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**RESEARCH ARTICLE**
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# RARE INHERITED CLOTTING FACTOR DEFECTS OF COMMON PATHWAY

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## ABSTRACT

**Objective:** To access the coagulation factor activity of common pathway in rare inherited bleeding disorder.

**Study Design:** Cross-Sectional

**Duration:** The study was carried out in 6 months from 01-09-2022 to 31-03-2023.

**Methods:** The Cross-Sectional study was carried out at the Dept. of Pathology (Hematology) and the Diagnostic & Research Laboratory – Liaquat University of Medical & Health Sciences, Jamshoro. 60 suspected cases of inherited clotting factor deficiencies involved in common pathway were taken, after taking informed written consent. All the diagnosed cases of acquired bleeding disorders, inherited clotting factors defect involved in extrinsic and intrinsic pathway and patient with Platelets functional disorders (Bernard soulier syndrome and Glanzman's thrombasthenia) were excluded from the study. This study was conducted via nonprobability, convenient sampling and the data was analyzed via SPSS 21.0.

**Results:** Out of the total population of 60 patients with rare bleeding disorders, 55.2% (33) patients were male and 44.9% (27) were female. The median age at presentation to the tertiary care hospital was 9 years and 3 months, ranging from 4 months to 42 years. Among the rare blood disorders observed in a group of 60 patients, the distribution of cases varied across different conditions. Factor I (FI) accounted for 5 patients, making up approximately 8.33% of the total. Factor II (FII) exhibited a slightly higher prevalence, with 7 patients constituting around 11.67% of the sample. Factor V (FV) presented in 9 patients, representing approximately 15.00% of the total cases. Combined factor V and

factor VIII (FVIII) showed the highest occurrence, with 12 patients making up around 20.00% of the sample. Factor VII (FVII) had a lower incidence, affecting 4 patients, or roughly 6.67% of the group. Factor X (FX) was observed in 6 patients, accounting for approximately 10.00% of the cases. Similarly, factor XI (FXI) presented in 8 patients, making up around 13.33% of the sample. Factor XIII (FXIII) had a relatively low prevalence, affecting 3 patients, or approximately 5.00% of the group. Lastly, the vitamin Kdependent clotting factors were identified in 6 patients, representing roughly 10.00% of the cases.

**Conclusion:** Among the rare blood disorders, combined factor V and factor VIII deficiencies were found to be most prevalent followed by deficiency of Factor V which is more prominent in male population.

**Keywords:** Rare Bleeding Disorders, Common Bleeding Pathway, Factor V, Factor VIII

## INTRODUCTION

The heterogeneous diseases known as rare bleeding disorders (RBDs) are primarily inherited in an autosomal recessive fashion. They arise from the absence or malfunction of one or more clotting factors, such as factor I (FI), factor II (FII), factor V (FV), combined FV and factor VIII (FVIII), factor VII (FVII), factor X (FX), factor XI (FXI), factor XIII (FXIII), and vitamin K-dependent clotting factors.From 1 to 4 Three to five percent of all hereditary coagulation defects are rare bleeding diseases, or RBDs.* [5] Depending on the cause of each condition, these patients' presentations and bleeding patterns differ. Individuals suffering from fibrinogenemia may bleed to varying degrees. Cord, mucosa, GI tract, genitourinary, or central nervous system (CNS) haemorrhage are among the common symptoms. Hematatomas and hemarthroses are two more typically occuring signs. Fabrinogenemic women frequently undergo first-trimester abortions.[3].

Type I deficiency, or genuine hypoprothrombinemia, and type II deficiency, or dysprothrombinemia, are the two phenotypes of prothrombin deficiency (PD), which affects about 1 in 2 million people [6]. Symptoms of factor V [FV] deficiency include menorrhagia, epistaxis, and bleeding from the skin and mucous membranes. A million to one is the prevalence [7]. With an estimated frequency of 1 in 300,000–500,000, factor VII deficiency manifests as a bleeding condition akin to haemophilia [8]. Mutations in the LMAN1 and MCFD2 genes are linked to combined deficit of factors V and VIII [9]. Patients with this condition typically exhibit a broad spectrum of clinical symptoms, from post-traumatic bleeding to mucosal/oral bleeding and spontaneous hematomas (12).

Serious bleeding symptoms, such as CNS, GI, or umbilical cord bleeding, as well as recurring hemarthroses and hematomas, are present in patients with undetectable FX coagulant activity [3]. Initially, factor XI deficiency may present as an unintentional test abnormality or as a bleeding problem. Roughly one in every million incidents occur [10]. Patients with FXIII coagulant activity that is undetectable present with severe bleeding symptoms, such as hematomas and recurrent hemarthroses, or bleeding in the central nervous system or umbilical cord. In women with significant deficiencies, miscarriages are fairly prevalent. Only mucocutaneous bleeding may occur in patients with moderate and mild insufficiency, or they may show no symptoms at all [3].

Standard laboratory coagulation tests are employed in the examination and diagnosis of uncommon bleeding disorders, with the exception of FXIIID, wherein platelet count, thrombin time (TT), prothrombin time (PT), activated partial thromboplastin time (APTT), and bleeding time (BT) are all normal [11]Molecular analysis and specific factor activity can be utilised to validate the diagnosis and detect RBDs precisely, respectively [12].

## MATERIALS AND METHODS

This study was carried out at the Dept. of Pathology (Hematology) and the Diagnostic & Research Laboratory – Liaquat University of Medical & Health Sciences, Jamshoro. There was a consistent mechanism involved in all probable cases of hereditary clotting factor deficits. Both male and female age groups were represented.

Diagnoses of hereditary clotting factor defects involving both intrinsic and extrinsic pathways were excluded from the analysis. cases of functional platelet abnormalities (Glenzman's thrombasthenia

and Bernard Soulier syndrome) that have been diagnosed. Every case of acquired bleeding disorders that has been diagnosed.

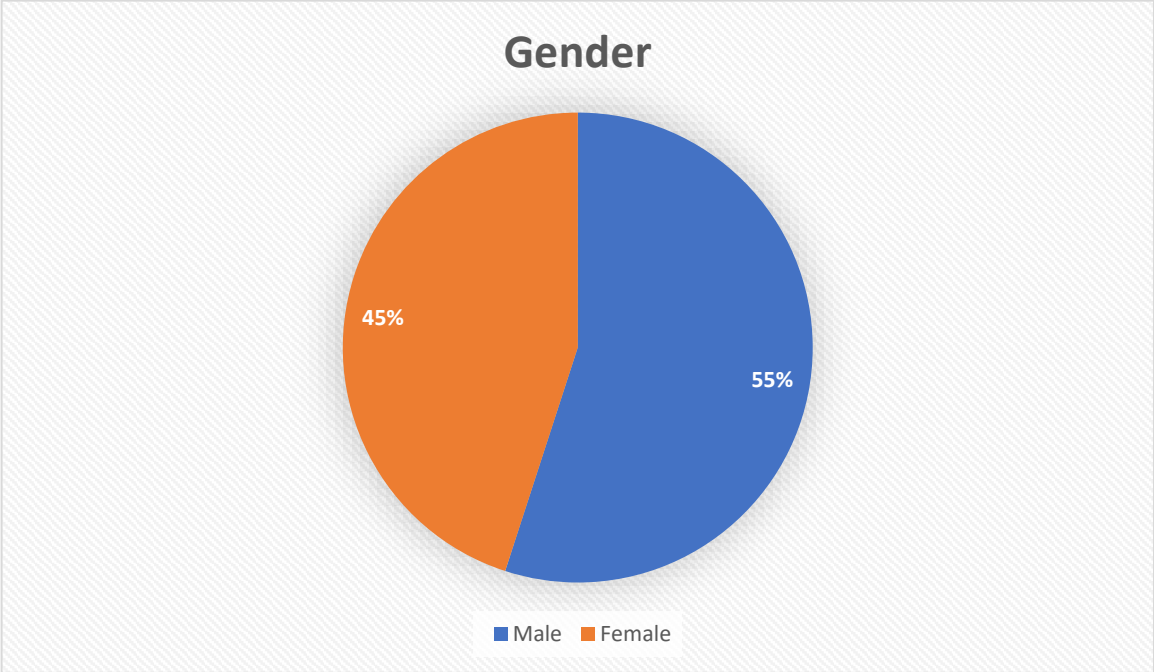
Sociodemographic information was gathered from patients who satisfied the inclusion criteria at the Liaquat University of Medical & Health Sciences, Jamshoro Diagnostic & Research Laboratory and the Department of Pathology (Haematology), after the ethics committee of LUMHS's acceptance of the research proposal. Informed consent was gained from the chosen patients before to the trial, after they were informed about its nature and goal. The researcher employed a standardised proforma to gather data. Age, gender, the presenting complaint, clinical and laboratory characteristics, and other information were noted. Comprehensive laboratory tests, including a full blood count on a Sysmex analyser, were carried out following the collection of 3 ml samples in sodium citrate tubes and 3 ml in EDTA. After that, the Sysmex CA 600 Series automatic coagulation analyser was used to perform the PT, APTT, Thrombin time, fibrinogen, and Factor assays (FV, FX, FII).

SPSS v. 21.0 and Microsoft Excel 2016 were used for data analysis. Number and percentage (No & %) were used to describe qualitative data (such as the type of hemostatic disease and the presenting complaint). The statistical information, which included age, the frequency of specific hemostatic diseases, and laboratory results, was presented as mean ± standard deviation (X ± SD).

## RESULTS

Out of the total population of 60 patients with rare bleeding disorders, 55% (33) patients were male and 45% (27) were female. The median age at presentation to the tertiary care hospital was 9 years and 3 months, ranging from 4 months to 42 years.(figure 1)

**Figure-1:** Gender distribution




Among the rare blood disorders observed in a group of 60 patients, the distribution of cases varied across different conditions. Factor I (FI) accounted for 5 patients, making up approximately 8.33% of the total. Factor II (FII) exhibited a slightly higher prevalence, with 7 patients constituting around 11.67% of the sample. Factor V (FV) presented in 9 patients, representing approximately 15.00% of the total cases. Combined factor V and factor VIII (FVIII) showed the highest occurrence, with 12 patients making up around 20.00% of the sample. Factor VII (FVII) had a lower incidence, affecting 4 patients, or roughly 6.67% of the group. Factor X (FX) was observed in 6 patients, accounting for approximately 10.00% of the cases. Similarly, factor XI (FXI) presented in 8 patients, making up around 13.33% of the sample. Factor XIII (FXIII) had a relatively low prevalence, affecting 3 patients, or approximately 5.00% of the group. Lastly, the vitamin Kdependent clotting factors were identified in 6 patients, representing roughly 10.00% of the cases. (table 1)

**Table-1:** Distribution of rare bleeding disorders

| RARE BLEEDING DISORDER | PERCENTAGE | NUMBER |
|---|---|---|
| Factor I (FI) | 8.33% | 5 |
| Factor II (FII) | 11.67% | 7 |
| Factor V (FV) | 15% | 9 |
| Combined FV and FVIII | 20% | 12 |
| Factor VII (FVII) | 6.67% | 4 |
| Factor X (FX) | 10% | 6 |
| Factor XI (FXI) | 13.33% | 8 |
| Factor XIII (FXIII) | 5% | 3 |
| Dependent ClottingFactor | 10% | 6 |
| Total | **100%** | **60** |

In terms of referral sites, the majority (35%, 21 individuals) were referred to medical facilities, while 15% (9 individuals) were referred for surgical consultations. Additionally, 20% (12 individuals) were referred to OBGYN services, 10% (6 individuals) to the casualty department, and the remaining 20% (12 individuals) to other departments. In terms of history of blood.(table 2)

**Table-2:** Site Referral

| SITE OF REFERRAL | PERCENTAGE | NUMBER |
|---|---|---|
| Medical | 35% | 21 |
| Surgical | 15% | 9 |
| OBGYN | 20% | 12 |
| Casualty | 10% | 6 |
| Other | 20% | 12 |
| **TOTAL** | **100%** | **60** |

Hematological indices indicated a mean hemoglobin level of 10.5 with a standard deviation (SD) of 1.2, a mean corpuscular volume (MCV) of 90.2 with an SD of 5.7, a white blood cell count (WBC) of 8.9 with an SD of 2.3, platelet count of 150 with an SD of 30, prothrombin time of 13.6 with an SD of 1.9, and activated partial thromboplastin time (APTT) of 32.1 with an SD of 4.5.(table 3)

**Table-3:** Hematological Indices

| INDICES | MEAN | ± SD |
|---|---|---|
| Hemoglobin Level | 10.5 | 1.2 |
| MCV | 90.2 | 5.7 |
| WBC | 8.9 | 2.3 |
| Platelets | 150 | 30 |
| Prothrombin Time | 13.6 | 1.9 |
| APTT | 32.1 | 4.5 |

Among the peripheral film findings, 35% (21 individuals) showed normal findings, 22% (13 individuals) had microcytosis, 18% (11 individuals) exhibited thrombocytopenia, 12% (7 individuals) had anisocytosis, 8% (5 individuals) displayed poikilocytosis, and 5% (3 individuals) had multiple findings combining the aforementioned conditions. These comprehensive findings provide valuable insights into the demographic, clinical, and hematological aspects of patients with rare blood disorders, aiding in their understanding and management.(table 4)

**Table-4:** Most common Peripheral results

| PERIPHERAL FILM FINDINGS | PERCENTAGE | NUMBER |
|---|---|---|
| Normal | 35% | 21 |
| Microcytosis | 22% | 13 |
| Thrombocytopenia | 18% | 11 |
| Anisocytosis | 12% | 7 |
| Poikilocytosis | 8% | 5 |
| Multiple findings (Combination of above) | 5% | 3 |
| **TOTAL** | **100%** | **60** |

## DISCUSSION

Among a cohort of sixty patients, the current study examined the distribution and prevalence of uncommon bleeding diseases. The gender distribution showed that, at 55% of the sample, men made up the majority, while women made up 45%. This result is consistent with earlier research showing a higher incidence of uncommon bleeding diseases in men [13, 14]. Hormonal profile differences between the sexes or hereditary variables could be the cause of the small male predominance [15].

With a median age of 9 years and 3 months and a range of 4 months to 42 years, the age range at presentation in this study was wide. These results suggest that uncommon bleeding problems can appear in children, adults, and infants at different phases of life. Previous research on uncommon bleeding disorders has revealed age patterns that are similar [16, 17].

Mansouritorghabeh et al. [18] showed an incidence of 15.6% in the Iranian community, but 21.3% of patients in Pakistan with inherited bleeding disorders had uncommon bleeding diseases. In our community, combined FV and FVIII factor shortages accounted for 20% of rare bleeding disorders, with factor XI deficiency coming in second at 13.33 percent. The most common unusual bleeding illness, according to a study done at the Fars Haemophilia Centre, which is connected to Shiraz University of Medical Sciences in Iran, is factor VII insufficiency, which is followed by factor X deficiency [19]. According to Sharma et al. [20], factor VII and XIII deficiencies are the next most frequent uncommon bleeding disorders after factor X deficiency. The most prevalent uncommon bleeding diseases were found to be factor VII and factor V deficits in a retrospective examination of 156 patients in Turkey [21].

The prevalence of autosomal recessive illnesses is higher in areas with a high rate of consanguinity, which makes the creation of diagnostic facilities necessary to guarantee correct diagnosis and timely treatment [22]. 47.2% of Turkish people and 81.2% of our patients had consanguinity among patients with uncommon bleeding diseases [23]. The most frequent complaint in our population was mucocutaneous haemorrhage. Similar results were reported by Sharma et al. [24]. Clinically substantial bleeding was seen in our sample of patients with factor X deficiency. Two patients with factor X deficit, one with factor VII and the other with factor XIII deficiency, experienced intracranial bleeding. However, the most frequent cause of cerebral haemorrhage, according to an Indian study [25], is factor XIII insufficiency.

By examining the particular rare blood illnesses found in this investigation, several prevalence patterns were found. The highest frequency was seen in factor V plus factor VIII (FVIII), which is in line with earlier studies emphasising the importance of this combination among uncommon bleeding diseases [26]. Variations in prevalence rates for particular rare bleeding disorders have been observed in other research, and these variations have been related to regional and genetic variances [27].

When comparing the results of this study to those of other studies, it's critical to take into account differences in sample sizes, study sites, and methodology used. Regarding the gender distribution and prevalence of particular rare bleeding disorders, some studies have found similar trends, while others have found different patterns [28]. Variations in study design, genetic variability, and environmental factors may all have an impact on these differences.

## CONCLUSION

Among the rare blood disorders, combined factor V and factor VIII deficiencies were found to be most prevalent followed by deficiency of Factor V which is more prominent in male population.

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