Research Article

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Frequency of von Willebrand Disease Among Children With Bleeding Disorders at a Tertiary Care Hospital

Muhammad Anees Farooqi
Department of Paediatric Medicine, The Children's Hospital and University of Child Health Sciences, Lahore, Pakistan; dr.anees.farooqi@gmail.com

Ahmad Yar
Department of Paediatric Medicine, The Children's Hospital and University of Child Health Sciences, Lahore, Pakistan

Muhammad Usman Javed
Department of Pathology, Sahara Medical College, Narowal, Pakistan

Afsheen Batool Raza
Department of Paediatric Medicine, The Children's Hospital and University of Child Health Sciences, Lahore, Pakistan

Safwan Ahmad
Department of Paediatric Haematology and Oncology, The Children's Hospital and Institute of Child Health, Multan, Pakistan

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Abstract

von Willebrand disease (VWD) is the most common inherited bleeding disorder and an important cause of mucocutaneous bleeding in children. Its reported frequency varies considerably among clinical populations with bleeding disorders, highlighting the importance of region-specific investigations. The objective of this study was to determine the frequency of VWD among children presenting with bleeding disorders at a tertiary care hospital. This descriptive cross-sectional study was conducted in the Department of Haematology and Oncology, The Children's Hospital and University of Child Health Sciences, Lahore, from May to November 2025. A total of 143 consecutively recruited children aged 14 years or younger with clinically diagnosed bleeding disorders were evaluated. Venous blood samples were collected for von Willebrand factor ristocetin cofactor activity testing, and a value below 30 IU/dL was considered indicative of VWD under the study's operational definition. Data were analysed using SPSS version 27.0, with descriptive statistics and chi-square tests for selected associations. According to the study criterion, VWD was identified in 19 of 143 children, giving a frequency of 13.3% (95% confidence interval: 8.2–19.9%). Among the 19 cases, 13 (68.4%) were reported as type 1, five (26.3%) as type 2, and one (5.3%) as type 3. A positive family history of bleeding and blood group O were associated with higher observed frequencies of VWD, with reported p-values of 0.01 and 0.03, respectively. The findings support considering VWD during the assessment of children with bleeding disorders, particularly when the family history is suggestive. However, a single ristocetin cofactor activity result does not provide complete diagnostic or subtype confirmation; comprehensive laboratory assessment remains necessary for accurate classification and clinical management.

Keywords: bleeding disorders, children, von Willebrand disease, von Willebrand factor, ristocetin cofactor activity, family history

1. INTRODUCTION

Bleeding disorders comprise a heterogeneous group of conditions associated with recurrent or lifelong bleeding tendencies. They may arise from quantitative or qualitative abnormalities in coagulation factors, platelet number, platelet function, or proteins involved in primary haemostasis. Inherited bleeding disorders present with a range of clinical manifestations, including bruising, epistaxis, mucosal haemorrhage, prolonged bleeding after injury, and, in severe cases, substantial haemorrhagic complications. Their early recognition is particularly important in children because repeated bleeding episodes can interfere with normal development, daily activities, and access to appropriate medical or surgical treatment [1]. von Willebrand disease (VWD), the most common inherited bleeding disorder, is caused by a deficiency or functional abnormality of von Willebrand factor (VWF), a circulating glycoprotein that facilitates platelet adhesion at sites of vascular injury and protects coagulation factor VIII from premature degradation [2].

VWD is conventionally classified into three principal types. Type 1 is characterised by a partial quantitative deficiency of VWF; type 2 includes several qualitative functional abnormalities; and type 3 is associated with a virtually complete absence of circulating VWF and usually represents the most severe phenotype. The presence and severity of bleeding may differ markedly within and between these categories. Clinical diagnosis therefore requires interpretation of the personal and family bleeding histories alongside appropriate laboratory investigations, rather than reliance on a single clinical feature or isolated test result [3]. This distinction is particularly relevant when evaluating children whose bleeding symptoms may be subtle, intermittent, or initially attributed to other childhood conditions.

The treatment of VWD depends on the disease type, severity and anatomical location of bleeding, individual characteristics, and the anticipated response to available therapies. Desmopressin, a synthetic vasopressin analogue, can increase endogenous circulating levels of VWF and factor VIII in selected patients, particularly those with type 1 VWD and some forms of type 2 disease. Other management approaches include antifibrinolytic medications, local haemostatic measures, appropriate care around surgical or dental procedures, and hormonal interventions when menstrual bleeding becomes relevant. Patients with severe disease, particularly type 3 VWD, may require VWF-containing concentrates to prevent or control haemorrhage. Selection of treatment should be individualised and supported by the established disease subtype and clinical response [4, 5].

The clinical burden of VWD extends beyond the occurrence of isolated haemorrhagic episodes. Recurrent mucocutaneous bleeding, iron-deficiency anaemia, joint-related complications in severe cases, and persistent uncertainty about the cause of bleeding can affect daily activities and healthcare use. Delayed recognition may also lead to avoidable investigations and inappropriate management of bleeding events. Systematic reviews and clinical studies have described differences in the reported disease burden, healthcare resource use, and diagnostic experiences across healthcare settings [6, 7]. Paediatric studies likewise demonstrate that the frequency and clinical features of bleeding may differ by age and sex, emphasising the need for careful assessment of affected children [8]. Evidence of bleeding episodes before formal diagnosis further supports the value of timely evaluation and access to specialist care [9].

The proportion of VWD cases among patients referred with bleeding disorders differs substantially across populations. In a national referral centre in Iraq, VWD accounted for 43.9% of children evaluated for inherited bleeding disorders, with type 3 forming a substantial proportion of the reported VWD cases [1]. In contrast, a hospital-based investigation in eastern India identified VWD in 4.76% of patients with inherited bleeding disorders [10]. The latter study included individuals across a broader age range and thus is not directly equivalent to a paediatric-only sample. Differences in referral practices, inclusion criteria, case mix, availability of specific laboratory assays, and the diagnostic definition employed can influence the proportions observed in individual studies. Consequently, an estimate obtained in one specialist centre should not be assumed to represent the underlying community prevalence or the experience of another hospital.

Determining the local frequency of VWD is especially relevant in Pakistan, where access to specialist haemostasis investigations may vary across institutions. An effective evaluation pathway must balance the need to identify affected children against laboratory costs, the availability of trained personnel, and the clinical value of additional testing. Inadequate investigation can leave children with unresolved bleeding complaints, while indiscriminate testing may use limited clinical resources without proportionate diagnostic benefit. Evidence from a tertiary care paediatric population can help describe the children presenting for assessment, indicate the frequency of reduced VWF activity under a specified laboratory criterion, and inform decisions about further diagnostic assessment. Such hospital-based findings should nevertheless be interpreted within the clinical setting from which the patients were recruited.

The considerable variation in published frequencies, together with the limited institution-specific evidence from Pakistan, prompted the present study. In addition to describing VWD frequency and reported subtype distribution, the investigation examined selected demographic and clinical characteristics of children referred with bleeding disorders. The purpose was to provide locally relevant evidence for diagnostic consideration, while recognising that definitive VWD diagnosis and subtype classification require a broader clinical and laboratory assessment than a single functional assay. The objective of this study was to determine the frequency of von Willebrand disease among children with bleeding disorders

attending a tertiary care hospital in Lahore, Pakistan.

2. METHODOLOGY

This descriptive cross-sectional investigation was conducted in the Department of Haematology and Oncology at The Children's Hospital and University of Child Health Sciences, Lahore, Pakistan, from May to November 2025. The calculated sample size was 143 children, based on an expected VWD frequency of 4.76%, a 95% confidence level, and a margin of error of 3.5%. Participants were selected through non-probability consecutive sampling from children attending the paediatric haematology service with clinically diagnosed bleeding disorders. The study focused on the frequency of VWD within this referred clinical population, rather than on an estimate of disease prevalence among all children living in Lahore or Pakistan.

Children of either sex aged 14 years or younger who met the study's operational definition of a bleeding disorder were eligible for enrolment. Patients with clinical and laboratory findings characteristic of acquired bleeding disorders were excluded. The same eligibility criteria were applied throughout recruitment. Written informed consent was obtained from a parent or legal guardian before any study-related procedures. Each participant underwent a structured clinical assessment and relevant demographic information was recorded on a standardised study proforma. Recorded variables included age, sex, ABO blood group, and family history of bleeding, alongside the available laboratory observations and clinical details relevant to suspected inherited bleeding disorders.

A 5-mL venous blood sample was collected aseptically into citrate-containing specimen tubes and transported to the hospital laboratory for testing. Plasma was prepared in accordance with laboratory procedures, and VWF ristocetin cofactor activity was measured. Under the prespecified operational definition used for this study, a ristocetin cofactor activity value below 30 IU/dL was considered indicative of VWD. Laboratory findings were reviewed by an experienced consultant and entered in the structured proforma for analysis. The original study material does not specify the complete set of confirmatory assays used to determine VWD subtypes; consequently, the reported subtype distribution is presented as recorded in the study and should not be interpreted as proof that every subtype was independently confirmed by comprehensive laboratory testing.

Data were entered and analysed using the Statistical Package for the Social Sciences (SPSS), version 27.0. Continuous variables, including age and laboratory measurements when available, were described using means and standard deviations. Categorical variables, including sex, ABO blood group, family history of bleeding, VWD status, and recorded disease subtype, were summarised as frequencies and percentages. The primary outcome was the proportion of eligible children meeting the study's VWD criterion. A 95% confidence interval was calculated to reflect uncertainty around the estimated frequency. Associations between VWD status and selected categorical characteristics were assessed using chi-square tests, and the study treated p-values of 0.05 or less as statistically significant. Results from small subgroups were interpreted cautiously because only 19 children met the operational VWD criterion. The aggregate findings were presented in tables to facilitate interpretation and comparison across participant characteristics.

3. RESULTS

A total of 143 children with clinically identified bleeding disorders were enrolled. Their mean age was 7.8 ± 3.4 years, and the age range was 1–14 years. Among the participants, 83 (58.0%) were boys and 60 (42.0%) were girls. Blood group O was the most common ABO group, accounting for 66 children (46.2%), followed by groups A, B, and AB. A positive family history of bleeding was reported in 41 (28.7%) children, while the remaining participants had no reported positive family history. Table 1 presents the demographic characteristics and clinical information recorded for the full study population, including the distribution of sex, blood groups, and family history.

Table 1. *Demographic and Clinical Characteristics of the Study Population*

Parameter	Total (n = 143)
Mean Age (Years)	7.8 ± 3.4
Age Range (Years)	1–14
Male, n (%)	83 (58.0%)
Female, n (%)	60 (42.0%)
Blood Group O, n (%)	66 (46.2%)
Blood Group A, n (%)	39 (27.3%)
Blood Group B, n (%)	28 (19.6%)
Blood Group AB, n (%)	10 (6.9%)
Positive Family History, n (%)	41 (28.7%)

Using the study's operational criterion of ristocetin cofactor activity below 30 IU/dL, VWD was identified in 19 of 143 children. The resulting frequency was 13.3%, with a 95% confidence interval of 8.2–19.9%. The remaining 124 children (86.7%) did not meet this laboratory-based study criterion. Among the 19 identified cases, 13 (68.4%) were recorded as type 1, five (26.3%) as type 2, and one (5.3%) as type 3. Accordingly, type 1 was the most frequently recorded subtype in this clinical population. Table 2 summarises the proportions with and without VWD under the study definition and the recorded subtype distribution within the 19 cases. The subtype proportions refer to the children classified as having VWD, rather than to the entire sample of 143 children.

Table 2. *Frequency and Subtype Distribution of von Willebrand Disease*

Outcome	Frequency (n)	Percentage
VWD Present	19	13.3%
VWD Absent According to Study Criteria	124	86.7%
Total Participants	143	100.0%
Type 1 Among VWD Cases	13	68.4%
Type 2 Among VWD Cases	5	26.3%
Type 3 Among VWD Cases	1	5.3%

A positive family history of bleeding was associated with a higher reported frequency of VWD than the absence of such a history (29.3% versus 6.9%, respectively; reported p = 0.01). Similarly, VWD was more frequently recorded among children with blood group O than among children with non-O blood groups (19.7% versus 7.8%, respectively; reported p = 0.03). These associations are displayed in Table 3. Neither sex (reported p = 0.41) nor age group (reported p = 0.67) showed a statistically significant association with the laboratory-based VWD classification in the original analysis. As the investigation was observational and cross-sectional, the group differences describe associations within the recruited children and do not establish causal relationships.

Overall, 13.3% of the evaluated children met the operational study definition of VWD, with type 1 constituting the largest recorded subgroup. The tabulated results also indicate a higher frequency among children with a positive family history and among those with blood group O. The interpretation of these findings depends on the referral setting, the selected diagnostic threshold, and the available laboratory investigations. The relatively small number of VWD cases also limits the precision of comparisons between subgroups and highlights the importance of appropriately considering uncertainty when interpreting the observed percentages.

Table 3. *Associations Between Selected Characteristics and von Willebrand Disease*

Characteristic	Reported VWD Frequency	p-value
Positive Family History	29.3%	0.01
Negative Family History	6.9%	—
Blood Group O	19.7%	0.03
Non-O Blood Groups	7.8%	—

4. DISCUSSION

The present study examined the frequency of VWD among 143 children aged 14 years or younger who attended a tertiary paediatric haematology service in Lahore with bleeding disorders. Nineteen children met the study's laboratory-based VWD criterion, corresponding to an observed frequency of 13.3% (95% confidence interval: 8.2–19.9%). This proportion demonstrates that VWD merits consideration when children present with recurrent, unexplained, or otherwise suggestive bleeding complaints. The disorder may manifest through mucocutaneous bleeding ranging from mild, intermittent symptoms to clinically important haemorrhage, and the opportunity to establish a diagnosis may depend on the clinical history and local availability of haemostasis testing. Published work has also identified considerable variation in recognition and clinical management of VWD between healthcare settings [6]. These observations support careful interpretation of the findings within the present hospital population rather than direct extrapolation to the general community.

Comparison with other published investigations illustrates the influence of patient selection and diagnostic setting. The Iraqi paediatric referral-centre study reported VWD in 43.9% of patients with inherited bleeding disorders, while the eastern Indian clinical study identified VWD in 4.76% of a more broadly aged group with inherited bleeding disorders [1, 10]. The observed frequency in Lahore falls between these proportions, although the populations are not directly comparable. A separate Saudi Arabian clinical study further illustrates the range of VWD presentations encountered in specialist services and the importance of combining clinical history with appropriate laboratory interpretation [11]. Differences in referral thresholds, sample composition, disease awareness, diagnostic assays, and availability of specialised

investigations may all influence reported frequencies. Accordingly, hospital-based findings should be interpreted as the frequency among patients assessed under specified conditions, not as a population prevalence estimate.

Among the 19 children identified in this investigation, type 1 VWD was the most frequently recorded subtype, accounting for 13 cases (68.4%). Type 2 was recorded in five children (26.3%) and type 3 in one child (5.3%). This distribution may be compatible with the commonly reported predominance of quantitative VWF deficiency in many clinical populations, but its interpretation requires particular caution. Reliable distinction among VWD types depends on the relationship between VWF antigen, platelet-dependent VWF activity, factor VIII activity, and, where indicated, specialised studies of VWF multimers, collagen binding, or other functional characteristics. The present description of a ristocetin cofactor threshold alone does not establish how the specific subtypes were confirmed. Published proposals for consistent VWD definitions and diagnostic guidance emphasise that disease classification should be based on appropriately selected investigations and clearly defined criteria [2, 12]. The recorded subtype proportions are therefore descriptive observations from this hospital sample, rather than independent evidence of the diagnostic accuracy of subtype classification.

The participants were between 1 and 14 years old, with a mean age of 7.8 $\pm$ 3.4 years; 83 were male and 60 were female. Neither sex nor age group was significantly associated with VWD classification according to the p-values reported in the original study. These findings do not imply that demographic characteristics have no relationship with the clinical presentation of inherited bleeding disorders in larger populations. Differences in exposure to haemostatic challenges, the timing of recognition, and variations in bleeding phenotype may affect the clinical populations being investigated. Research on paediatric VWD has shown differences in bleeding and treatment patterns between young boys and girls [8], while clinical reviews describe substantial heterogeneity in presentations and laboratory findings [3]. The modest number of children classified as having VWD in the current study reduces the ability to detect smaller demographic differences, and the results should be considered in the context of the specific referral population.

A positive family history of bleeding was associated with a higher reported frequency of VWD. The recorded frequencies were 29.3% among children with a positive family history and 6.9% among those without one. This difference underscores the clinical value of obtaining a detailed family history when investigating suspected inherited bleeding disorders. Information about bleeding after injury, surgery, childbirth in affected family members, dental procedures, or recurrent mucosal haemorrhage may help identify families requiring particular attention. Nevertheless, the absence of an identified family history does not exclude VWD because relatives may have mild manifestations, remain undiagnosed, or not recognise bleeding symptoms as abnormal. International diagnostic guidelines recommend structured evaluation of the bleeding phenotype together with appropriate laboratory investigations, rather than reliance on family history as an isolated diagnostic criterion [2]. Consequently, the observed association can inform clinical assessment but does not replace individual testing or establish that family history itself causes the disorder.

Blood group O was also associated with a greater recorded frequency of VWD in this study, with 19.7% of children in the O group and 7.8% in the combined non-O groups meeting the study criterion. This pattern is biologically plausible because ABO blood group influences circulating VWF concentrations. Evidence from laboratory research indicates that people with group O generally have lower VWF levels than people with non-O blood groups [13]. However, ABO group is not an acquired clinical exposure, and the observed association does not establish that group O causes inherited VWD. Nor should blood group be used independently to classify a child as affected or unaffected. Current diagnostic approaches emphasise assessment of the bleeding history and specific VWF investigations rather than blood-group-specific diagnostic thresholds [2, 14]. The finding in this clinical sample warrants consideration in future investigations of ABO distribution and VWF activity among children, including studies with larger numbers and complete diagnostic testing.

The choice of laboratory assay has important implications for interpreting the findings. The study operationally identified VWD when VWF ristocetin cofactor activity was below 30 IU/dL. Although this assay measures a platelet-dependent functional property of VWF and has long been used in clinical investigations, the result can be affected by analytical variability and assay-specific limitations. Research evaluating ristocetin-dependent cofactor testing has shown that interpretation based on a single activity measure may be problematic in some patients [15]. Broader laboratory reviews likewise emphasise that test selection depends on available resources, local laboratory capabilities, and the clinical question being addressed [14]. In many cases, VWF antigen, an appropriate platelet-dependent VWF activity assay, and factor VIII activity are needed for the initial assessment, while further investigations are selected according to the suspected subtype and clinical presentation [2].

The threshold itself also requires careful interpretation. The investigation used a value below 30 IU/dL as its criterion, whereas contemporary diagnostic recommendations consider clinical bleeding symptoms, VWF levels, testing context, and thresholds relevant to the suspected disease category. A low VWF activity result can support clinical suspicion, but a comprehensive evaluation remains necessary to determine whether the patient meets diagnostic criteria and to characterise the underlying defect. A systematic review of VWF levels in VWD diagnosis has highlighted the clinical importance of laboratory cut-offs and their relationship with bleeding manifestations [16]. In the current study, the reported 13.3% is therefore most appropriately described as the proportion of referred children meeting the specified laboratory criterion. It

should not be treated as a definitive estimate of fully confirmed VWD in the wider paediatric population without additional supporting investigation.

These results may inform everyday clinical practice in paediatric units where children present with epistaxis, easy bruising, prolonged bleeding after minor injuries, or bleeding associated with dental or surgical procedures. A structured assessment incorporating personal bleeding history, family history, relevant examination findings, and carefully selected laboratory tests can help identify children who may benefit from specialist evaluation. Clinical guidance for the general medical assessment of VWD reinforces the importance of considering this diagnosis in patients with otherwise unexplained bleeding symptoms [17]. Difficult cases, including those with inconsistent clinical and laboratory findings, may require repeat testing or additional specialised assessment before decisions are made about disease classification or management [18]. In confirmed VWD, management should be matched to the subtype, bleeding severity, and clinical circumstances, rather than initiated solely from an abnormal screening result [4, 5].

The clinical implications also extend to communication with families and long-term care. Children and their caregivers may experience repeated healthcare visits and uncertainty before an inherited bleeding disorder is recognised. Timely specialist assessment, clear counselling about bleeding precautions, and appropriate plans for future medical or dental procedures may improve continuity of care. Published work on patient-centred VWD care has described the consequences of delayed diagnosis, uneven access to services, and the importance of incorporating patient needs into management decisions [19]. Although the present study did not measure treatment outcomes, quality of life, or healthcare resource utilisation, these considerations provide context for why improved access to appropriate diagnostic services may matter for families attending a tertiary care centre.

Several limitations should be acknowledged when interpreting the study. First, its cross-sectional design and recruitment from a single tertiary hospital limit the generalisability of the observed frequency to all children in Lahore or Pakistan. Second, the number of children meeting the VWD criterion was comparatively small, which restricts the precision of subtype estimates and subgroup comparisons. Third, the described laboratory definition relied on one ristocetin cofactor activity threshold, and the available methods do not fully document confirmatory investigations required to distinguish the VWD subtypes accurately. Fourth, the reported associations with family history and ABO blood group are observational and do not establish causal effects. The source report also provides percentages and p-values for subgroup analyses without participant-level statistical output, limiting independent assessment of the originally reported statistical procedures. These considerations support larger multicentre investigations with standardised bleeding assessments and more complete laboratory characterisation of VWF.

Overall, the study identified reduced VWF ristocetin cofactor activity consistent with its operational VWD criterion in 19 of 143 children presenting with bleeding disorders. Type 1 formed the largest recorded subtype category, and positive family history and blood group O were associated with higher observed frequencies in the clinical sample. The findings reinforce the role of VWD in the differential diagnosis of persistent or unexplained childhood bleeding, while also demonstrating the importance of clearly specified laboratory definitions and full diagnostic confirmation. Future prospective and multicentre investigations should examine the reliability of diagnostic pathways, assess appropriately defined subtypes, and clarify the clinical implications of VWF activity testing in different paediatric populations.

5. CONCLUSION

Among 143 children with bleeding disorders attending a tertiary paediatric haematology centre in Lahore, 19 (13.3%) met the study's operational criterion for von Willebrand disease. Type 1 was the most frequently recorded subtype, and positive family history of bleeding and blood group O were associated with higher observed frequencies. The findings highlight the importance of considering VWD in children who experience persistent, recurrent, or otherwise unexplained mucocutaneous bleeding. A detailed personal and family history may help identify children who warrant further assessment, particularly in clinical environments where specialist investigations are limited. Nevertheless, neither family history nor ABO blood group can substitute for appropriate diagnostic testing, and the restricted laboratory criterion used in this study is insufficient by itself for comprehensive subtype confirmation. The estimated frequency should therefore be interpreted in the context of the hospital referral population, sample size, and available diagnostic methods. Larger multicentre studies incorporating standardised clinical assessment, confirmatory VWF testing, and clearly specified laboratory definitions are recommended to provide more accurate regional estimates and to support better diagnosis and management of inherited bleeding disorders in children in Pakistan.

Author Contributions

All authors contributed equally to the conception and design of the study and to the preparation or critical revision of the manuscript. All authors reviewed and approved the final manuscript and accept accountability for the accuracy and

integrity of their respective contributions.

Conflicts of Interest

The authors declare that they have no financial or non-financial conflicts of interest relevant to the research, authorship, or publication of this article.

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Ethics Approval and Informed Consent

Written informed consent was obtained from the parents or legal guardians of all enrolled children before participation.

Data Availability

Requests regarding access to the study data may be directed to the corresponding author.

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