Original Article

Demographic Profile and Real World Data of Persons with Hemophilia in a Resource Constrained Setup

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Abstract

Background: Hemophilia is underdiagnosed in India, and there is lack of state specific data on the extent and morbidity. This article provides the real world demographic and clinical data of patients with hemophilia (PwH) in a resource-constrained setting in Punjab, India. **Patients and Methods:** This is a retrospective analysis of PwH in the institutional hemophilia registry over 9 years. Eligible patients who had a confirmed diagnosis at our institute were included in the analysis. Demographic, clinical, and treatment data used in the current analysis were extracted from medical records using a standardized data collection form. **Results:** A total of 211 patients were from Punjab, comprising 175 PwH A (91.3%) and 36 with PwH B for uniformity. The mild, moderate, and severe hemophilia in the cohort were 32 (15.1%), 45 (21.3%), and 132 (62.5%), respectively. No patient was on continuous prophylaxis. Inhibitors were positive in 7.9% of patients. Joint deformity was found in 83.5% of severe PwH. Transfusion-transmitted infections were found in 24 (18.3%). There were no statistically significant differences between hemophilia A and B groups with regard to demographic or clinical characteristics. The current median age of the group was 22 years against a national average of 27.6 years. Only 7.4% of the estimated cases of PwH are diagnosed in Punjab. **Conclusion:** There are significant underdiagnoses, increased incidence of transfusion-transmissible infection, and joint deformity among PwH in Punjab. Therefore, it warrants an immediate need to develop a registry, increase awareness about hemophilia, and provide comprehensive care.

Keywords: *Demographics, hemophilia, Punjab, real world data, resource constrained*

Introduction

Punjab is a North-Western state of India with a population of 27.7 million, comprising 52.7% males.[1] With gross domestic product per capita of Rs. 128821 (US$ 1972) in 2016–2017 at current prices, the state ranks 3rd among the 29 states and seven union territories in India.[2] Although there are multiple health schemes to promote healthcare in Punjab, there has been limited programs for hemophilia.[3] Hemophilia A and B are sex-linked disorders occurring due to a mutation in coagulation factor VIII and IX genes, respectively, located on the X chromosome.[4] Hemophilia A is more common than hemophilia B, constituting 80%–85% of the total hemophilia population.[5]

According to the World Bank Atlas method, India belongs to the lower-middle income countries with a gross national income per capita income of US$ 1680 (between US$1,026 and 4,035).[6] As per the world federation of hemophilia (WFH) 2016 global survey, India harbors the highest number (18,353) of patients with hemophilia (PwH).[7] However, this represents a significant under diagnosis, as with a population of 1.32 billion and a prevalence of 1/10000 male births, and the expected number of PwH in India should be approximately 1,32,000. This indicates that the proportion of patients actually diagnosed is <15%.

This reflects low awareness, poor diagnostic facilities, and limited "registry data". Only an estimated 1% of patients under the age of 18 years undergo prophylaxis in India as against 85% in the United States, 95% in UK, and 77% in Brazil.[7,8] The reported median age of presentation of hemophilia in the Maharashtra is 11–15 years, which is much later than that reported in the Western population.[9]

PwH have life-long history of bleeding leading to musculoskeletal (MSK) complications. Asymptomatic patients or PwH with mild disease may experience

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bleeding only with trauma or during surgery. Lack of treatment with clotting factor concentrates (CFC) results in progressive disability, especially in severely affected PwH. A study from Southern India, in 2007, showed that the proportion of disability-free patients in the 5–12, 13–24, and >25 years of age groups were only 14.3%, 4.4%, and 0%, respectively.[10]

At present, there is limited published data on demographic details and clinical status of the PwH from Punjab. The objective of this study is to detail the real-world scenario of PwH in Punjab.

Patients and Methods

This is a retrospective analysis of PwH from the institutional hemophilia registry over 9 years (from July 2008 to June 2017) maintained at the Department of Clinical Hematology. Eligible patients with a confirmed diagnosis at our institute were included in the analysis. Demographic, clinical, and treatment data used in the current analysis were extracted from medical records using a standardized data collection form. The severity of hemophilia was classified based on plasma levels of factor VIII (FVIII) or IX (FIX) activity as follows: severe if <1%, moderate if between 1% and 5%, and mild if >5 and <40% of normal.[11] As all our patients belonged to out-of-pocket (OOP) expense group, inhibitor, and blood-borne viral markers screen were performed only in patients who could afford the same. Hemophilia joint health score (HJHS) and functional independence score in hemophilia (FISH) were done in patients who consented.[12] The presence of a restricted range of movements (ROMs) and clinical evidence of synovial thickening were considered to be joint deformity in this analysis. Data that were unavailable were recorded as missing data, and the rest of the data was analyzed with valid percentages (excluding the missing data). The analysis was performed using SPSS version 21 (IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY) and it is being reported as per the Strengthening the Reporting of Observational Studies in Epidemiology statement.[13] 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.

Results

A total of 256 patients were registered in our institution between July 2008 and June 2017, of which 231 had a confirmed diagnosis of hemophilia A or B. Two hundred and eleven (91.3%) patients belonged to Punjab and 20 (8.7%) were from other states. The distribution of PwH in each district, population, and the expected numbers is given in Table 1.

Majority of the patients were from urban (152, [72%]) and rest (59, [28%]) belonged to rural areas with a median distance of 63 km (range 1–214 km) from our center. The median age of first bleed was 1.5 years (range 1–48 years) and the median age of diagnosis was 3 years (range 1–50 years). The current median age of the group was 22 years against a national average of 27.6 years.[14] No patient was on continuous replacement therapy (prophylaxis). There was no significant difference in the demographic profile or clinical characteristics between hemophilia A and hemophilia B groups [Table 2].

Table 1: Distribution of patients with hemophilia in Punjab

District name	*n* (%)	Population as per 2011 census[1]	Expected patient numbers @ 1:10000
Amritsar	6 (2.8)	2,490,891	249
Barnala	0	596,294	60
Bhathinda	8 (3.8)	1,388,859	139
Faridkot	1 (0.5)	618,008	62
Fatehgarh Sahab	5 (2.4)	599,814	60
Fazilka	1 (0.5)	1,063,737	106
Ferozepur	7 (3.3)	2,026,831	203
Gurdaspur	7 (3.3)	2,299,026	230
Hoshiarpur	3 (1.4)	1,582,793	158
Jalandhar	23 (10.9)	2,181,753	218
Kapurthala	1 (0.5)	817,668	82
Ludhiana	93 (44.1)	3,487,882	349
Mansa	2 (0.9)	768,808	77
Moga	5 (2.4)	992,289	99
Mohali	2 (0.9)	986,147	99
Muktsar	3 (1.4)	902,702	90
Nawanshahr	2 (0.9)	614,362	61
Pathankot	1 (0.5)	676,598	68
Patiala	29 (13.8)	892,282	89
Ropar	1 (0.5)	683,349	68
Sangrur	10 (4.7)	1,654,408	165
Taran Taran	1 (0.5)	1,120,070	112
Total	211 (100)	28,444,571	2844

Twenty-nine (13.7%) patients from the cohort required surgery over 9 years with 75% of patients requiring major and 25% requiring minor surgeries. Twenty-four (18.3%) patients were found to have transfusion-transmitted infections and all of them were noted to have prior exposure to fresh-frozen plasma (FFP). In contrast, no TTIs were noted in patients who had received only CFCs (both plasma derived and recombinant) [Table 3].

In this study, missing data were missing completely at random and no imputation methods were used to include them in the analysis.[15]

Discussion

This study describes the prevalence and baseline characteristics of PwH from Punjab, India. The study has shown significant underdiagnoses with only 7.4% of the

Table 2: Demographic profile of patients with hemophilia

	Hemophilia A *n* (valid %)	Hemophilia B *n* (valid %)	Total *n* (valid %)	*P*
Total number	175 (83.0)	36 (17.0)	211	0.735
Mild	26 (15.0)	6 (16.7)	32 (15.1)	
Moderate	39 (22.5)	6 (16.7)	45 (21.3)	
Severe	108 (62.4)	24 (66.7)	132 (62.5)	
Missing	2 (1.1)	0	2	
Median age of the first bleed (range) (years)	1.5 (0-48)	2 (1-48)	1.5 (0-48)	0.749
Median age of the diagnosis (range) (years)	3 (1-50)	2 (1-46)	3 (1-50)	0.879
Current median age (range) (years)	22 (1-67)	22 (2-48)	22 (1-67)	0.949
0-4	10 (5.7)	3 (8.3)	13 (6.2)	0.966
5-13	40 (22.9)	8 (22.2)	48 (22.7)	
14-18	25 (14.3)	4 (11.1)	29 (13.7)	
19-44	82 (46.9)	17 (47.2)	9 (46.9)	
>45	18 (10.3)	4 (11.1)	22 (10.4)	
Type of first bleed				
Joint	32 (31.7)	5 (27.8)	37 (31.1)	0.971
Muscle	7 (6.9)	2 (11.1)	9 (7.6)	
Subcutaneous	8 (7.9)	1 (5.6)	9 (7.6)	
Intracranial	3 (3.0)	1 (5.6)	4 (3.4)	
Gastrointestinal	2 (2.0)	0	2 (1.7)	
Genitourinary tract	1 (1.0)	0	1 (0.8)	
Mucosal Bleed	27 (26.7)	4 (22.2)	31 (21.6)	
Traumatic	18 (17.8)	5 (27.9)	23 (19.3)	
Dental procedures	2 (2.0)	0	2 (1.7)	
Others	1 (1.0)	0	1 (0.7)	
Missing data	74 (42.3)	18 (50)	92 (43.6)	

Table 3: Clinical characteristics of patients with hemophilia

	Hemophilia A (*n*=175)	Hemophilia B (*n*=36)	Total (*n*=211)	*P*
Positive family history *n*/total number† (%)	74/146 (50.7)	19/34 (55.9)	93/180 (51.7)	0.362
Inhibitor status *n*/total number† (%)	11/128 (8.6)	1/24 (4.2)	12/152 (7.9)	0.404
TTI *n*/total number† (%)	19/105 (18.1)	5/26 (19.2)	24/131 (18.3)	
HIV, *n* (%)	1 (0.9)	0	1 (0.8)	0.972
HCV, *n* (%)	14 (13.3)	4 (15.4)	18 (13.7)	
HBsAg, *n* (%)	3 (2.9)	1 (3.8)	4 (3.1)	
HIV + HCV	0	0	0	
HCV + HBsAg	1 (0.9)	0	1 (0.8)	
FFP only	0	0	0	
CFC only *n*/total number† (%)	13/175 (7.4)	2/36 (5.6)	15/211 (7.1)	
FFP and CFC *n*/total number (%)	103/175 (58.9)	22/36 (61.1)	125/211 (59.2)	
Surgery	21 (12)	8 (22)	29 (13.7)	
Major (*n*/total number)	15/21 (71)	7/8 (87.5)	22/29 (75.8)	0.167
Minor (*n*/total number)	06/21 (29)	01/8 (12.5)	07/29 (24.2)	
HJHS				
Median (range), *n*	32 (4-74) 84	28 (6-66) 15	31 (4-74) 99	0.189
FISH, median (range), *n*	25 (12-32) 21	27 (14-32) 7	25 (12-32) 28	0.391
Joint deformity	122	25		
Mild*	8 (61.7)	1 (50)	9 (60)	0.506
Moderate#	20 (66.7)	4 (80)	24 (68.6)	
Severe$	66 (83.5)	15 (83.5)	81 (83.5)	
Missing data	53	11	64	

*Hemophilia A (*n*=13), Hemophilia B (*n*=2), #Hemophilia A (*n*=30), Hemophilia B (*n*=5), $Hemophilia A (*n*=79), Hemophilia B (*n*=18), †Rest missing data. TTI: Transfusion transmitted infection, HIV: Human immunodeficiency virus, HCV: Hepatitis C virus, HBsAg: Hepatitis B surface antigen, FFP: Fresh frozen plasma, CFC: Clotting factor concentrate, HJHS: Hemophilia joint health score, FISH: Functional independence score in hemophilia

estimated 2844 PwH in the state being diagnosed. The gap between the expected and diagnosed patients in each district is depicted in Figure 1.

Our data also show a much higher percentage of severe hemophilia. The distribution of mild, moderate, and severe PwH in high-income countries is 40%, 15%, and 45%, respectively, in contrast to 15%, 22%, and 63% in this study.[7] This may be due to undiagnosed mild disease with the lack of symptoms, early mortality among severe and moderate hemophilia patients due to unaffordability and inaccessibility of CFCs, and transfusion-transmitted infections.

The study has shown a lower median age (22 years) in PwH as compared to the national average (27.6 years) and also had a lesser proportion of PwH in the age group >45 years (10% vs. 18%).[16] This is much lower than that reported in the developed countries (20%–40%).[7]

Multiple plasma transfusions predispose hemophilia patients to be at a higher risk of developing TTIs. In this study, 24 (18.3%) PwH were found to be seropositive for either HIV/hepatitis B virus surface antigen (HBsAg) or hepatitis C virus (HCV), and one patient had coinfection with HCV and HBsAg. All these patients had prior exposure to FFP. None of the PwH who received only CFC (both plasma-derived/recombinant) was found to be seropositive. A large proportion of patients remain untested due to financial constraints.

The reported median life expectancy of severe PwH over the years has increased significantly due to the availability of FFP, cryoprecipitate, and improved hemophilia care.[17-20] However, in the 1980s, with an estimated 60% of PwH in the US affected with HIV and HCV, with plasma and plasma-derived factors, and the median life expectancy dropped to 39.8 years.[21]

A study from the Western India in 2000, noted that HIV, HBsAg, and HCV infection rates among PwH were 3.8%, 6%, and 23.9%, respectively, which was only 0.8%, 3.1%, and 13.7% in this study. Almost 50% of reduction in the positivity rates as compared to the former study is possibly due to improved screening mechanisms in the blood banks and better access to CFCs. This is analogous to multiply-transfused thalassemia patients in India, where the TTI rates are 1.04%, 1.04%, and 25%, respectively.[22] Although higher generation ELISA screening and NAT testing of blood products may reduce the prevalence, it does not obviate the risk of TTI. Exclusive treatment with CFCs by improving its availability and avoiding FFP transfusions would be the best alternative to prevent this complication among PwH.

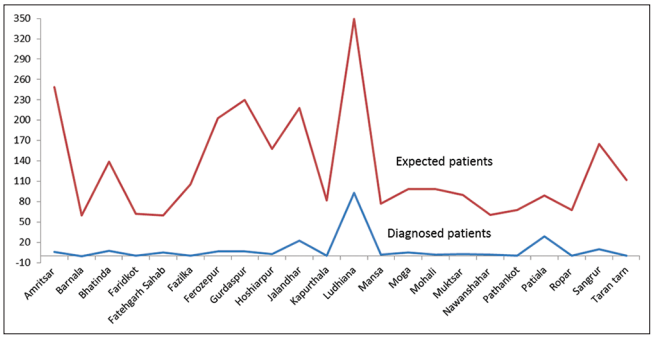

Figure 1: District-wise distribution of expected and diagnosed patients

In PwH, approximately 90% of bleeding episodes involve the MSK system, and in 80% of cases, the joints are particularly affected.[23] In this study, the prevalence of joint deformity (restricted ROM and clinical evidence of synovial thickening) was 83.5% in those with severe disease and much lesser in moderate and mild PwH. This is due to nonaffordability for prophylaxis and inaccessible CFC supply.

The lifetime risk to develop inhibitors is 25%–30% for severe hemophilia A and 1%–6% for hemophilia B.[5] The study showed an inhibitor incidence of 8.6% in hemophilia A and 4.2% in hemophilia B, similar to a study from the Western India in which the reported incidence was 8.2% and 2.8%, respectively.[24] Another study from India reported the incidence to be 13%.[25] The lower incidence of inhibitor development as compared to the Western literature is postulated to several variables such as lesser exposure days, reduced infusions of high-purity or recombinant factors, and undiagnosed transient inhibitors due to the low frequency of testing and probably ethnic differences.[24]

Surgical interventions in PwH require close laboratory monitoring and a significant amount of factor use. Approximately 200–300 units/kg per surgery is suggested by the WFH guidelines in the context of resource constraints.[5] In this study, 13.7% of patients required surgical intervention during 9 years, with 2/3rd of them undergoing major procedures.

The prevalence of sporadic hemophilia was earlier estimated to be 1/3rd of cases.[26] Our analysis showed that an overall 51.7% of PwH (50.7% hemophilia A and 55.9% hemophilia B) had a definite family history and the rest was sporadic (first affected sibship in the family). A study evaluating the prevalence of sporadic and familial hemophilia, reported that 45%–57% of patients with severe and 70% with mild and moderate hemophilia had a positive family history.[27] The reason for increased sporadic cases is probably due to undiagnosed mild PwH.

The HJHS provides an objective measure of joint structure and function, and can help to pick up early signs of joint damage. It is primarily designed for children with hemophilia who are on prophylaxis and can be used as an outcome measure of physiotherapy interventions. The HJHS 2.1 provides a total worse score of 124.[28] In this study, it was used to define a baseline in joint assessment. A total of 99 patients consented for evaluation and were

found to have a median HJHS score of 31 (range 4–74). While this is comparable with a Lithuanian study with an HJHS score of 24.5 in those who are not on prophylaxis, it should be contrasted to the PwH in Utrecht, and the Netherlands on regular prophylaxis playing sports with a median score of 0 (range 0–3).[29,30]

The FISH is intended to measure the activity of a person with a disability in the areas of self-care, transfer, and locomotion. This can be used to evaluate the change in functional independence over time, or after a therapeutic intervention.[31] The baseline FISH among our cohort of patients was 25 (12–32) which was comparable mean FISH scores in the Egyptian (23.32) and Mexican studies (25.8), where regular prophylaxis is unavailable.[32,33]

Prophylaxis in hemophilia is considered standard of care, and it has superiority over on-demand therapy.[34] Prophylaxis prevents bleeding and joint destruction and should be the goal of therapy to preserve normal MSK function. However, in our cohort, no patient was on regular prophylaxis, and the majority received only intermittent prophylaxis or episodic therapy. This explains the high incidence joint deformity among severe PwH. Subsidized treatment services have limited availability of CFCs which leads to significant OOP expenditure for PwH in India.[35]

In the past 8–10 years, HFI and its constituent chapters have positively engaged state Governments to provide free factors. As per the annual report of 2014-15, 110 million units of factor concentrates were used by 16,000 PWH in India amounting to almost 7,000 IU of factor concentrate/PwH/year. Although this amount is far below the requirement, it is much higher than 200–500 IU/PwH/year in the 1990s.[36] India has one of the lowest factor usages as per the global survey and according to the recent report, the per capita use of FVIII concentrate in India is 0.105 IU as compared to a global average of 2.91 IU. The per capita use of FIX in India is 0.002 as compared to the global average of 0.38 IU.[7] The extremely low per capita use of treatment product, despite having the largest number of global persons with hemophilia, illustrates the large treatment gap in the country. Almost 75% of states in India now provide free factors to PwH, which will suffice for at least on-demand use.

One of the limitations of the study is the missing data in many parameters evaluated. However, they were eliminated and only the valid percentages were depicted in the descriptive analysis. This is inevitable in a situation where clinical, laboratory, and comprehensive services have evolved in the absence of Governmental funding and OOP expenditure by patients for the diagnosis and treatment with the very limited availability of factor support and lack of well-maintained medical records. However, the reported data still provide a snapshot of real-world scenario. Second, radiological imaging (X-rays, ultrasonography, or magnetic resonance imaging) could have been utilized for accurate enumeration of MSK complications and scoring. However, when resources, workforce, and clinic time are limited, more acute hematological problems take precedence over detailed evaluation and documentation among PwH. Hence, utility-based evaluation of ROM of each joint and documentation of synovial thickening remain pragmatic solutions to describe joint deformity. Third, annual bleeding rate or annual joint bleeding rate would have been a very good parameter which could have been collected to establish a baseline for the cohort of patients intended to be followed up. In the future, this could be achieved through adequate patient education on simultaneous documentation of the events to prevent recall bias.[12]

There exists a significant gap for care of PwH in Punjab.[37] A brief survey of hemophilia treatment centers showed there are a total of four centers (three Government and one private) in Punjab of which, three are Level-IV clinical and laboratories facilities[38] and only one center with Level I clinical and Level-II laboratory facility (unpublished data). The recent availability of CFCs through the WFH humanitarian aid has improved the access as a life-saving measure, although it is not an alternative to sustainable hemophilia care in the long run.[39] Provision of free factors to the states through National Health Mission is the initial step taken by the government. Prioritizing the services and infrastructure based on the existing and perceived needs is central to the future progress in developing countries.[40]

Conclusion

This study highlights under diagnosis and under reporting due to missing data in real world settings. The baseline data will serve as a platform to take definite pragmatic steps towards improving care among PwH. It also emphasizes the need for maintaining prospective registries and to prioritize capacity building, infrastructure development and provision of clotting factor concentrates through government programs.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the Ethical Standards of the Institutional and/or National Research Committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Although for this type of retrospective study, formal consent is not required; all patients had given consent for data collection and analysis.

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Conflicts of interest

There are no conflicts of interest.

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