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Bleeding disorders in Saudi Arabia, causes and prevalence: a review

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As bleeding disorders are a worldwide health concern, Saudi Arabia is experiencing a notable prevalence of such disorders. Studying the frequency and cause of hemostatic disorders is the key to successful clinical interventions and instigating effective public policies that limit the spread of such disorders. The current review aims to highlight the major findings of the body of literature that has investigated the causes, prevalence, and major challenges associated with bleeding disorders in the country. The current review summarizes the major findings of different studies that have been conducted in Saudi Arabia regarding different bleeding disorders.

Multiple causes and symptoms of bleeding disorders have been reported by different studies. Some studies investigated the genetic aspect of bleeding disorders and revealed specific mutations in coagulation factor genes influencing the symptoms of different bleeding disorders. Moreover, rare bleeding disorders such as Glanzmann thrombasthenia and Henoch–Schonlein purpura, have been reported in different regions of Saudi Arabia. Combining clinical presentations, genetic factors, and epidemiological data, the current review of the literature provides a comprehensive insight into bleeding disorders in the kingdom. This will help in advancing the diagnostic capabilities and genetic counseling enhancing management strategies and therapeutic interventions benefiting bleeding disorder patients and the kingdom.

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Introduction

Globally, bleeding disorders constitute a major health concern affecting people of different backgrounds, ethnicities, and ages. These disorders represent a complicated challenge for researchers and healthcare systems. Understanding the epidemiology and causes of bleeding disorders is important for efficient therapeutic interventions and the strategies of public health institutions. Multiple researchers in Saudi Arabia have highlighted the cause and the frequency of such medical conditions [1,2]. Their published literature concluded that platelet disorders, von Willebrand disease (vWD), and hemophilia are some of the most prevalent bleeding disorders in the kingdom [3]. As the genetic factor is one of the major causes of bleeding disorders, consanguinity magnifies the prevalence of hereditary bleeding disorders among the Saudi population [4]. Such cultural practice elevates the risk of inheriting defective genes that could be associated with the development of bleeding disorders and other hereditary illnesses. Strategies to tackle the rise of bleeding disorders in the country must deal with different sociocultural factors including consanguinity [5]. For instance, awareness about the hereditary nature of bleeding disorders could be raised through premarital screening and other counseling services providing the public with a comprehensive understanding of the risk of not only bleeding disorders but also other hereditary diseases [6].

Several studies have identified specific genetic mutations that could lead to defective expression of coagulation factors giving the clinical presentations of hemophilia and other bleeding disorders among Saudis [7]. The constant evolution of molecular tools has enhanced diagnostic techniques as well as early detections improving therapeutic interventions [8]. A comprehensive understanding of the status of bleeding disorders in the kingdom will enhance therapeutic intervention, early detection, and better management of the resources allocated for the disease. Altogether could lead to enhancing the quality of life for individuals affected by bleeding disorders in the Kingdom.

Most prevalent bleeding disorders

Al-Fawaz *et al.* in 1996 conducted a study in Riyadh and they described that hemophilia is the most prevalent bleeding disorder in their cohort followed by qualitative platelet disorders, Von Willebrand's disease, Glanzmann's thrombasthenia then Bernard–Soulier disease. The study contained 168 participants where hemophilia A was prevalent in 41 participants whereas hemophilia B affected 16 participants.

Thirt-three study participants were presented with qualitative platelet disorders with an elevation in defective

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platelet aggregation response among this group. The second most prevalent coagulation factor deficiency, after hemophilia, in this study was Von Willebrand's disease where 25 participants had the disease. vWF affected male and female individuals in an equal ratio in this study. The rest of the participants had other types of coagulation factor deficiencies.

Glanzmann's thrombasthenia affected 18 participants who had a history of mucocutaneous bleeding. Only five participants had Bernard–Soulier disease. They were diagnosed based on having giant platelets with abnormal function in their blood films. Fourteen participants had normal calculation profiles except for prolonged bleeding time tests [9].

Deficiency of coagulation factors in Saudi young adults

Estimating coagulation factor deficiency among young adults in the country was the target of another national survey that was performed by (Alsaleh *et al.*, 2020). This study involved 848 young adults who at least have reported one bleeding symptom. Laboratory testing was performed on samples only from 640 of these participants. 54.2% were male individuals whereas 45.7% were female individuals. The laboratory testing for coagulation and platelet functions showed abnormalities in APTT (63.7%), PT (35.9%), PFA-ADP (15.2%), and PFA-EPI (11%). Defective levels of other coagulation factors such as F-X (1.8%), FV-II (3.1%), F-V (26.1%), F-II (3.3%), vWF activity (8%), F-IX (7.6%), and F-VIII (7.4%) have also been reported. Notably, 90% were classified as patients with bleeding of unknown cause (BUC) as their lab findings for coagulation studies were normal. Three patients, who manifested the symptoms of Glanzmann's thrombasthenia and Bernard–Soulier syndrome, were suspected to have platelet dysfunction (PPD) as their samples abnormally reacted to agonists during their platelet function testing. This study has also investigated the levels of hemoglobin and ferritin among participants and found variations between genders. Researchers in the study correlated iron deficiency anemia (IDA) and abnormal factor levels and they noticed low factor IX ranking and low ferritin levels only in one patient (2.3%) indicating a limited connection in male patients [10].

Bakr *et al.* in 2021 screened adolescent girls with a history of heavy menstrual bleeding aiming to understand the pattern of hemostatic defects among Saudi university students. This research included 463 young girls with heavy days of menstrual cycles. Menorrhagia was reported among 109 girls who went through a comprehensive evaluation. The Pictorial Blood Assessment Chart (PBAC) was used for accurate measurement of menstrual bleeding. Assessing hemostatic abnormalities was done in the laboratory using PT, aPTT, vWF:Ag, vWF:RCo, PFA-100, coagulation factors assay, and regular CBC. Ultrasonography of the pelvis was also used in the screening process. Twenty-eight girls out of 109 had confirmed menorrhagia (25.6%) based on the PBAC score exceeding 100. 30.8% of this group were diagnosed with a hemostatic abnormality or bleeding tendency, including one case of factor V (FV) deficiency, two cases of probable platelet dysfunction, and five cases of probable vWD based on the low levels of vWF:Ag and/or vWF:RCo. 39.28% of those cases were anemic; however, only 36% [4] of them received iron supplementation [11].

National surveys

In a recent study, Owaidah *et al.* in 2018 conducted a survey that aimed to identify the prevalence of bleeding symptoms among young adults in Riyadh. Three thousand eight hundred and eighty-one participated in this survey where 47.6% reported a positive response to one of the eight questions that inquired about bleeding disorders. Among 72 participants who reported being diagnosed with different bleeding disorders, 3 were diagnosed with platelet disorders, 8 with hemophilia, and no one reported having von Willebrand disease. 28.4% who provided positive responses during the first stage of the study have participated in a follow-up interview for the second stage of the study. The total frequency of different bleeding symptoms was 84.2%, 43.6% for epistaxis, and 52.9% for oral cavity bleeding, which makes it the most common cause. Epistaxis was more common in boys than girls where it occurred spontaneously. Bleeding from minor wounds, heavy menstrual bleeding, bleeding episodes after surgery, and cutaneous symptoms were also reported among the participants of the study. Fifty percent of the study participants reported frequent bleeding from several sites with a common combination of bleeding from the oral cavity and cutaneous symptoms [12].

Alsaleh *et al.* in 2021 carried out a survey at the national level aiming to gain an understanding of the causes of bleeding symptoms among young adults. One thousand one hundred and thirty-eight medical students (52% female individuals and 48% male individuals) were the participants of this study. This survey inquired about different bleeding symptoms such as epistaxis, cutaneous symptoms, bleeding from minor wounds, oral bleeding, gastrointestinal bleeding, bleeding because of surgery, intramuscular or joint bleeding, and menorrhagia. More female participants reported different bleeding symptoms and attended universities in Dammam, Riyadh, and Makkah. Twenty-eight percent of female participants have reported a high prevalence of menorrhagia. Bleeding secondary to different dental procedures, oral bleeding, and cutaneous symptoms were also more frequent among female individuals. Male participants have suffered mainly from epistaxis; however, bleeding because of other causes such as dental procedures, cutaneous symptoms, and menorrhagia were present among male participants but

at a lower ratio compared with female participants in this study. Females seem to be more susceptible to bleeding symptoms (54.9%) compared with males (45.1%). Geographical variation was also evaluated in this study where they described a significant difference between cities in terms of regional frequency of bleeding symptoms. Participants out of Riyadh showed the highest prevalence of bleeding symptoms compared with participants from Dammam and other cities. This study also conducted a regression analysis to correlate bleeding after surgery to other bleeding symptoms. A negative correlation against menorrhagia was observed whereas no other significant correlation was reported for the other symptoms [3].

Researchers have highlighted different symptoms of frequent bleeding among the preparatory year students at Taibah University in Almadinah Almunawwarah to understand the prevalence of self-reported bleeding symptoms among adolescents (Zolaly *et al*., 2021). They collected questionnaires from 680 young participants with an average age of 19 years old, 55.6% of the study participants were female individuals whereas 44.4% were male individuals. More than half of the participants reported symptoms of bleeding tendency rising to 70.9% when including mild bleeding symptoms. Most of the study participants reported one to five episodes of epistaxis per year. Spontaneous bleeding was prevalent among 83.1% of the participants. 22.65%, reported symptoms of cutaneous bleeding, with bruises at 83.9% and hematomas 14.9%. 39.6% of participants reported bleeding from the oral cavity and 71.5% noticed the bleeding after brushing their teeth. Bleeding in the gastrointestinal tract occurred in 5.9% with hematemesis being the most prevalent. Post-surgery bleeding was reported by 21% of participants and 10% after tooth extraction, however, most of the study participants did not seek medical attention for this type of bleeding. 3.2% have experienced hemarthrosis or muscle hematoma with few seeking special medical intervention. 16.1% of female participants reported heavy menstrual cycles in 6–10 days [13].

Inherited bleeding disorders and molecular patterns

In an early study aimed to formulate an idea about the inherited bleeding disorders at the eastern province of the country (Ahmed *et al*., 1988). Thirty-four cases have been examined for different inherited breeding disorders. All the study participants were Saudis who live in the eastern province of the country. Out of the 34 cases, there were 15 cases of hemophilia, 12 Glanzmann's thrombasthenia, 5 with unspecified platelet function disorders, 1 with factor X deficiency, and 1 with factor VII deficiency. The most common factor between most of the participants of the study is consanguinity which points out the high risk of developing bleeding disorders among any population who follows that cultural tradition [14].

In a study that aimed to provide molecular and clinical characterization of hereditary factor V deficiency (FVD) (Al-Numair *et al*., 2019) investigated 11 patients (aged 5–53 years old), 9 female and 2 male individuals, who suffered from FVD. Through implementing next-generation sequencing, the researchers in this study used a hematology panel that contains 393 known genes. The results identified six variations within the sequence of the FV gene where a splicing variant (c.1118+5G>T) and four missense mutations (p. Pro189Leu, p. Trp2004Arg, p. Met2148Thr, p. Arg2202Cys), a deletion (p. Arg872Lysfs*12) have been observed. Interestingly, a novel discovery of four of these variants has been made for the first time in this study. Among the study participants, seven participants were heterozygous for their respective mutations, three patients were homozygous, and a pathogenic variant remained elusive for one patient [15].

To study the molecular genotyping of hemophilia A, mutations within the factor VIII (F8) gene were analyzed by (Owaidah *et al*., 2009). The researchers in this study analyzed 22 men, ages ranging from 4 to 37 years, who suffered from hemophilia A secondary to F8 deficiency. All the study participants have been tested for F8 coagulant activity and inhibitors.

Only 2 patients out of the 22 developed inhibitors, with no abnormal correlation to the genotype. Preliminary PCR screening has shown negative results of intron 22 inversion. Thus, further screening for other F8 mutations was required. In half of the cases, inversion of intron 22 of F8 was detected combined with five-point mutations. Moreover, different exons were affected by either an insertion or a deletion. All the detected mutations were associated with a severe form of hemophilia except one, which was associated with the mild phenotype of the disease [16].

The genotypic and phenotypic signatures of exon 18 of the von Willebrand factor gene were investigated by another research (Alzahrani *et al*., 2022). Saudi patients, who also lived in the eastern province, have been diagnosed with type 1 vWD (type 1 vWD) were the participants of this study.

Sixty individuals with type 1 vWD from 19 families were the participants of this study. They were divided into three study groups: 22 index cases, 21 affected family members, and 17 unaffected families.

The demographic characteristics of the three study groups were compared with those of a control group made up of 100 healthy volunteers. Following the assessment of the phenotypic characteristics such as bleeding symptoms, score, and blood group analysis, a significant difference was detected among the three study groups.

Most of the study participants were blood group O and significantly more among the 22 participants of the index cases. Moreover, the median of the bleeding scores was

higher in the index cases compared with the other two groups. Affected family members have shown multiple bleeding symptoms including menorrhagia, postpartum hemorrhage, cutaneous bleeding, bleeding from minor wounds, muscle hematomas, and oral cavity bleeding, bleeding after tooth extraction. The laboratory analysis of exon 18 of the *VWF* gene revealed different variations that could make the clinical significance of the disease either benign or likely benign. For instance, no significant association with disease groups or controls was found with the c.2365A>G polymorphism. Likewise, the c.2385T>C genotype has shown no significant association with disease or nonaffected groups.

The correlation analysis in the control group showed no statistically significant correlation between the different genotypes and the level of expression of VWFAg, or VWF, factor VIII:RCo. Similarly, among healthy individuals, rs1063857 did not demonstrate any significant association with VWFAg, or VWF, factor VIII:RCo [7].

Rare bleeding disorders

Tarawah *et al.* in 2023 have reported a high prevalence of Glanzmann thrombasthenia, which is a rare bleeding disorder In AlMadinah. Based on the 2022 population count, Glanzmann thrombasthenia was prevalent among 1 in every 10 000 Saudis. In this study, among 125 participants with, an average age of 16.5 years, a higher prevalence of Glanzmann thrombasthenia was observed among female individuals (54%) compared with male individuals (46%). Type 1 Glanzmann thrombasthenia was prevalent in 79% where the majority (98%) of the participants were the offspring of consanguineous marriages. Sixty-five percent of these participants were children of first-degree cousin parents. Eighty-six percent of the patients had a family history of Glanzmann thrombasthenia while some families had two to five siblings who suffered from Glanzmann thrombasthenia. Most of the bleeding symptoms have been reported at the age of 2 years where symptoms such as bruises, gum bleeds, and epistaxis have been reported.

Sixteen percent of patients suffer from severe bleeding, 35% have moderate episodes of bleeding and 50% have a minor clinical presentation. Most female participants have been affected by menorrhagia (86%). Ninety-five percent of these women have received hormonal therapy to reduce the symptoms of menorrhagia.

Twenty-eight participants have reported pregnancies whereas 75% have reported postpartum hemorrhage. Sixty-six percent of patients were presented with iron deficiency anemia.

Eighteen different mutations were reported among the participants where 15 mutations were in the *ITGA2B* gene and three other mutations in the *ITGB3* gene. Remarkably, one tribe had a novel mutation (ITGA2B: exon13: c.1210+5G>A) whereas another tribe was mainly affected by the most frequent type of mutation (ITGB3:exon13: c.2112delC) exclusively. Even though there has been no clear association found between the phenotype and the genotype, patients with specific types of mutations (exon13:c.2112delC and exon13:c.1210+5G>A) tended to have more severe clinical symptoms. Nine percent of the patients had antibodies against platelets, however, an improvement in this condition was observed when patients reached puberty limiting the severity of menorrhagia [17].

Recently, Owaidah *et al.* in 2023 aimed to show the features of the clinical and laboratory presentation of vWD at a single center in the country.

This study included 189 participants: 127 female individuals (66.70%) and 62 male individuals (32.30%) with an age average of 30 years old. Around 48% of the cases have been presented with bleeding at multiple sites mainly in muscles and joints. 68.10% of the participants presented with spontaneous bleeding whereas 19.58% had a familial history of bleeding.

In terms of blood groups and iron status among the study participants, blood group O was the most prevalent among the participants (61.91%), followed by B (16.40%) and then A (15.87%). Variations in the levels of ferritin have been observed with normal levels of hemoglobin and mean corpuscular volume.

Fifty female individuals and five male individuals suffered from Iron deficiency anemia. PFA 100 and PTT were prolonged in 92.90 and 40.4% of patients, respectively.

The laboratory analysis of vWD identified type 1 as the most frequent (58.01%), then by type 3 (25.96%) followed by type 2 (16.02%). In relevance to blood group types, the variance analysis revealed a significant correlation between vWF:Ag, vWF:RCo, and FVIII levels and the blood type. There was a significant difference between FVIII and vWF:Ag in O and non-O groups with a greater difference for vWF:RCo indicating that people with AB blood groups tend to have higher levels of vWF [18].

To describe the clinical pattern of Henoch–Schönlein purpura (HSP), Rasheed *et al.* in 1991 conducted a retrospective study on 40 Saudi Arabian children diagnosed with HSP. In all patients were presented with skin rash. More than half of the cases were diagnosed during the winter season; however, there was no immediate correlation between B-hemolytic streptococcal infection and HSP. Fifty-eight percent of the participants had gastrointestinal and joint symptoms whereas 38% experienced renal manifestations [19].

HSP was the target for another study that was conducted in the southern part of the country. Fifty-five children ages ranged from 8 months to 18 years, with an average of 8.6 ± 5 years (29 girls and 26 boys, 18 were examined;

Harbi, 1996). Seventy-three percent of the study participants were over 5 years old at the time of the initial diagnosis. Typical HSP rash was reported in all cases. Abdominal pain was prevalent in 78% of the patients whereas 11% had significant gastrointestinal bleeding. Seventy-six percent of the children suffered from joint pain or discomfort. Twenty percent of the participants had initial symptoms of renal involvement. Moreover, 13% of the patients were presented with hemolytic-uremic syndrome (HUS) [20].

Henoch–Schönlein purpura status in the eastern province of the country was studied by (Lardhi, 2012). This study involved 78 children diagnosed with HSP, 46 male individuals and 32 female individuals, about 46% of patients were under 5 years, and 90% were under 10 years. The highest number of cases were reported in autumn (33.3%), followed by winter (25.6%), then summer (24.3%), and spring (16.6%). Before HSP was observed, 44% reported having a trigger condition such as upper respiratory tract infection that was reported in 52.5% of the cases.

Thrombocytopenic palpable purpura was found in all patients mostly affecting the upper limbs, legs, and buttocks. 66.7% of patients experienced some sort of joint involvement that mainly affected knees and ankles. Forty-seven percent of the patients had gastrointestinal manifestations whereas 24% suffered from renal involvement such as gross and microscopic hematuria.

Fifteen percent of the boys in this study had testicular involvement. Twenty-six percent of patients developed renal complications such as nephritic syndrome where one case led to pulmonary bleeding and acute respiratory distress syndrome (ARDS). Two patients experienced seizures whereas edema affected 10% of children. HSP recurrence happened in 7.7% of the participants. Laboratory investigations have found that 13% of the patients were anemic, 15% had thrombocytosis, and 31% had elevated white blood cells. Erythrocyte sedimentation rate (ESR) was elevated in 53% of the children and C reactive protein (CRP) was high among 70.5% of the patients. Forty-six percent of the study participants had positive ASO titers whereas most cases were subjected to simple analgesia and supportive treatment [21].

Conclusions

The research on bleeding disorders in Saudi Arabia provides valuable insights into their prevalence, causes, and management. Genetic factors, particularly the impact of consanguinity, play a significant role in the high prevalence of these disorders. Specific mutations in coagulation factor genes associated with hemophilia, von Willebrand disease, and platelet disorders have been identified.

Epidemiological studies highlight the diversity of bleeding disorders, emphasizing their hereditary nature and the cultural practice of consanguinity, which amplifies the risk of genetic abnormalities. Comprehensive screening programs, early detection through advanced molecular genetics, and awareness campaigns are integral to addressing these disorders. Well-designed prevention and management strategies, considering socio-cultural factors, are crucial.

Surveys among various populations provided insights into symptoms, prevalence, and geographical variations. The identification of patients with Bleeding of Unknown cause underscores the complexity of diagnosis, necessitating ongoing research. Moreover, advanced genetic techniques in research on inherited bleeding disorders contribute to understanding the genetic landscape and offer potential advancements in personalized medicine.

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Conflicts of interest

There are no conflicts of interest.

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