong association between higher bleeding scores and reduced QoL, especially in physical and general health domains,[6] underscoring the need for holistic, patient-centered care.

In many low-resource settings, data on VWD prevalence, subtype distribution, and treatment outcomes remain scarce, limiting the development of locally relevant clinical guidelines. This study aims to address this gap by evaluating the frequency and distribution of VWD subtypes, correlating BAT scores with bleeding severity, characterizing bleeding symptoms, and assessing treatment outcomes, including changes in annual bleeding rates (ABR) and QoL, at a hemophilia treatment center (HTC) in Karachi, Pakistan. The findings aim to inform individualized and context-appropriate management strategies for VWD in resource-limited settings.

Patients & Methods

This prospective observational study was conducted at the HTC in Karachi, Pakistan, between July 2023 to February 2025. Ethical approval was obtained from the HTC Ethics Committee, and all procedures conformed to the Declaration of Helsinki. A total of 147 patients with a confirmed diagnosis of VWD were enrolled and the data was entered in World Bleeding Disorder Registry (WBDR). Individuals with other inherited bleeding disorders were excluded.

Diagnosis was established through comprehensive clinical evaluation and confirmatory laboratory investigations, including prothrombin time (PT), activated partial thromboplastin time (APTT), complete blood count (CBC), VWF: Ag, VWF: RCo, and FVIII activity assays. Blood groups were also recorded. VWF multimer analysis and genetic testing were not performed because these investigations are not routinely available in Pakistan. Consequently, subtype classification was based primarily on phenotypic and functional assays, consistent with commonly adopted approaches in resource-limited settings. All analyses were performed at the CAP- and JCI-accredited Clinical Laboratories of Aga Khan University Hospital, Karachi, using fully automated hemostasis analyzers Sysmex CS-2500i and standardized commercial reagent kits, in accordance with manufacturer protocols and the laboratory's quality assurance framework. Specimens were collected in sodium-citrate tubes, processed to obtain platelet-poor plasma by centrifugation, and analyzed promptly following internationally accepted guidelines to ensure accuracy and reproducibility. VWF: Ag was measured using an immunoturbidimetric assay, while VWF activity was assessed by the VWF: RCo assay and factor VIII activity was determined by a clotting-based assay on the same analyzer. Patients were classified as having type 3, type 1, or type 2 von Willebrand disease, or low VWF, according to the following criteria: VWF: Ag <5% for type 3, VWF: Ag 6%–30% for type 1, a VWF: RCo/VWF:Ag ratio <0.6 for type 2, and VWF: Ag 30%–50% for low VWF.

To standardize bleeding assessment, ISTH-BAT was administered at baseline. BAT scores were documented by the duty physician or attending pharmacist to ensure consistency and reproducibility. Demographic and clinical data—including age, sex, marital status, family history, and detailed bleeding history was documented using the standardized BAT, (eg, bruising,

epistaxis, gum bleeding, heavy menstrual bleeding, hemarthrosis, gastrointestinal bleeding)—were collected to capture the disease burden comprehensively. Patients were classified into VWD subtypes (type 1, 2, or 3) according to World Federation of Hemophilia guideline to enable meaningful clinical and laboratory comparisons.

Annual Bleeding Rate was calculated for each patient to quantify bleeding frequency over a 12-month observation period following treatment initiation, and if follow-up was shorter than one year, the number of events was annualized to a 365-day equivalent. Treatment regimens included tranexamic acid, desmopressin, hormonal therapy with oral contraceptive pills, iron supplements and factor replacement therapy (cryoprecipitate or VWF/FVIII concentrates). Patients were followed for twelve months post-treatment initiation. Outcomes assessed included changes in ABR and quality of life, the latter was evaluated using the EQ-5D-5L questionnaire, encompassing physical, psychological, and social domains.

Statistical analyses included Analysis of Variance ANOVA for normally distributed variables and the Kruskal–Wallis test for non-parametric data. Key comparisons were made across VWD subtypes to assess differences in BAT scores, laboratory parameters, ABR, and QoL outcomes.

Results

A total of 147 patients with confirmed VWD were enrolled in the study, with a median age of 14.5 ± 10.9 years. VWD types (1, 2, 3) distribution demonstrated a pronounced predominance of type 3 VWD, accounting for 80.9% of cases, followed by type 2 (12.2%) and type 1 (6.8%).

Bleeding manifestations varied in both frequency and severity among patients. Gum bleeding was the most common symptom, reported in 80.7% of cases, followed by heavy menstrual bleeding in females (63%), hemarthrosis (35%), hematomas (30%), bleeding following tooth extraction (29%), bruising (27.2%), and epistaxis (17.8%) (Figure 1). Figure 1 illustrates the baseline bleeding profile of patients with von Willebrand disease, reflecting disease severity prior to any therapeutic intervention.

The BAT scores showed clear differences between VWD types. BAT scores stratified patients into mild (<7; 12.9%), moderate (8-11; 7.5%), and severe (>12; 79.6%) categories. Most type 3 patients (93.3%, n = 111) had BAT scores higher than 12 and only a few type 2 patients (16.7%, n = 3) had such a high score. A similar trend was seen in bleeding episode frequency — more than 30 bleeding episodes in a year were reported in type 3 patients (n = 109) 91.6% and (n = 4) 22.2% in type 2 patients, see Table 1 for all the demographic details of our study patients.

Joint health evaluation showed statistically significant differences in joint scores between subtypes (ANOVA, $F = 2.283$, $p = .003$), with type 3 patients exhibiting markedly higher scores compared to type 1 and type 2. Type-wise comparison revealed that type 3 versus type 1 state the observation ($F = 2.102$, $p = .002$), and type 3 versus type 2 showed ($F = 2.041$, $p = .004$), indicating greater musculoskeletal involvement in type 3 due to recurrent hemarthrosis. The relatively low F-values reflect that while differences are significant, intra-group variability remains considerable. However, comparisons between type 1 and type 2 patients using the Kruskal–Wallis test revealed no significant differences in quality of life ($p = .527$), joint scores ($p = .100$), Hemophilia Joint Health

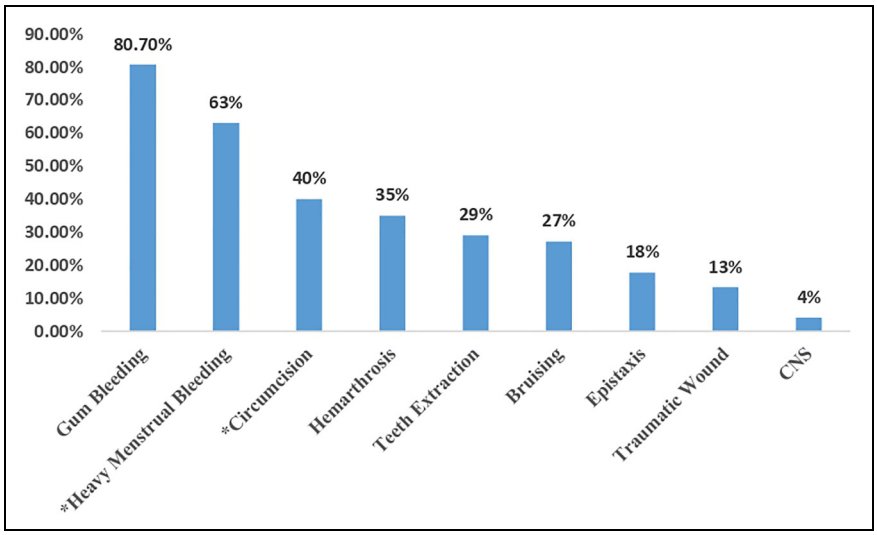

Figure 1. Baseline bleeding profile of von Willebrand Disease patients. *Circumcision calculated in male patients only. * Heavy menstrual bleeding scored in adult female.

Table 1. Demographic and Clinical Characteristics of Patients with von Willebrand Disease (n = 147).

Variable	Category / Statistic	Value
Age	Mean ± SD	14.51 ± 10.91 years
Gender	Male	57.4% (n = 84)
	Female	42.6% (n = 63)
Marital Status	Unmarried	84.2% (n = 124)
	Married	15.8%(n = 23)
VWD Type	Type 1	6.8% (n = 10)
	Type 2	12.2% (n = 18)
	Type 3	80.9% (n = 119)
Most Common Bleeding Symptoms	Gum Bleeding	80.7% (n = 119)
	Heavy menstrual bleeding (Females)	63% (n = 93)
	Joint Bleeding	35% (n = 51)
	Bruising	27.2% (n = 40)
	Epistaxis	17.8% (n = 26)
	Postpartum Hemorrhage	8% (n = 12)

Score (HJHS) (p = .126) and Functional Independence Score in Hemophilia (FISH) (p = .795).

Laboratory assessment further distinguished type 3 von Willebrand disease, with significantly lower mean hemoglobin levels (Hb: 6.2 g/dL; $p = .001$) compared with other subtypes, consistent with a higher bleeding burden and chronic blood loss. In contrast, platelet counts were comparable across all groups, reflecting the preserved platelet numbers typical of VWD pathophysiology.

Following intervention, improvements were observed across several clinical and patient-reported outcomes. Overall quality of life improved in 110 patients. Limitations in daily functioning decreased from 118 patients at baseline to 59 post-treatments. Psychological well-being also improved, with reported stress and anxiety cases declining from 100 to 30 patients. School and work attendance showed improvement, with 59 of the 90 patients reporting poor baseline attendance demonstrating better participation after treatment.

Among patients with type 3 VWD, 12 of 119 experienced a notable improvement in quality of life following targeted management at the Hemophilia Treatment Center. Table 2 provides a comparative summary of pre- and post-treatment clinical and psychosocial outcomes for the overall cohort (n = 147), with particular emphasis on changes in BAT scores following intervention.

All 147 patients received management tailored to subtype and bleeding severity, including hormonal therapy, tranexamic acid, desmopressin, cryoprecipitate, and factor replacement therapy. Among type 1 patients (n = 10), all were managed effectively with episodic treatment — primarily tranexamic acid, oral contraceptive pills and supportive measures — and none required factor replacement or CP. In type 2 patients (n = 18), most were treated with tranexamic acid, hormonal therapy, and supportive care; factor replacement was required in 4 patients (22.2%) for moderate to severe bleeds, and CP was used in 3 patients (16.7%) during procedures or acute bleeds. In contrast, type 3 patients (n = 119) represented the most treatment-intensive group. Factor replacement was administered to 112 patients (94.1%), often in higher doses and repeated infusions, particularly for joint bleeds (n = 42) and severe mucosal bleeding such as epistaxis, gum bleeding (n = 96). CP was used in 87 patients (73.1%) either when factor concentrates were unavailable or as part of acute bleed management.

Following targeted management, patients across all subtypes demonstrated a reduction in ABR. Among type 3 patients (n = 119) ABR decreased from a median of >30 episodes/year in 109 patients (91.6%) at baseline to <10 episodes /year in 68 patients (57.1%) after treatment, although recurrent bleeds persisted in some patients with high-severity disease. Improved bleed control translated into fewer joint bleeds and stabilization of joint scores, particularly in type 3 patients with prior hemarthrosis. The markedly lower hemoglobin levels in type 3 patients (mean 6.2 g/dL, p = .001) leading to iron deficiency anemia in these patients were treated with IV iron sucrose and folic supplements, see Table 2.

Discussion

This study aimed to evaluate the clinical spectrum, subtype distribution, bleeding severity, and treatment outcomes in patients diagnosed with VWD in a real-world clinical setting in Pakistan. Our cohort demonstrated a striking predominance of type 3 VWD (80.9%), contrasting with global epidemiological patterns where type 1 VWD is most common, accounting for up to 70%–80% of cases, while type 3 typically represents less than 5%.[7,8] This discrepancy is consistent with our last study on VWD[1] and data from other South Asian and Middle Eastern countries, where high consanguinity rates contribute to autosomal recessive transmission and higher frequencies of type 3

Table 2. Pre- and Post-Treatment Clinical and Psychosocial Outcomes in VWD Patients (n = 147).

Variable	Pre-Treatment (Mean ± SD Or % Patients)	Post-Treatment (Mean ± SD Or % Patients)	p-Value
Annualized Bleeding Rate (ABR)	28.6 ± 6.3 episodes/year (median >30; 91.6% of type 3 > 30/year)	9.8 ± 4.2 episodes/year (57.1% of type 3 < 10/year)	<.001
Age (Years)	14.5 ± 10.9 (n = 147)	15.5 ± 11.9 (n = 147)	-
BAT score			<.001
Mild (<7)	19 (12.9%)	48 (~32.7%)	
Moderate (8-11)	11 (7.5%)	34 (~23.1%)	
Severe (>12)	117 (79.6%)	65 (~44.2%)	
Joint bleeds / year	6.8 ± 3.1	2.9 ± 1.8	.003*
Joint score (overall)	8.1 ± 2.4	6.2 ± 1.9	.002
Hemoglobin (g/dL)	6.2 ± 1.1	9.4 ± 1.3	.001
HJHS	10.4 ± 3.7	7.6 ± 3.2	.005
FISH	25.1 ± 3.9	27.4 ± 3.3	.041
Psychological status (anxiety score**)	8.7 ± 2.6	5.2 ± 1.8	<.001
Quality of Life (EQ-5D)			
Overall improvement in quality of life	147 (baseline)	110	
Fewer limitations in daily functioning	118 (had functional limitations)	59	
Improved psychological well-being	100 (with anxiety/stress)	30	
Improved school/work attendance	90 (had poor attendance)	59	
Significant QoL improvement in Type 3	119 (total Type 3 patients)	12	

VWD.[9,10] For example, a study from India reported type 3 prevalence at 67% among clinically significant VWD patients,[11] while data from Iran and Saudi Arabia also highlight type 3 as the dominant subtype in tertiary care populations.[12,13] Our findings therefore reinforce the genetic and epidemiological distinctions between LMICs and Western population, where milder type 1 disease predominates due to better recognition and screening.

The mean age of 14.5 years in our study aligns with the early-onset diagnosis reported in other LMIC-based studies,[8,12] reflecting both the younger demographic profile of these populations and the early presentation of severe type 3 disease. The observed male predominance is noteworthy but likely reflects referral bias, as VWD affects both sexes equally. However, women with heavy menstrual bleeding may remain underdiagnosed due to sociocultural barriers in seeking care for gynecological symptoms.[14]

Bleeding patterns in our cohort were predominantly characterized by gum bleeding, heavy menstrual bleeding, and hemarthrosis, findings that are consistent with previous reports from South Asian populations.[11,15] In contrast, Western cohorts more commonly report epistaxis and easy bruising as dominant manifestations, particularly in patients with type 1 von Willebrand disease.[16] The high prevalence of heavy menstrual bleeding among females in our study highlights the substantial impact of VWD on gynecologic and reproductive health, contributing to iron deficiency anemia, school absenteeism, and reduced quality of life.[17] Although relatively uncommon, severe complications such as intracranial hemorrhage underscore the significant morbidity and potential mortality associated with untreated type 3 VWD, in line with observations from Iran and India.[12,15]

The BAT demonstrated utility in stratifying bleeding severity, with 93.3% of patients with type 3 VWD scoring >12, compared with 16.7% of those with type 2 disease. This pattern is consistent with international studies that have validated the BAT as a tool for assessing bleeding burden and guiding clinical decision-making.[18,19] The high baseline bleeding frequency observed in our cohort—exceeding 30 bleeding episodes per year in more than 90% of patients with type 3 VWD—highlights the substantial disease burden in this group. While formal prophylaxis strategies were not uniformly applied in our setting, these findings align with reports from European and North American cohorts and underscore the need for further evaluation of optimal management approaches for severe VWD in resource-limited settings.[20,21]

Joint health evaluation revealed significantly higher joint scores in type 3 patients, reflecting recurrent hemarthroses and musculoskeletal morbidity. These findings mirror studies from India and Iran, where delayed access to factor concentrates leads to higher rates of hemarthropathy in severe VWD.[11,12] In contrast, studies from Europe and North America report fewer joint bleeds in VWD patients, largely due to earlier diagnosis and availability of prophylactic factor replacement therapy.[21]

Laboratory findings showed markedly lower hemoglobin in type 3 patients (mean 6.2 g/dL), consistent with chronic blood loss and iron deficiency anemia, a pattern also documented in LMIC cohorts.[9,15] Platelet counts remained normal across subtypes, in line with the pathophysiology of VWD.[22]

Treatment outcomes in our study underscore the value of comprehensive, multidisciplinary care delivered through Hemophilia Treatment Centers (HTCs). In patients with type 1 and most type 2 VWD, bleeding episodes were generally managed with antifibrinolytic agents, hormonal therapy, and supportive measures, whereas patients with type 3 disease required more intensive interventions, including factor replacement and cryoprecipitate.

Although international guidelines advocate prophylactic regimens to reduce long-term morbidity in severe VWD, the implementation of such strategies in low-resource settings remains challenging because of limited factor availability and cost constraints. Consequently, treatment approaches in our setting differ from those in high-income countries, where the use of cryoprecipitate is discouraged due to infection risks and recombinant VWF concentrates are preferred.[23,24]

Within these constraints, management in our cohort was associated with reductions in annual bleeding rates and improvements in hemoglobin levels, as well as better patient-reported outcomes, including quality of life, functional capacity, and school or work attendance. These observations are in line with international registry data suggesting that structured, HTC-based care is associated with improved clinical and psychosocial outcomes in patients with VWD[25,26]

In conclusion, this study supports the utility of BAT scores as a marker of bleeding severity in patients with von Willebrand disease and highlights the substantial clinical and psychosocial burden associated with severe disease. Our findings emphasize the importance of a multidisciplinary care model that integrates medical management with functional and psychological support, particularly within Hemophilia Treatment Centers. While formal prophylactic strategies were not uniformly applied in our setting, the observed disease burden in severe VWD underscores the need for further evaluation of optimal management approaches. Future studies with longitudinal follow-up are warranted to assess the impact of prophylaxis and comprehensive care on joint health, hemoglobin stability, and psychosocial outcomes, as well as to examine the feasibility and cost-effectiveness of such approaches in resource-limited settings.

Limitations

The study is limited by its single-center design, lack of multimer analysis and genetic testing to accurately diagnose types and sub types of VWD and short follow-up, which may restrict generalizability and long-term outcome assessment.

Future Directions

Long-term follow-up studies are needed to evaluate treatment outcomes, quality of life, and complications such as joint damage. Genetic analysis should be explored to establish genotype–phenotype correlations and support personalized management. Particular emphasis is required on the role of prophylaxis in type 3 VWD patients, given their high bleeding burden and risk of musculoskeletal damage, while simultaneously addressing the challenges of cost and limited factor availability in low-resource settings. Efforts are also required to assess the cost-effectiveness and accessibility of therapies, and awareness and training programs for healthcare providers and families can help reduce diagnostic delays and improve timely interventions.

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Ethical Approval

This study was approved by the ethics committee of the HWSK/16-263/ 01-2022 in accordance with the declaration of Helsinki. Confidentiality of participants and privacy was maintained during the data collection process.

Consent

Written informed consent was obtained from the participants of the study for their anonymized information to be published.

Authors Contributions

MB conceived the idea of this study and wrote the manuscript. MU did data collection and physiotherapy assessment. HQ did data analysis and helped with writing along with NK. RA helped in overall execution of this study and counseling along with MB & NK All authors have read and approved the manuscript.

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Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Data Availability

The Dataset used and/or analyzed during the current study is available from the corresponding author on reasonable request.

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