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Etiology, Clinical Profile, And Demographics Of Hemophilia B In Eastern India

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Abstract
Background*: The most common severe inherited hemorrhagic disease is hemophilia, which means "love of blood." Deficiencies in Factors VIII and IX cause hemophilia, with inadequate levels or malfunctioning of these factors being the primary causes of hemophilia A and B, respectively. This study aims to assess the incidence and characteristics of inherited coagulation disorders, particularly hemophilia B.*
Objective: *The present investigation aims to evaluate the incidence and clinical traits of congenital anticoagulation diseases, specifically hemophilia B.*
Method*: The study included 98 Hemophilia B patients with a mean age of 25. Medical histories were recorded using a predesigned Performa, covering age, gender, bleeding site, and family history.*
Result: *The study included 98 hemophilia B patients, with 39 having severe and 59 moderate forms. The majority (60.2%) had moderate hemophilia, while 39.7% had the severe type. Most patients (17.4 ± 10.5 years) were aged*

21-30, with the mean age of onset being 17.4±10.5 years for severe hemophilia and 8.6±4.43 years for moderate cases. Knee joints were the most affected, found in 79.5% of cases and accounting for 98.9% of target joint infections, followed by elbow joints at 90.8%. Regular factor IX replacement was needed in 39.7% of severe cases. This highlights the importance of early diagnosis and treatment for managing joint-related complications in hemophilia B patients.

Conclusion: *The current study examines hemophilia B's sociodemographic and clinic-pathological characteristics. Early diagnosis may be beneficial only when the spectral manifestation of hemophilia B in the community is known.*

Keyword: *Epidemiology, F9 gene, hemophilia B, Varanasi, Utter Pradesh*

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I. Introduction:

The most common types of hemophilia are hemophilia A (classic hemophilia) and B (Christmas disease), which are prevalent hereditary disorders in India and worldwide. According to the World Federation of Hemophilia, approximately 400,000 people suffer from hemophilia globally, with India accounting for 80% of the cases **[1].** Hemophilia A (HA) and hemophilia B (HB) are X-linked disorders caused by mutations in genes located on the long arms of the X chromosome (Xq28 for HA and Xq27 for HB). Hemophilia A accounts for about 80% of all cases, while hemophilia B constitutes 20%. Hemophilia A occurs in approximately one in 30,000 male births, while hemophilia B (HB) is found in about one in 10,000 male births. Factor deficiency, specifically Factor VIII and Factor IX, is one of the most prevalent coagulation irregularities. Hemophilia A and B are inherited in an X-linked recessive pattern **[2].** Bleeding into muscles, joints, and soft tissues is a clinical hallmark of hemophilia. In impoverished and densely populated countries like India, where access to medical care is limited, individuals with hemophilia often rely on blood and blood products as a more affordable alternative to factor concentrates. This increases the risk of transfusion-transmitted infections **[1,7].** However, the standard treatment for severe hemophilia is preventive therapy, which involves administering regular doses of clotting factors to prevent bleeding episodes. This approach reduces the long-term complications of the disease. Episodic treatment, which involves prompt administration of clotting factors during a bleeding episode, is also commonly used. In cases of mild hemophilia B, spontaneous bleeding is rare unless there is prior trauma to the affected area. The most common causes of bleeding in mild HB are injuries, surgical procedures, and dental operations.

Pre-treatment is required to normalize FIX levels before undergoing surgery or dental procedures for all types of hemophilia. Treatment is now administered using recombinant FIX products, some of which have been modified to extend the half-life of FIX in circulation. Hemarthrosis is the most prevalent manifestation of hereditary coagulation disorders. Joint bleeding, along with the resulting damage to weight-bearing joints, is the most common and debilitating symptom of severe hemophilia. Bleeding into the joints can cause pain, swelling, inflammation, warmth, and restricted range of motion. Bleeding into joints can result in pain, swelling, inflammation, warmth, and a restricted range of motion. The most commonly affected joints include the knees, elbows, ankles, shoulders, wrists, and hips **[4].** The incidence of spontaneous joint bleeding generally increases with age, reaching up to 60% by age 65. Recurrent joint bleeding often leads to hemophilic arthropathy, which is characterized by chronic proliferative synovitis and chronic osteochondral changes in major joints, primarily affecting the elbows, knees, and ankles (commonly referred to as "index joints"). Ecchymotic patches **[Figure No.1]** are also observed in some cases. The most critical treatment strategy for managing hemophilia is the continuous intravenous administration of prophylactic hematological therapy to prevent recurrent hemarthroses. In situations where intravenous treatment is only available on demand, regular monitoring is essential for the early diagnosis and management of intra-articular bleeding episodes **[5,6,7].** Magnetic Resonance Imaging (MRI) scores are often used to assess radiological changes in the joints. This research aims to investigate the incidence and diagnostic characteristics of hereditary coagulation disorders, with a particular focus on hemophilia B, in eastern India **[8,9,10,11].**

Aims and Objective

To evaluate the Clinical profile, demographics, and etiology of hemophilia B patients in Eastern India

II. Materials And Methods

Study Design

The present cross-sectional study was conducted between 2021 and 2024. A total of 98 hemophilia B (HB) patients were included, with a mean age of 25 years. A predesigned proforma was used to record the complete medical history of the patients, including information on their age, gender, initial bleeding site, and family history. A semi-automated clot analyzer was used to perform a "one-stage test" for the factor assay. Factor

concentrations were classified as follows: severe (<1% or 0.01 IU/mL), moderate (1-5% or 0.05 IU/mL), and mild (>5%-40% or 0.05-0.4 IU/mL) [8]. The data are presented as mean ± SD.

Patients: To document clinical details, a thorough clinical examination, pertinent laboratory testing, and the patient's history were used**.**

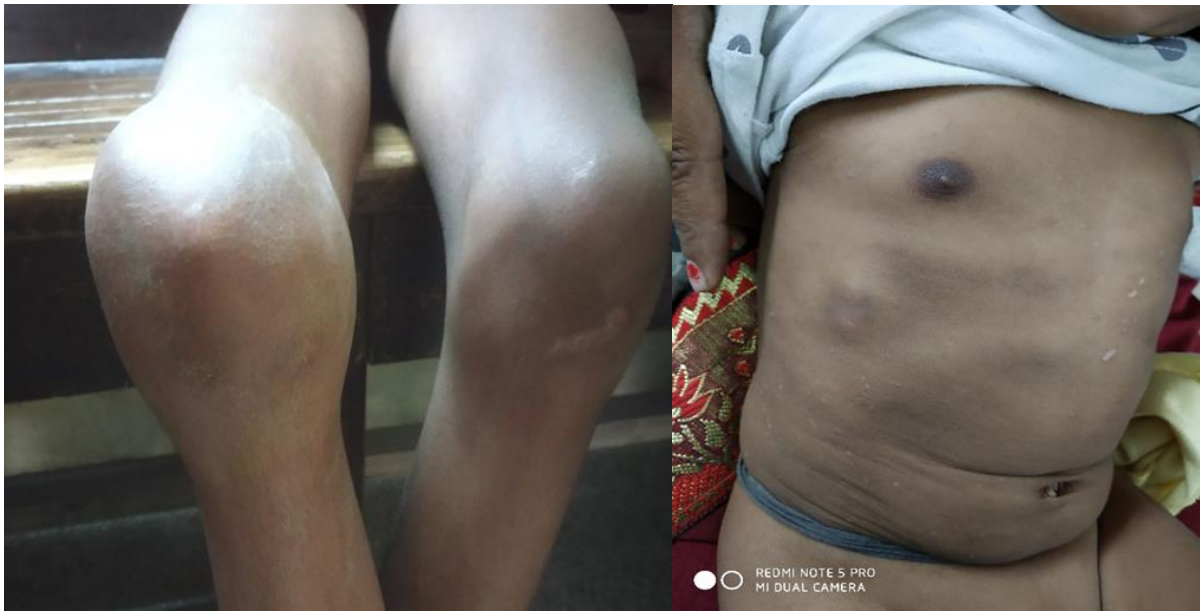

Figure No:1 Shown bleeding in the knee joint and Ecchymotic Patches

Inclusion Criteria
Patients with hemophilia B

Exclusion Criteria

Informed consent was obtained from each patient and their family members, with ages ranging from <1 year to >30 years. The clinical profile and demographic characteristics of hemophilia B were evaluated through complete hematological investigations, including complete blood count (CBC), GBP, prothrombin time (PT), and activated partial thromboplastin time (APTT). Coagulation factor assay tests, X-rays of joints, ultrasonography of suspected muscles, and abdominal computed tomography (CT) scans were performed on selected severe patients based on their symptoms.

Statistical Analysis

The statistically significant differences in mean categorical variables were compared using the Student's t-test, one-way ANOVA, and the Chi-square test, and were analyzed. Statistical significance is defined as a P value <0.05.

III. Result:

This is a cross-sectional study. Out of the 98 patients, 39 (39.7%) had severe hemophilia, and 59 (60.2%) had moderate hemophilia [Table 1, Figure 2]. Most respondents were aged between 21 and 30 years, with a mean age of 17.4 ± 10.5 years.

Patients are distributed based on severity.		
Severity of hemophilia	**Number of Patients**	**Percentage (%)**
Severe hemophilia	39	39.7%
Moderate hemophilia	59	60.2%
Total	98	100%

Table no. 1 **Shows the Patients are distributed based on severity.**

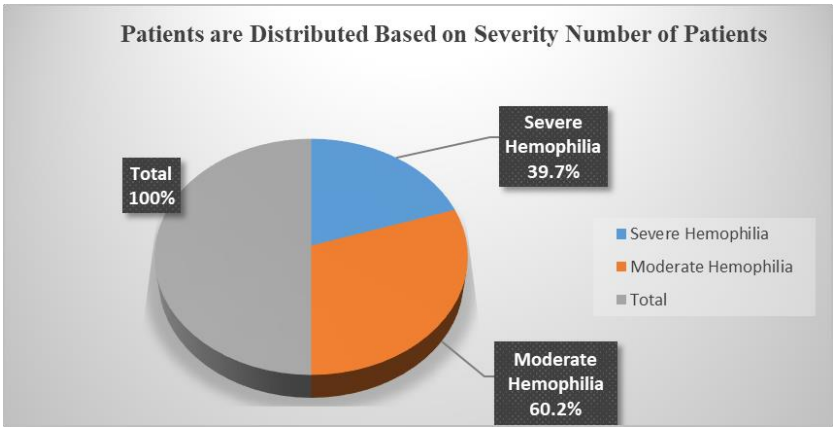

Figure No. 2 shows Patients are distributed based on severity.

The majority of participants 72 (73.3%) were from rural areas, 32 (32.6%) had at least completed their primary education, 21 (21.4%) were enrolled in school, and 47.9% had a monthly family income of at least 15,000 BDT. Sociodemographic characteristics were consistent across the range of hemophilia severity. A family history of hemophilia was present in 75.5% of the participants. The median age at first bleeding and diagnosis was 5.0 and 6.0 years, respectively. According to the assessment, nearly 57.1% of the individuals were diagnosed with hemophilia at the time of their first bleeding. No significant differences were found between individuals with severe and moderate hemophilia **[Table 2].**

Sociodemographic characteristics and Disease Profile of the patients			
		Severity of Hemophilia	
Variable	Total (n=98)	**Severe n (%)**	**Moderate n (%)**
Total, n (%)	98	39 (39.7%)	59(60.2%)
Age (years), Mean±SD	(17.4±10.5)	(5.5±2.7)	(8.6±4.4)
Age group (years)			
<1	3	2 (5.1%)	1(1.7%)
1-5	11	7 (17.9%)	4(6.7%)
6-10	16	6 (15.4%)	10(16.4%)
11-15	17	5 (12.8%)	12 (20.3%)
16-20	13	3(7.7%)	10(16.94%)
21-30	26	11(28.2%)	15 (25.4%)
>30	12	5 (12.8%)	7(11.8%)
Residence			
Rural	72(73.3%	29(74.3%)	43(72.9%)
Urban	26(26.5%)	10(25.6%)	16(27.1%)
Education			
Llliterate	2(5.1%)	1(2.6%)	1(1.7%)
Pre-schooler	19(19.4%)	8(20.5%)	11(18.6%)
Primary	32(32.6%)	13(33.3%)	19(32.2%)
SSC	21(21.4%)	9(23.1%)	12(20.3%)
HSC	15(15.3%)	7(17.9%)	8 (13.5%)
Graduate and Above	9(9.2%)	4(10.2%)	5(8.5%)
Occupation			
Toddler	3(3.1%)	1(2.6%)	2(3.4%)
Student	29(29.6%)	11(28.2%)	18(30.5%)
Job	19(19.4%)	8(20.5%)	11(18.6%)
Business	34(34.7%)	13(33.3%)	21(35.6%)
Farmer	8(81.6%)	3(7.7%)	5(8.5%)
Unemployed/dependent	5(5.1%)	2(5.1%)	3(5.1%)
Monthly Family Income			
<15,000	47(47.9%)	16(41.0%)	31(52.5%)
15,000-30,000	38(38.8%)	17(43.6%)	21(35.6%)
>30,000	13(13.3%)	6(15.4%)	7(11.8%)
Family History			
Present	75(76.5%)	31(79.5%)	44(74.6%)
Absent	23(23.5%)	8(20.5%)	15(25.4%)
Median age at first bleeding (years)	5.0	2.0	3.0
Age at diagnosis (year) Median	6.0	6.4	6.0

The duration between the initial bleeding incident and the diagnosis			
None	56(57.1%)	25(64.1%)	31(52.5%)
<10	27(27.5%)	11(28.2%)	16(27.1%)
≥10	14(14.3%)	5(12.8%)	9(15.3%)
Missing Value	1		

Table No. 2 Sociodemographic characteristics and disease profile of the patients

Clinical manifestation and Investigation			
Clinical Manifestation	**Total (n=98)**	**Severity of Hemophilia**	
		Severe (n=39)	**Moderate (n=59)**
Mode of Bleeding			
Spontaneous	98(100.0)	39(100.0)	59(100.0)
After major trauma	98(100.0)	39(100.0)	59(100.0)
After manor trauma	98(100.0)	39(100.0)	59(100.0)
Joint Swelling			
Yes	97 (98.9%)	38(97.4%)	59(100)
No	1(1.0%)	1(2.6%)	0
Target Joint			
Knee	78(79.6%)	24(61.5%)	45(76.3%)
Knee+ Elbow	56(57.1%)	33(84.6%)	23(38.9%)
Ankle + Knee + Elbow	41(41.8%)	36(92.3%)	26(44.0%)
Shoulder	23(23.5%)	13(33.3%)	18(30.5%)
Hip	6(6.1%)	8(20.5%)	2(3.4%)
No	1	2	0
Soft tissue/ Muscle swelling			
Yes	64(65.3%)	38(97.4%)	49(83.0%)
No	34(34.69%)	1(2.56%)	10(16.9%)
Muscle wasting			
Yes	97(98.9%)	36(92.3%)	59(100%)
No	1(1.0%)	3(7.7%)	0
Bleeding/ecchymosis from skin/ other orifices			
Yes	75(76.5%)	35(89.7%)	47(79.7%)
No	23(23.5%)	2(6.6%)	12(20.3%)

Table no. 3 clinical presentation and Investigation of hemophilia B patients

According to **[Table 3],** all types of bleeding were present in every patient. The knee was the most frequently targeted joint (79.6%), followed by the knee plus elbow (57.1%). Muscle wasting was observed in 98.9% of patients, while 70.7% experienced bleeding/ecchymosis from the skin or other orifices, and 65.3% had soft tissue or muscle swelling. The majority of respondents (48.9%) could attend school or work with some restrictions, while 42.8% had limited ability to work or attend school. Additionally, 2.0% could only manage minimal self-care, and 5.1% could carry out activities without limitations. However, none of these traits showed significant differences between individuals with moderate and severe hemophilia. 92.8% of cases displayed changes in the affected joint on X-ray, 66.3% had muscle hematomas visible on ultrasound, and 28.6% had a retroperitoneal hemorrhage in the abdomen on ultrasonography **[Table 4].**

Functional Status			
Unrestricted activity	5(5.1%)	3(7.7%)	0
Full school/work with some limitation	48(48.9%)	25(64.1%)	49(83.0%)
Restricted school/work	42(42.8%)	9(23.0%)	10(16.9%)
Restricted self-care	2(2.04%)	2(5.1%)	0
Investigation			
PT	65.6(13.5)	56.8(13.5)	65.3(13.5)
APTT (sec)	90.20(45.1-122.0)	89.56(73.0-99.0)	89.3(49.5-121.0)
X-ray of the affected joint			
Joint changes present	91(92.8%)	36(92.3%)	58(98.3%)
No change	6(6.1%)	2(5.1%)	1(1.7%)
Mixing Value	1(1.0%)	1(2.5%)	0
Ultra sonogram of the suspected muscle group			
Normal	31(31.6%)	6(15.4%)	21(35.6%)
Muscle hematoma	65(66.3%)	31(79.5%)	37(62.7%)
Missing value	1(1.0%)	0	
Ultra sonogram of the whole abdomen			
Normal	69(70.4%)	21(53.8%)	43(72.9%)
Retroperitoneal hemorrhage	28(28.6%)	17(43.6%)	15(25.4%)

missing value	1(1.0%)	1(2.6%)	

Table no. 4 shows the Functional status of patients with hemophilia B

Location and Incidence of Spontaneous Bleeding by Severity of Hemophilia (n=98)			
Clinical Manifestations	**Total (n=98)**	**Severe (n=39)**	**Moderate (n=59)**
Spontaneous bleeding			
Bruises and ecchymosis	39(39.8%)	22(56.4%)	17(28.8%)
Joint haemorrhage			
Knee	97(98.9%)	36(87.1%)	43(72.9%)
Ankle	89(90.8%)	32(82.0%)	34(57.6%)
Elbow	89(90.8%)	32(82.0%)	34(57.6%)
Wrist Joint	40(40.8%)	11(11.2%)	6(6.1%)
Hip joint	36(36.7%)	17(43.5%)	19(32.2%)
Shoulders	34(34.7%)	12(28.2%)	22(37.3%)
Mucosal Bleeding			
Gum Bleeding	49(50%)	25(64.1%)	24(40.6%)
Epistaxis	23(23.4%)	12(30.7%)	11(18.6%)
Gastrointestinal bleeding			
Hematemesis	7(7.1%)	4(10.3%)	3(5.1%)
Retroperitoneal	19(19.4%)	8(20.5%)	11(18.6%)
Oro-pharyngeal	13(13.2%)	5(12.8%)	7(11.8%)
Melaena	14(14.3%)	7(7.1%)	7(11.8%)
Haemoptysis	6(6.1%)	6(15.4%)	-
Muscle hemorrhage			
Thigh	50(51.0%)	26(66.6%)	24(40.7%)
Calf Muscle	53(54.0%)	25(64.1%)	28(28.6%)
Scalp	3(3.06%)	-	-
Facial	7(7.1%)	4(10.2%)	3(5.08%)
Iliopsoas	36(36.7%)	18(46.1%)	18(30.5%)
Flexor Muscle of the forearm	26(26.5%)	12(30.7%)	14(23.7%)
Buttock	28(28.6%)	9(23.0%)	19(32.2%)
Ocular Bleeding			
Vitreous hemorrhage	6(6.1%)	-	6(10.4%)
Subconjunctival hemorrhage	11(11.2%)	9(23.0%)	3(3.38%)
Genito-urinary bleeding			
Hematuria	47(47.9%)	28(71.8%)	19(32.2%)

Table No. 5 shows the location and incidence of spontaneous bleeding by severity of hemophilia.

[Table No. 3] and **[Figure No. 2]** display the location and incidence of spontaneous bleeding among the study's hemophilia participants, categorized by severity. The average number of spontaneous bleeding incidents over the past two years for severe, moderate, and all hemophiliac participants was 5, 10, and 16, respectively. The knee joint was the most frequently affected (98.9%), followed by the ankle and elbow joints (90.8% each) [Table No. 5]. The knee joints had the highest median number of joint hemorrhage occurrences (12, range: 1-40). Elbow joints followed, with a median of 9 occurrences per episode and a range of 1 to 32. Joint hemorrhages in the knee, elbow, and ankle were more common in severe hemophiliacs, with the knee joint being the most frequently affected (88.6%), followed by the elbow and ankle joints (64% each). The knee joint had the highest median number of occurrences (12, range: 1-40), while the elbow joints had a median of 9 occurrences, with a range of 1 to 32. Severe hemophiliacs were more likely to experience knee joint bleeding, while moderate hemophiliacs had more frequent joint hemorrhages in the ankle, elbow, and shoulder. However, no statistically significant difference was observed. In terms of frequency, number of episodes, and range, the thigh muscle was the most commonly affected in moderate hemophiliacs compared to severe hemophiliacs. Again, no statistically significant difference was found. Nearly half of the patients in both groups experienced gum bleeding, with more severe patients experiencing a higher number of bleeding episodes. Melia was observed in both patient groups with almost equal frequency.

IV. Discussion:

Hemophilia is an X-linked genetic disorder caused by a mutation in the factor IX gene, leading to a bleeding disorder due to impaired coagulation **[7].** Hemophilia patients can experience mild, moderate, or severe illness, depending on the plasma levels of clotting factors. The severity of hemophilia influences the variety of bleeding manifestations, which can occur at any age. This study examines bleeding occurrences in individuals with moderate and severe hemophilia in terms of their locations and frequency, as well as their socio-demographic profiles. A total of 98 patients were included in the study, with an average age of 17.4 ± 10.5 years. In our observation, the average age of symptom onset was 5.5 ± 2.7 years in severe patients and 8.6 ± 4.4 years in moderate patients. According to Karim MA et al. (2013), the average age of onset was 15.8 years **[12].** This study

included only male patients. Of the 98 patients, 59 (60.2%) had moderate hemophilia B (HB) with a factor IX concentration of 1-5%, while 39 (39.7%) had severe hemophilia B with a factor IX concentration of <1%. According to Ahmad et al. (2008), 69.6% of hemophilia B patients had severe hemophilia, and 19.2% had moderate hemophilia [13]. Higher percentages of severe hemophilia cases (87% and 84%) were reported in studies by Sahoo et al. **[14]** and Pawan et al. **[15]** for the years 2020 and 2024, respectively.

The location of initial bleeding can be influenced by various factors. Hemarthrosis in the joints is the most typical presentation, observed in 97% of cases. According to Ahmad et al. **[16],** 82% of hemophilia patients present with hemarthrosis as one of their primary symptoms. In the current study, joint bleeding (hemarthrosis) was the most prevalent clinical manifestation (57.3%), followed by skin bleeds (18%), muscle bleeds (10.7%), epistaxis (7.3%), and petechiae (6.7%). In contrast, Pawan et al. (2021) found that 88% of severe hemophilia B (HB) patients had hemarthrosis, and 96% had hematomas. Our study, however, found that 98.97% of all participants had hemarthrosis, with 87.17% of severe HB patients and 72.88% of moderate HB patients presenting with this symptom **[2].** These differences may be due to variations in geographic areas and populations. This study included only male patients, as carriers are typically female, and patients with hemophilia A and B are more likely to have X-linked hereditary coagulation bleeding disorders. Persistent bleeding following a cut was the most common clinical characteristic in the current study (79.10%). Other bleeding manifestations included: hematemesis (33.44%), hematuria (31.73%), petechiae (22.45%), skin bleeds (16.40%), muscle bleeds (15.33%), post-traumatic bleeds (15.17%), epistaxis (10.68%), tooth extraction (3.25%), bleeding after tonsillectomy (3.26%), bleeding after circumcision (2.32%), and bleeding after cephalohematoma **[17].**

Treatment Modalities:

The aPTT-based one-stage assay (OSA) is the most frequently used method for evaluating FIX activity, while the chromogenic test is used less often [58]. In contrast, both assays may be required for hemophilia A to accurately diagnose and classify the severity of the condition. The OSA is the recognized method for FIX concentrate potency labeling according to the European Pharmacopoeia. It is a quick, easy-to-automate, low-cost method. However, it is associated with a significant degree of variability depending on the aPTT reagent and apparatus used. While these assays are useful for diagnosing patients and measuring FIX or FVIII plasma levels, they do not contribute to our understanding of the clinical heterogeneity of hemophilia **[18].** Hemophilia is a disorder characterized by impaired thrombin production, with most thrombin being generated during clot formation, a process not measured by the fibrin-clotting endpoints typically used to assess hemostasis. Recently, there has been a growing focus on global hemostatic assays. Global assays, which are based on the viscoelastic properties of blood or thrombin generation, provide a more comprehensive view of thrombin generation and clot formation. These assays have the potential to offer a more objective measurement of the hemophilic phenotype and predict clinical responses, as they quantitatively measure several variables using real-time monitoring of the entire clotting process. This is particularly useful after treatment with bypassing agents or novel non-factor replacement therapies **[19].**

V. Conclusion:

Hemophilia B, a genetic bleeding disorder, presents with diverse clinical signs that require ongoing management. Primary care physicians are often the first point of contact for diagnosis and treatment. The symptoms of hemophilia B usually necessitate comprehensive and continuous care. However, specialized tests, such as factor concentration and mutation analysis, which are essential for diagnosing inherited bleeding disorders, are available only in a limited number of clinics in our demographic region. Earlier studies on hemophilia B in India primarily focused on hospital-based data, which failed to provide an accurate assessment of disease severity across broader populations. This study aims to address that gap by offering insights into the relationship between factor concentration levels and disease severity. It also provides valuable demographic and clinicopathological data on hemophilia B within the studied population.

Key Points

For the best possible care and management in the future, hemophilia B must be accurately and promptly diagnosed, considering the patient's factor level, family history, disease severity, and clinical characteristics. The current study gives doctors and other healthcare professionals crucial information for accurate early disease diagnosis and management.

Ethics approval and consent to participate- The institutional ethical approval was taken from the ethical committee (No: Dean/2022/EC/3611) Institute of Medical Science, Banaras Hindu University.

Consent for publication- The written informed consent was obtained from the patient/participant for publication.

Availability of data and material- The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Authors' contributions:

Chanda Hemaliya[1], Lalit Prashant Meena[1] **,** Arun Kumar Singh[1], Ajeet Kumar [2], Akhtar Ali[2]**,** , Avijit Howlader[1], Anupam Aich[1]**,**Sandip Kumar[3] , Vineeta Gupta[4]**,** Ishan Kumar[5],

Chanda Hemaliya- Experimental work, Data collection, reviewing the literature, Data analysis, and manuscript writing. Lalit Prashant Meena- Supervised the study, conceived and designed the experiments; Arun Kumar Singh- Data analysis, reviewing the literature, Ajeet Kumar, Contributions to the manuscript: data analysis, Akhtar Ali, Contributions to the manuscript: data analysis, reviewing the literature. Avijit Howlader- Data analysis, reviewing the literature, manuscript writing, Anupam Aich: Data analysis, reviewing the literature, Sandip Kumar- Sample collection, Data analysis, manuscript writing. Vineeta Gupta- Data analysis, reviewing the literature. Ishan Kumar- Data analysis, reviewing the literature,

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