Original Article

# Rare but not Abdicated: Status of Haemophilia in foothills of Himalaya, Uttarakhand: A cross-sectional study

**Vyas K. Rathaur[1], N. K. V. Vigneshwar[2], Ayesha Imran[3], Monika Pathania[4], Sonam Agrawal[5], Swathi Chacham[6], Prashant K. Verma[7], Nowneet K. Bhat[8]**

*[1]Professor and Head of the Department, Department of Pediatrics, Veer Chandra Singh Garhwali Govt. Institute of Medical Science & Research, N. K. V. Vigneshwar, [4]Associate Professor, Department of Internal Medicine, [2]Junior Resident, [5]Assistant Professor, [6]Additional Professor, [7]Associate Professor, [8]Professor and Head of the Department, Department of Pediatrics, All India Institute of Medical Sciences, Rishikesh, [3]Assistant Professor, Department of Pediatrics, Government Doon Medical College, Dehradun, Uttarakhand, India*

## Abstract

**Background:** Haemophilia is one of the bleeding disorders, which is inherited, in an xlinked recessive pattern. The diagnosis is by estimation of factor levels of 8 and 9. Timebound treatment for people living with Haemophilia (PWH) is factor replacement during bleeding manifestation. The prevalence of Haemophilia was mostly underestimated, and it is more so in hilly terrains like the state of Uttarakhand. **Materials and Method:** This is a crosssectional study by compiling the data of PWH visiting the tertiary care centre for Haemophilia in Uttarakhand. We collected data from the patients with bleeding disorder reporting to the Haemophilia centre from July 2017 to December 2018. In this manuscript, we try to describe the pattern of Haemophilia and the degree of severity and incidence of inhibitors among the sample population of PWH who represent the population of Uttarakhand. The magnitude of problems faced by PWH from this hilly terrain to assess basic treatment in case of emergency is also being depicted. **Result:** We reported Haemophilia A contributing about 80% of the PWH in our centre. Average distance a PWH has to travel to obtain treatment was about 131.5 km (SD ± 83.7 km). Incidence of inhibitors was about 5%. **Conclusion:** We infer from our study that Hemophilia A is more common than Hemophilia B. Through this manuscript we hope to spread awareness of the Haemophilia care that is ongoing, the role of prophylaxis therapy and the future role of primary care physicians that may change the care of PWH in future.

**Keywords:** Factor eight, haemophilia, haemophilic arthropathy, inhibitors, Royal disease

## Background

Under the rubric of prevalent bleeding disorders, haemophilia takes the major chunk worldwide and the main brunt of the disease is borne by males of the society, as it is a mainly x-linked recessive disorder. Females usually act as the carriers of this vitiation and are rarely affected. Haemophilia is one among the high cost and low volume diseases because of uncommon nature and heavy expenses involved in treatment and managing the complication.[1] This has prevented government health policymakers to conjure comprehensive care for such conditions.

**Address for correspondence:** Dr. Monika Pathania, Department of Internal Medicine, All India Institute of Medical Sciences, Rishikesh, Uttarakhand, India.
E-mail: anshupathania@gmail.com

**Received:** 13-08-2020 **Revised:** 06-10-2020
**Accepted:** 28-10-2020 **Published:** 08-04-2021

Access this article online

Quick Response Code:

Website: www.jfmpc.com

DOI: 10.4103/jfmpc.jfmpc_1613_20

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**How to cite this article:** Rathaur VK, Vigneshwar NKV, Imran A, Pathania M, Agrawal S, Chacham S, *et al*. Rare but not Abdicated: Status of Haemophilia in foothills of Himalaya, Uttarakhand: A cross-sectional study. J Family Med Prim Care 2021;10:1437-42.

Unlike infectious and non-communicable diseases like cardiovascular disease, asthma, diabetes and hypertensive disorders, genetic diseases are given a low priority in India. Complex and money consuming diagnostic processes, lack of awareness among the general population and huge costs involved in disease management are methodological challenges which make the approach of these rare diseases difficult from a public health standpoint.[2] Even with the 4.1% increase in the health budget of 2020 as against previous years, it is not enough to tackle the financial burden that these rare diseases lay upon a normal individual.

In the year 2020 India ranks in second place next to China with a total population reaching up to 1.39 billion. With 70,000 births per day, Indian demographics may contribute to a high prevalence of most genetic disorders which are mostly underdiagnosed. Any health programme begins by understanding the disease burden and the estimated costs involved to bring about any revelation for its management. The data to decipher the above-mentioned information is obtained from various registries, case series and descriptive studies which are carried out all across the country. This data lacuna is filled up by a patient's organisation like Haemophilia Federation of India, which has dedicated itself in improving the haemophilia care in our country till date. In our descriptive study, we give valuable information about a cohort of haemophilic patients of Uttarakhand state. This might help to shine light in the future scenarios while improving the care of haemophilic patients of this region.

## History of haemophilia

Mutation in the gene coding for clotting factor VIII or IX leads to their deficiency resulting in disease Haemophilia A and B respectively. Haemophilia B is also called the Christmas disease after the surname of the first child reported with this condition. The Royal disease was the unique name given to haemophilia after it manifested in the European royal family when Prince Leopold died of this disease in the year 1884. The disease was then traced back to Queen Victoria who might have developed de-novo mutation and this later went down the royal family tree.[3] The X chromosome contains the loci for these genes which are Xq28 and Xq27.1-q272 respectively.[3,4] Repeated bleeding manifestation involving soft tissues like hematoma involving muscles and hemarthrosis are the presenting features of this disorder, at times the bleeding can be life-threatening involving the central nervous system. The residual factor level and the underlying genotype are the main deciding factors for frequency and severity with which the bleeding manifestation occurs.[5] The classification of disease severity is based on active clotting factor percentage with severe deficiency having <1%, moderately severe having 1-5% and mild disease having 5-40% of the normal clotting factor levels.

Haemophilia with typical X linked recessive inheritance is reported in about 70% individuals whereas sporadic cases account for 30% of total cases. Mother is a carrier in familial cases with sons having 50% chance of inheriting the defective gene.[4]

## Epidemiology of haemophilia (Actual vs Expected)

The estimated incidence of spontaneous mutation of haemophilia A is 1 per every 5000 male newborn whereas for haemophilia B is 1 in every 30000 newborn males.[6,7] As per the National Haemophilia Registry Statistics 2019, patients with bleeding disorders were reaching nearly twenty-two thousand (21824), with Haemophilia A contributing to about 17606 patients, haemophilia B amounting to 2715 patients.[8] The prevalence of inhibitors was about 787, which was about 3.6% of the total bleeding disorders registered in India. Anita Kar *et al.* estimated 48,407 cases considering data of 2011 census.[2] India with a population of 1.39 billion and assuming 4 per 100000 as combined case detection rates which are at par with the USA, we estimate the total number of case of haemophilia in India would be 55,600 which is 33,776 patients more than the number estimated by the haemophilia federation of India 2019 report. This accounts for a case detection rate of 1.6 patients per 1, 00,000 population which has improved when compared to the earlier estimated 0.9 patients per 1, 00,000 population in previous studies.[2]

## Problems faced by people living with haemophilia (PWH)

On demand, infusion while active bleeding and prophylactic infusion of specific factor concentrate are the available treatment for PWH. But many a times owing to the high cost and their non-availability has led to most of the bleeding manifestation to be managed by simplified first aid measures. 'RICE 'is the acronym to remember the steps to be followed in case of bleeding and denote rest, ice application, compression and elevation of affected limb respectively.[9]

With substandard treatment and repeated joint bleeds confers chronic and progressive joint damage for PWH. The chronic pain associated with arthritis may result in frequent absenteeism, poor education and job opportunities for PWH. In a country like India where gender-related injustice is prevalent, haemophilia may result in victimization of the mother or maternal guilt. The high cost of factor, frequent hospitalisation, insufficient subsidization of the clotting factors and cost involved in the management of complication increases the financial burden of PWH.

Above factors, also reduce productivity and makes PWH dependable on their family.[10-12] Kar *et al.* in their descriptive study in assessing disability in PWH noted a significant association between socioeconomic status of family and severity of disability score. This emphasises the fact that improper treatment is a predictor of disability in PWH.[12] Transfusion acquired infection such as HIV, Hepatitis C and Hepatitis B adds to the burden of PWH.

## Inhibitors in PWH

Alloantibodies also called inhibitors are IgG molecules that act against factor VIII. They were more likely to be formed in PWH

with severe disease and on irregular treatment.[2] They are more likely to be associated with haemophilia A than haemophilia B. Inhibitors act by neutralizing clotting factor concentrate and they pose a challenge while managing PWH as they treatment unresponsive. The likely prevalence of inhibitors may range from 8.2 to 13% in India.[13,14] Nijmegen-modified Bethesda assay or simple Bethesda assay are methods used to confirm the presence of inhibitors.[15-17] Immune tolerance induction, recombinant activated factor VII and plasma-derived activated prothrombin complex concentrate are the available modalities for tackling the inhibitors while managing PWH.[18] Unfortunately, diagnosis and treatment of inhibitors in PWH are expensive hence many remain untreated.

### Prophylaxis management of haemophilia

Factor replacement has been the mainstay for management of haemophilia. On-demand factor replacement has been used for treatment for acute onset soft tissue bleeds including hemarthrosis. This is overtaken by the concept of prophylactic factor replacement, which is usually started in childhood and eliminating the joint damage in PWH.[8,19] This idea was based on the observation that the PWH with the milder illness have less probability of spontaneous joint bleeds, chronic arthropathy and have a better joint function in comparison with acute severe disease.[20] If such individuals were to receive low dose prophylaxis treatment regularly, (often 2 to 3 times per week) might inhibit the joint disease. This assumption is backed by a Swedish cohort study, which showed constant prophylaxis which started at a young age and continued for years showed reduction in joint disease, number of bleeding episodes and resulted in high quality and productive life for PWH.[21] A recent study conducted in Eastern India showed a decrease in the annual rate of joint bleeding, an increase in child's day-to-day activities, a decrease in school absenteeism, a decrease in total factor consumption and consequently reduced cumulative management expense.[22] Earlier prophylaxis initiation has shown to reduce the incidence of inhibitors in PWH. The main drawback that limits prophylaxis use in a developing country like India is the high cost involved. In our centre, we follow RICE strategy and on-demand factor replacement for any hemophilic patient presenting with a bleeding episode.

### Role of primary care physician

A primary physician is the point of first contact for any patient. With scarcity of the specialty centres and increasing patient load, a mismatch arises that impairs patient care. Such disadvantage can be buffered by trained primary physicians who can identify, register and carry out prompt referral for disease like haemophilia. Even though primary health centres (PHC) are ill equipped to initiating specific treatment, a simple practice of enforcing the acronym RICE may go a long way in decreasing morbidity for PWH in their process of referral. Primary care physician can serve as the missing link to tackle the under-reported prevalence of haemophilia in India. Micro-registries at PHC level in collaboration with Haemophilia Federation of India may enhance the case detection rate for haemophilia in India.

With the advent of " Era of prophylaxis factor administration", trained primary care physician in future may monitor, regulate and educate PWH locally. This can avoid the excess time and money spent by PWH in reaching the speciality centre to obtain optimum treatment.

## Aims and Objective

### Primary

1. To estimate the total number of cases of haemophilia reporting to a tertiary care centre in Uttarakhand from July 2017 to December 2018.
2. To determine the distribution of type, severity and age distribution of PWH.

### Secondary

1. Incidence of inhibitors.
2. To find out any direct or temporal association of haemophilia with different blood groups.
3. Average time and distance which is taken for a PWH to reach haemophilia centre.

## Materials and Method

This is a cross-sectional study was conducted at a haemophilia centre of government medical college Dehradun during the period July 2017 to December 2018. It caters the bleeding disorder patients from hilly areas of Chamoli, Pauri Garhwal, Tehri and planes of Dehradun, Roorkee and Haridwar district mainly. Permission to conduct the study was obtained from institutional ethical committee. All patients who were previously diagnosed with haemophilia or the ones newly diagnosed with prolonged bleeding episodes attending the haemophilia clinic and raised Aptt levels with decreased factor eight or nine assays were included. Others bleeding disorders were excluded from the study. The persons with haemophilia not responding to the usual recommended doses corresponding to the site of bleeding underwent Bethesda assay for detection of inhibitors. Data regarding age, place of residence, deficient factor, degree of factor 8 deficiency, blood group of the individual, the average time taken for travel and average distance travelled to reach the centre for treatment were collected and the data were entered in excel 2018, latest SPSS version was used to analyse data. The severity of haemophilia was classified based on plasma levels of factor VIII (FVIII) or IX (FIX) activity as follows: less than 1% being severe, between 1 to 5% being moderate, and if >6 to 40% of normal is mild disease. Descriptive data are presented as the means and standard deviations, medians and ranges, or percentages. Chi-square test and Fisher's exact test were used to compare categorical variables. Ethical committee date of approval: 02/07/2017.

## Results

One hundred and one patients were registered between July 2017 and December 2018 of which 100 had a confirmed diagnosis of haemophilia A or B and one patient with von-Willebrand disease. Almost 80% of all the diagnosed haemophilia had factor eight deficiency and rest 20% was contributed by factor nine deficiency with a ratio of haemophilia A/haemophilia B as 80/20. About 5 patients who were known case of haemophilia A were found to have inhibitors through Bethesda assay, this is depicted in Figure 1. Of the age group presentation, the 11-20 age group accounted for the majority, which is depicted in Figure 2. The mean age of presentation in our centre was 19.2 (±13.1) for haemophilia A whereas for haemophilia B it was 20.8 (±11.6 years). As shown in Figure 3, Factor levels for all the haemophilia A were quantified In whom, severe deficiency contributed to 61 out of 80 patients. Among the 100 patients, 87 had their blood group estimated and it was noted that most common blood group were A and B, as shown in Figure 4. We used Chi-square analysis to test the strength of association between various blood groups and both types of haemophilia [Table 1] and found no significant relationship (p = 0.97).

Figure 5 shows the regional distribution of haemophilia cases of which forty-six (48.4%) patients belonged to Dehradun

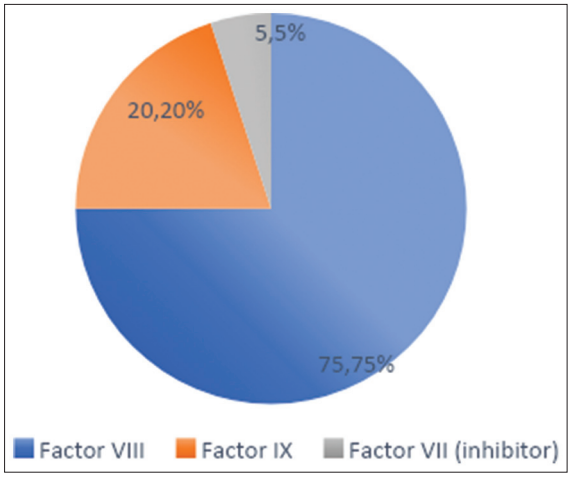


**Figure 1:** Distribution of factor deficiency

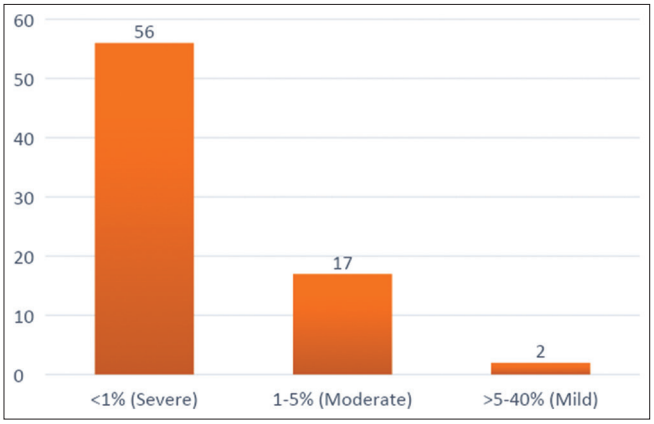


**Figure 3:** The severity of factor 8 deficiency

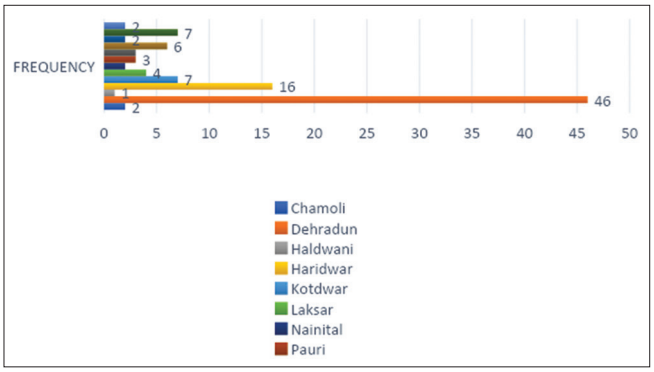


**Figure 5:** Region-wise distribution of thalassemia cases

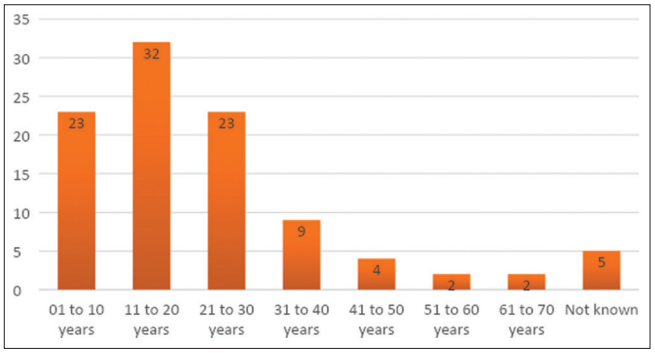


**Figure 2:** Age group distribution

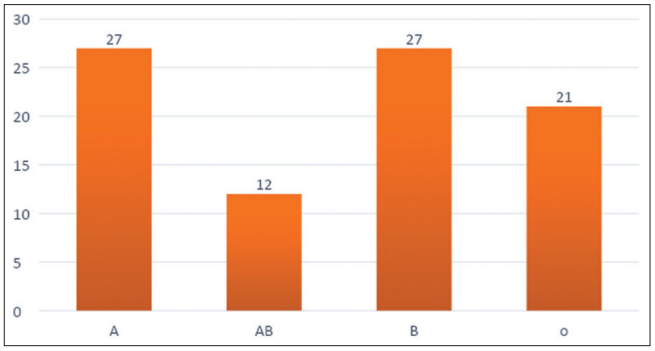


**Figure 4:** Blood group distribution among the study population

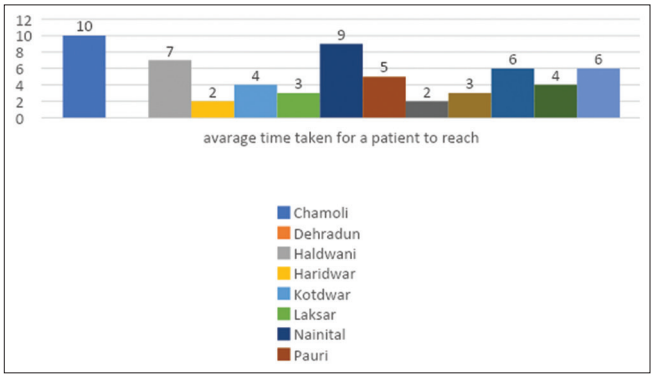


**Figure 6:** Average time taken for travel

**Table 1: Chi-square statics testing strength of association between blood group and types of haemophilia**

| Blood group type | Haemophilia A | Haemophilia B |
|---|---|---|
| A | 21 | 5 |
| B | 23 | 5 |
| AB | 10 | 2 |
| O | 18 | 3 |
| | 67 | 15 |

The Chi-square statistics is 0.21 with a $P$=0.97

contributing to a major chunk followed by Haridwar, which accounted for sixteen patients (16.8%). For the patient who is not a resident of Dehradun an average distance to cover was 131.5 km (SD ± 83.7 km) with the shortest distance being 47 km (Rishikesh) and longest being 283 km (Nainital). The mean time taken for any patient to reach Dehradun was 4.6 ± 3.8 hours. As shown in Figure 6 the maximum time taken for travel was from Chamoli which was 10 hours and with Haridwar and Rishikesh accounting for minimum time it took about 2 hours.

## Discussion

The ratio of haemophilia A/haemophilia B has been reported between 78/22 and 87/13 throughout the world.[23] in our study, we report a ratio of 80/20.

In a study, out of the 50 cases diagnosed with haemophilia based on the laboratory tests, a majority of 82% were haemophilia A and rest was haemophilia B.[24]

This pattern where Hemophilia A contributing more than haemophilia B patients was similar to the study by Dube *et al.*[25] and Agarwal *et al.*[26]

A study from northern India reported 89% of its study population to have haemophilia A.[27] In our study we report about 80% was by haemophilia A and 20% of haemophilia B in our study which similar to the above observation.

Sixty-one out of 80 patients with Hemophila A had severe deficiency, which amounted to 76% of the total 80 whose factor levels were assessed. We also noticed severe deficiency more common than moderate and mild deficiency and the similar data was reported by Parthiban *et al.*,[24] Agarwal *et al.*,[26] Hazewinke *et al.*[28] in South Africa, Kim *et al.*[29] in the Korean population and Lusher *et al.*[30]

Rajendra Kumar and team reported in their study 52% were severe category.[27] our observation of prevalence of more sever disease can be explained by the fact that our centre is among the few tertiary care and primary referral centre for many surrounding primary and district hospitals. The probably of receiving critically ill patient including sever haemophilia is more when compared to other hospital.

The incidence of inhibitors was 5% which was lower when compared to the prevalence reported in previous studies.[13,14]

Studies have shown the ABO is an important covariate in determining the pharmacokinetic parameter while giving factor VIII. We tried testing the association between the types of blood group with the types of haemophilia and found that there was no significant association. Hazendonk *et al.* identified that half-life of infused factor VIII was related to the ABO blood group of the Recipient from a retrospective analysis. In their study, they showed blood group O was predictive of factor VIII under-dosing and associated with increased risk of bleeding complications.[31] A pooled analysis by Fischer *et al.* showed that half-life of factor eight in O blood group type was lesser then other blood groups.[32] This had led us to hypothesise the possibility of a particular blood group (like blood group O) being more associated with haemophilia disorder (haemophilia A). We tried testing the strength of association with the various blood groups and types of haemophilia and ended up finding no significant association.

On mapping, the distance and time taken for any haemophilia patient who has accessed his on-demand treatment has shown the burden faced by these individuals. Any haemophilia who are under our care circle has to travel an average distance of 131.5 km (SD ± 83.7 km) and takes an average time of 4.6 ± 3.8 hours to get their desired treatment. These lacunae not only expose the social difficulty faced by these individuals but also, may contribute to underdiagnoses and increased risk of inhibitor levels which will contribute to the total expenditure of the disease.

A practical solution for this can be the concept of prophylaxis therapy. With a familiar analogy of type 1 diabetes mellitus where the individual learns to administer insulin on their own. A hemophilic patient can be taught to self-administer low doses of factor on a regular interval in a nearest health centre under supervision of primary care physician. This assumption was supported by a study conducted in eastern India, showing clinical benefits and overall cost reduction making it a viable option for a developing country like India.[22] Even telemedicine can play a pivotal role in prescribing and guiding the prophylactic dose of factor administration especially in the epoch of COVID19. The PWH can also be taught to monitor for signs and symptoms of IV catheter infection or dysfunction, during which they can immediately report to the healthcare care centre to have it fixed. This approach may be safer than a scenario where a patient needs to travel long distance for treatment during ongoing life-threatening bleeding.

## Conclusion

We conclude that from the sample population from the hilly areas of Uttarakhand we observed that haemophilia A was more common. The severe deficiency contributed to the major part of the spectrum. The incidence of the inhibitor was about 5% and there was no temporal association between blood group and type of haemophilia. The average distance for PWH to reach the designated health care facility was 132 ± 84 km and the time taken

to reach for the help in hilly areas is almost double the time taken in plains. This showed the difficulty for PWH in assessing treatment in emergent condition. Even though the initial cost involved in starting prophylaxis-based treatment for PWH may be high but on the long run this will benefit in achieving good disease control, alleviating joint pathology and overall improving the quality of life of PWH. So low dose prophylaxis should supplant on-demand therapy. Primary care physicians who can educate and monitor the prophylaxis administration in PWH may serve as key for this transition in future. This may reduce the burden of long distance travel and ensure optimal case registration for PWH. Further studies are needed to estimate prevalence, to known the disease burden and to test the hypothesis that prophylaxis therapy of haemophilia may prove to bring about the significant difference of this disease in India.

## Financial support and sponsorship

Nil.

## Conflicts of interest

There are no conflicts of interest.

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