World Journal of Pharmaceutical and Life Sciences
WJPLS
www.wjpls.org
SJIF Impact Factor: 6.129

HEMOPHILIC ARTHROPATHY: CLINICAL, FUNCTIONAL AND RADIOLOGICAL EVALUATION: A CROSS- SECTIONAL STUDY

S. Geetha[1], P.C. Hmingmuanpuii[2] and S. Malathi*[3]

[1]Associate Professor of General Medicine, Government Royapettah Hospital/Government Kilpauk Medical College, Chennai -10.
[2]Consultant, General Medicine, Christian Institute of Health Sciences and Research, Dimapur.
[3]Associate Professor of General Medicine, Government Royapettah Hospital/ Kilpauk Medical College, Chennai -10.

***Corresponding Author: Dr. S. Malathi**
Associate Professor of General Medicine, Government Royapettah Hospital/ Kilpauk Medical College, Chennai -10.

Article Received on 09/05/2023 **Article Revised on 29/05/2023** **Article Accepted on 19/06/2023**

ABSTRACT
A cross sectional study involving hemophilic arthropathy by clinical, functional, radiological methods and using scoring systems like FISH, HJHS, Peterson system. Data was collected from 60 Hemophilia patients at government royapettah hospital for a follow-up period of 6 months. Results from this study using peterson scoring system with Xray demonstrated significant joint destruction in hemophilic arthropathy patients.

INTRODUCTION
Hemophilia is a group of hereditary X-linked recessive disorder characterised by deficiency of factor VIII or IX coagulant activity. The pathophysiology of HemophiliaA and Hemophilia B is based on the insufficient generation of thrombin by the factor IXa/factor VIIIa complex through the intrinsic pathway of the coagulation cascade.[1] It is the most common congenital bleeding disorder encountered in clinical practice affecting men, whereas females are usually carriers.[2] Depending on the level of factor activity, it is further classified as Mild (6-40%), Moderate (1-5%) and Severe (<1%).[3] Bleeding can occur anywhere from the body. The common sites are into joints and muscles and from the gastrointestinal tract. Approximately 75 percent of hemorrhage occurs in the joints and is the hallmark of hemophilia.[1] the most commonly involved joints are the ankles, knees and elbows. These three joints are therefore referred to as ***Index joints***. Spontaneous hemarthroses are characteristic of severe disease. Recurrent bleeding into joints leads to extensive destruction of articular cartilage, synovial hyperplasia and reactive changes which then leads to joint deformity, muscle atrophy and soft tissue contractures, eventually leading to permanent joint damage. This study aims at evaluation of Hemophilic joint clinically, functionally and radiologically using Hemophilia Joint Health Score 2.1, Functional Independence Score in Hemophilia and Pettersson score respectively. Hemophilia Joint Health Score 2.1(HJHS) is a clinical scoring to assess joint health, in the domain of body structure and function (i.e., impairment), of the joints most commonly affected. Functional Independence Score in Hemophilia (FISH) is a performance-based instrument used to objectively assess musculoskeletal function of patients with hemophilia.[4] The Pettersson score is a detailed radiologic classification of hemophilic joints that has been adopted by the World Federation of Hemophilia (WFH). It estimates joint destruction radiologically.[5]

Radiographic stages of hemophilic joint[8]

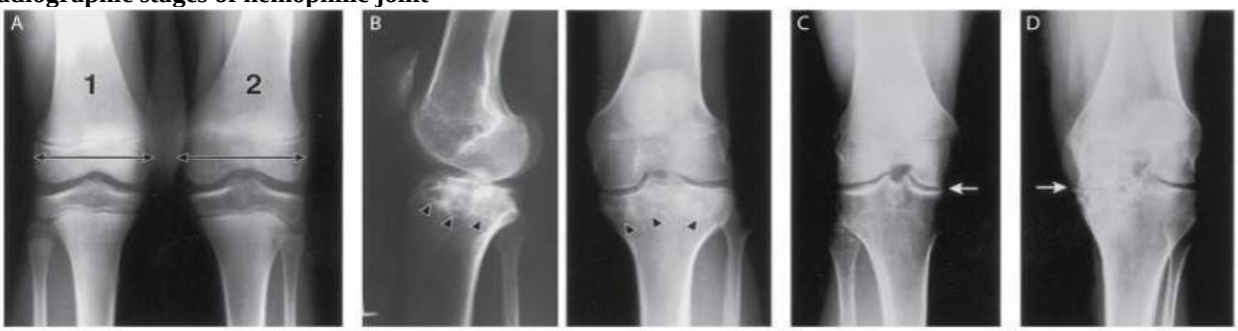

Fig. 5: Radiographic stages of hemophilic joint.

Stage 0 – Normal joint Stage 1 – fluid in the joint
Stage 2 – Osteoporosis and epiphyseal overgrowth – Fig A
Stage 3 – Subchondral bone cysts – Fig B (arrowheads)
Stage 4 – Prominent bone cysts with marked narrowing of joint space – Fig C(arrows)
Stage 5 – Joint obliteration with epiphyseal overgrowth

MATERIALS ANDMETHODS

This study was done at Government Royapettah Hospital, Chennai for a period of Six months from April 2017 to September 2017. The study was performed after procuring informed written consent from all the participants involved. Clearance was obtained from the Ethical Committee of Government Kilpauk Medical College & Hospital Chennai.

Study design

The study design is a cross sectional study.

Population

The study population included 60 persons with hemophilia who attended the Hemophilia Clinic at Government Royapettah Hospital.

Inclusion criteria

Patients confirmed with Hemophilia including;

1. Factor VIII deficiency (factor viii assay <40% of normal) with joint involvement.
2. Factor IX deficiency (factor ix assay <40% of normal) with joint involvement.
3. Age group: 4-18 years.

Exclusion criteria

1. Children <4 years or >18 years.
2. Patients with acute joint bleed or hemodyanamically unstable.
3. Hemophilia A or B with bleed other than joint.
4. Any bleeding disorders other than Hemophilia.
5. Not given consent for the study.

Methodology

Persons with Hemophilia A or B presenting to Hemophilia clinic were assessed after obtaining written informed consent. The sample size was set to be 60. Based on previous records and by obtaining history& physical examination, target joints were assessed using Hemophilia joint health score 2.1, functional scoring assessed as per FISH scoring system &conventional radiographs of the target joint taken and scores assigned using Pettersson's score. A detailed questionnaire assessing various factors which could influence the scores was taken into account, and final association established between them.

Functional independence score in hemophilia (Fish)[2]

The Functional Independence Score in haemophilia (FISH) is a performance- based assessment tool to objectively measure an individual's functional ability. It can also be used to evaluate change in functional independence over time. The advantage is that it can be used with persons of different linguistic abilities, as it is an objective, performance-based instrument. It includes the assessment of 8 activities: eating, grooming, dressing, chair transfer, squatting, walking, step climbing, and running. Each activity is graded according to the amount of assistance required to perform it.

Levels of function and their scores

1. The subject is able to perform the activity without any difficulty.
2. The subject is able to perform the activity without aids or assistance, but withslight difficulty.
3. The subject needs partial assistance/ aids/ modified instruments/ modified environment to perform the activity.
4. The subject is unable to perform the activity, or needs complete assistance.

Hemophilia joint health score 2.1

In the 1980s, Petterson and Gilbert developed a scoring system for assessment of hemophilic arthropathy- the World federation of hemophilia (WFH) physical examination (PE) scale which was the most widely used instrument. However, with the development of prophylaxis it seems to lack sensitivity. In 2003, the physiotherapy expert working group of International prophylaxis study group (IPSG) developed a more sensitive tool, the HJHS version 1.0, to evaluate and monitor effectiveness of treatment. In 2008, the HJHS version was developed in which modifications in axial alignment, joint pain, gait and instabilityto the HJHS 1.0 were made. The HJHS measures joint health in the domain of body structure and function of the joints. It is primarily designed for children aged 4-18years. Itcan be used when there is need for orthopaedic intervention or as outcome measure of physiotherapy intervention. It is appropriate for use in both patients receiving prophylaxis and On-demand therainterventions. HJHS 2.1 is an 8 item scoring tool for assessing impairment of six index joint (ankle,knee,elbow). It is numerically scored from zero to 20and global gait score of zero to 4. Score ranges from zero to 124 with higher scores being worst.

Pettersson score

It is a detailed radiologic classification of hemophilic joint that was recommended by the Orthopedic Advisory Committee and has been adopted by the World Federation of Hemophilia. It estimates joint destruction radiologically. In this scoring system, the extent of the arthropathy is estimated by following Eight characteristics:

- Osteoporosis,
- Epiphyseal enlargement,
- Narrowing of joint space,
- Irregularity of the subchondral surface,
- Erosion at joint margins,

- Subchondral cysts,
- Joint incongruency, and
- Joint deformity.

In each item, a score of 0 to 2 is given. The sum of these score will give the joint score which may range from 0 to 13 points. The concept of this system is to allow subtle grading of extent of pathology for the purpose of follow up.

Statistical analysis

The collected data were analysed with IBM.SPSS statistics software 23.0 Version. To describe about the data descriptive statistics frequency analysis, percentage analysis were used for categorical variables and the mean & S.D were used for continuous variables. To find the significant difference between in the multivariate analysis the Kruskal Walli's test was used. To assess the relationship between the variables Spearman's rank Correlation was used. In both the above statistical tools the probability value 0.05 is considered as significant level.

Table 4: Type of disease.

Type of disease	Frequency	Percent	Valid percent	Cumulative percent
A	55	91.7	91.7	91.7
B	5	8.3	8.3	100.0
Total	60	100.0	100.0	

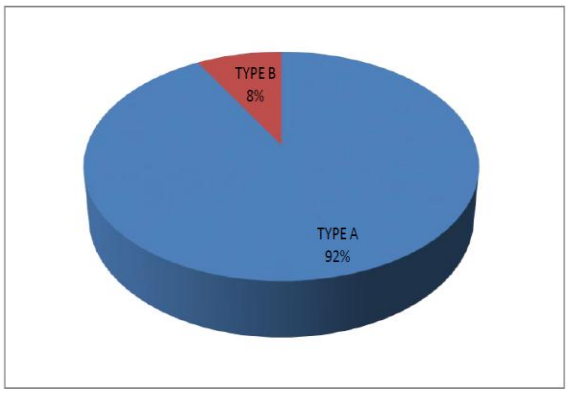

Fig. 9: Pie-chart showing frequency of type of hemophilia.

Out of 60 hemophilia patients, 92% were Hemophilia A; 8% were Hemophilia B

Table 5: Severity of disease.

	Frequency	Percent	Valid Percent	Cumulative Percent
Valid				
Mild	7	11.7	11.7	11.7
Moderate	11	18.3	18.3	30.0
Severe	42	70.0	70.0	100.0
Total	60	100.0	100.0	

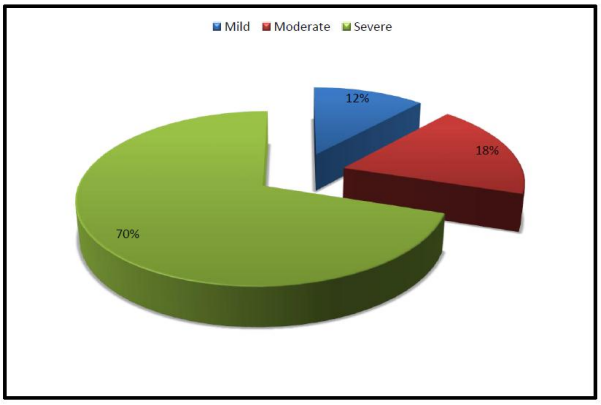

Fig. 10: Pie-chart showing frequency of severity of hemophilia.

Out of 60 patients, majority (70%) were persons with Severe; 18% moderate and 12%mild Hemophilia.

Table 6: Type of bleed.

	Frequency	Percent	Valid Percent	Cumulative	Percent
Valid					
JOINT	25	41.7	41.7	41.7	
JT +MM	19	31.7	31.7	73.3	
JT +MM + MS	2	3.3	3.3	76.7	
JT +MS	14	23.3	23.3	100.0	
Total	60	100.0	100.0		

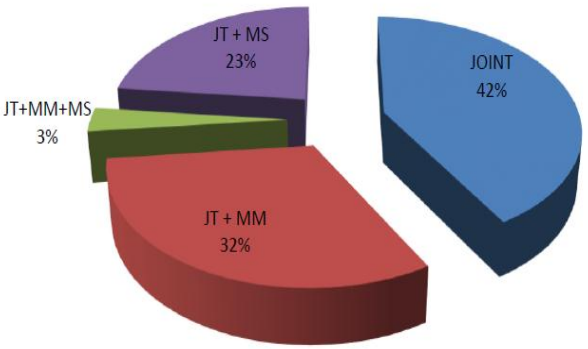

Fig. 11: Pie-chart depicting the type of bleed experienced.

*JT- JOINT; MM-MUCOUS MEMBRANE; MS-MUSCLE

Out of 60 patients, 42% had involvement of joint alone; 32% has joint and mucous membrane bleed; 23% had joint and muscle bleed; 3% had combination of joint, muscleand mucous membrane bleed.

Table 7: Number of joint involved.

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Multiple	28	46.7	46.7	46.7
	Single	32	53.3	53.3	100.0
	Total	60	100.0	100.0	

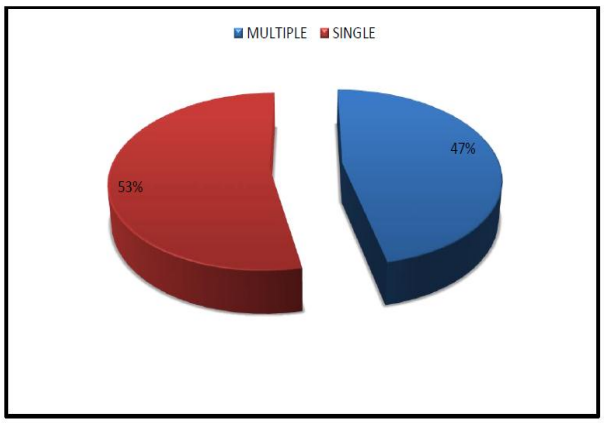

Fig. 12: Pie-chart showing number of joint involved.

Out of 60 patients, 53% had single joint; 47% had multiple joint involvement.

Table 8: Physiotherapy.

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Occasional	25	41.7	41.7	41.7
	Regular	35	58.3	58.3	100.0
	Total	60	100.0	100.0	

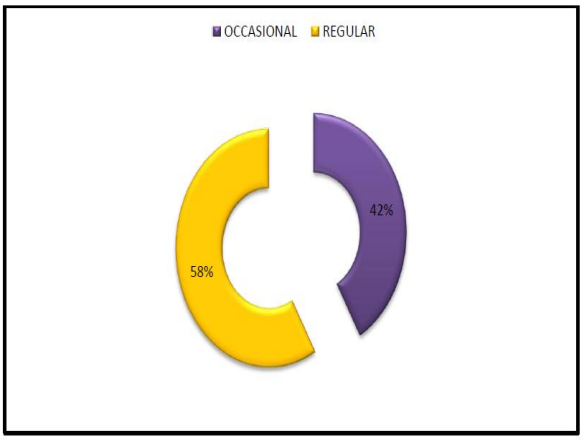

Fig. 13: Doughnut diagram showing frequency of physiotherapy.

Out of 60 patients, 58% were doing regular physiotherapy while 42% were doingoccasionally.

Table 9: joint affected.

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Ankle	24	40.0	40.0	40.0
	Elbow	11	18.3	18.3	58.3
	Knee	22	36.7	36.7	95.0
	Wrist	3	5.0	5.0	100.0
	Total	60	100.0	100.0	

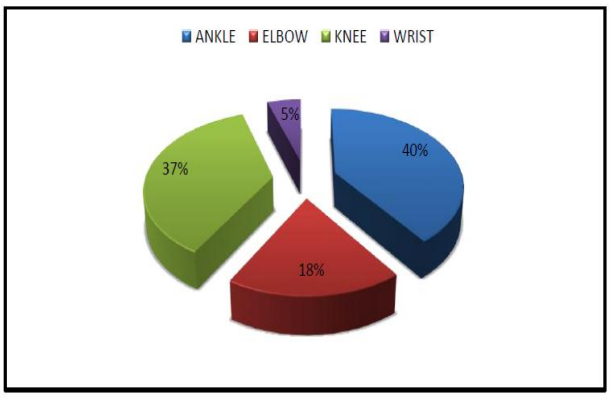

Fig. 14: Pie-chart showing the joints commonly affected.

Out of 60 patients, there was involvement of ankle joint in 40%; knee joint in 37%; elbow joint in 18%; wrist joint in 5%.

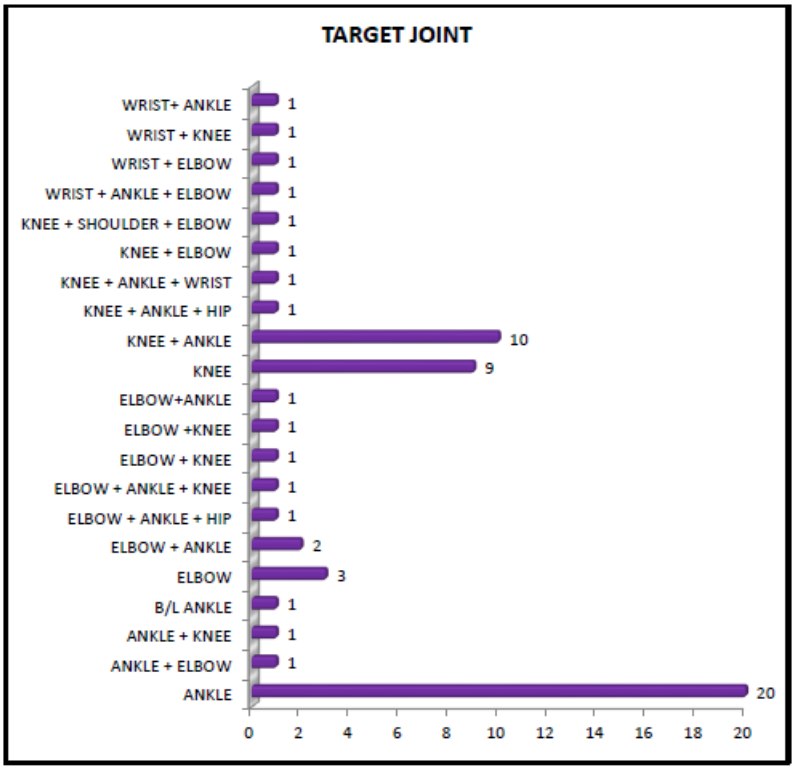

Fig. 15: Bar diagram showing the distribution of Target joint.

The above diagram showed that patients can develop more than one target joint. ***Anklewas the most common target joint***.

Table 10: Descriptive statistics.

		N	Mean	Std. Deviation	Minimum	Maximum
Age at hemarthrosis	Mild	7	4.4857	1.62832	2.40	7.00
	Moderate	11	2.4636	.81520	1.00	4.00
	Severe	42	1.4598	1.12038	.81	8.00
	Total	60	1.9968	1.49515	.81	8.00
Avg. BLEED/Yr	Mild	7	6.00	0.000	6	6
	Moderate	11	8.73	2.054	6	12
	Severe	42	12.02	3.204	6	18
	Total	60	10.72	3.528	6	18
SELF CARE(TOTAL-12)	Mild	7	12.00	0.000	12	12
	Moderate	11	11.91	.302	11	12
	Severe	42	11.24	1.144	8	12
	Total	60	11.45	1.016	8	12
TRANSFER(TOTAL-8)	Mild	7	7.29	1.254	5	8
	Moderate	11	7.18	.751	6	8
	Severe	42	6.74	.989	4	8
	Total	60	6.88	.993	4	8
LOCOMOTION(TOTAL-12)	Mild	7	10.29	1.254	8	12
	Moderate	11	10.73	1.104	9	12
	Severe	42	10.10	1.031	8	12
	Total	60	10.23	1.079	8	12
FISH TOTAL(32)	Mild	7	29.57	2.225	25	32
	Moderate	11	29.82	1.601	26	31
	Severe	42	28.12	1.811	24	31
	Total	60	28.60	1.942	24	32
HJHS(0-124)	Mild	7	9.43	4.756	5	16
	Moderate	11	11.18	7.068	4	27

	Severe	42	15.98	7.363	4	32
	Total	60	14.33	7.421	4	32
GLOBAL GAIT	Mild	7	1.29	.488	1	2
	Moderate	11	1.18	.603	0	2
	Severe	42	1.48	.890	0	3
	Total	60	1.40	.807	0	3
PETTERSSON	Mild	7	4.86	.900	4	6
	Moderate	11	6.00	1.897	3	9
	Severe	42	7.12	2.461	2	11
	Total	60	6.65	2.349	2	11

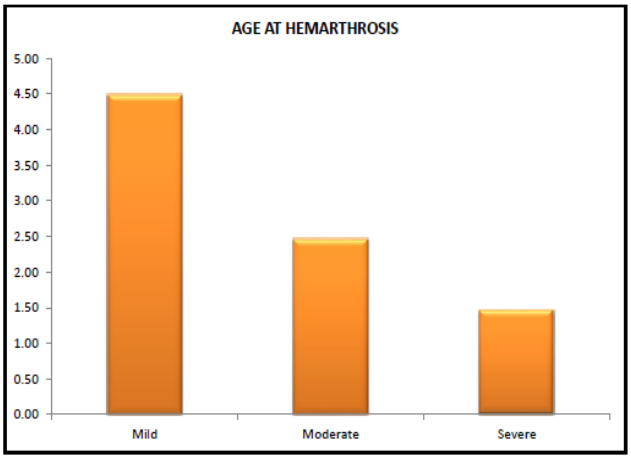

Fig. 16: Bar diagram showing Age of hemarthrosis in relation to severity of disease.

The mean age of first hemarthrosis in severe disease was 1.4years (ranges from 8 months to 8years). It was 2.4years and 4.4years in Moderate and Mild disease respectively. This shows that as factor activity decreases, there is earlier onset of first hemarthrosis.

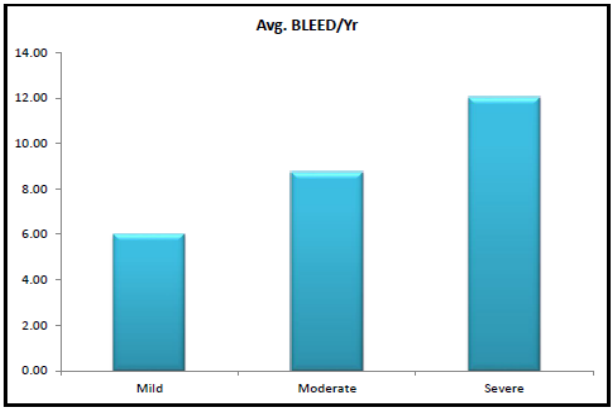

Fig. 17: Bar diagram showing average bleed experienced in relation to severity of disease.

The mean average number of bleed experienced per year was 12 (ranges from 6 to 18 times) in severe disease. It was 9 and 6 in Moderate and Mild disease respectively. This shows that those with severe disease experienced more number of joint bleed as compared to moderate and severe group.

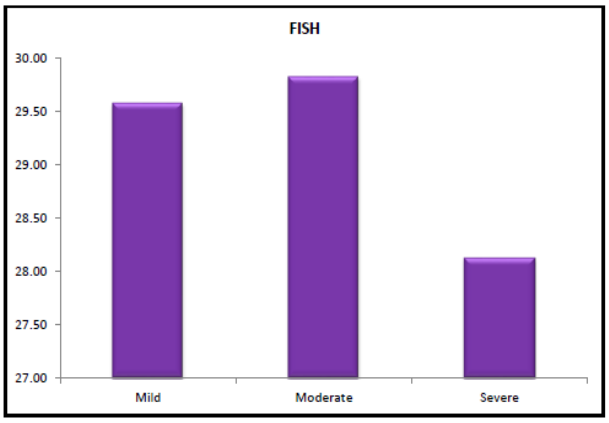

Fig. 18: Bar diagram showing FISH score among study groups.

The mean Functional Independence Score in Severe form of disease was 28.12(ranges from 24 to 31). The mean score in Moderate and Mild disease were 29.82 and 29.57 respectively. The maximum score was 32 and was found in patient with Mild disease; minimum score was 24 and was found in Severe disease.

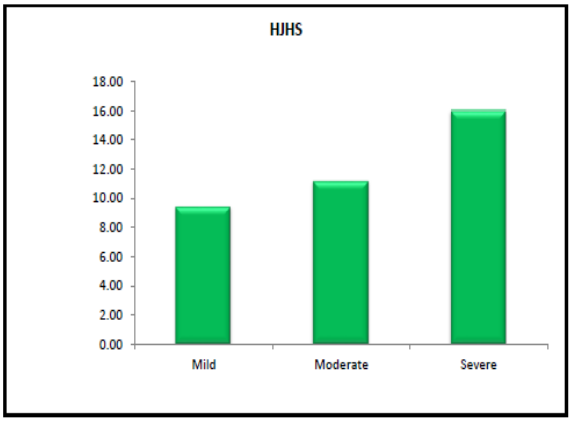

Fig. 19: Bar diagram showing HJHS among study group.

The mean HJHS was 16 (ranges from 4 to 32) in those with severe form of disease. It was 11 and 9 in those with Moderate and Mild form of disease respectively. The clinicaljoint health score was higher in group with severe disease which means that with severity of factor deficiency, the joint health declines.

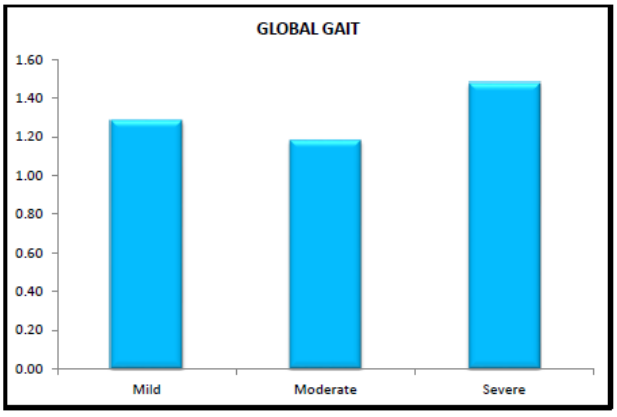

Fig. 20: Bar diagram showing global gait score.

The mean Global gait score was 1.48 (ranges from 0 to 3) in patients with severe disease while in those with Moderate and Mild disease were 1.18 and 1.29 respectively. This shows that with severity of the disease Global gait score also increase which they will have more impairment in their gait parameters namely walking, climbing stairs, runningand hopping on one leg.

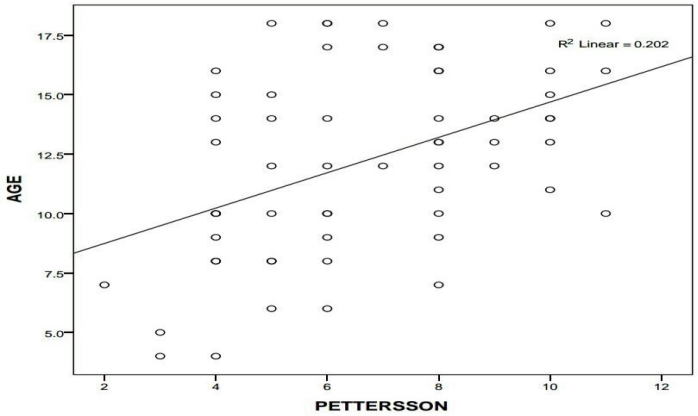

Fig. 21: Scatter diagram depicting correlation of pettersson score with Age of hemarthrosis.

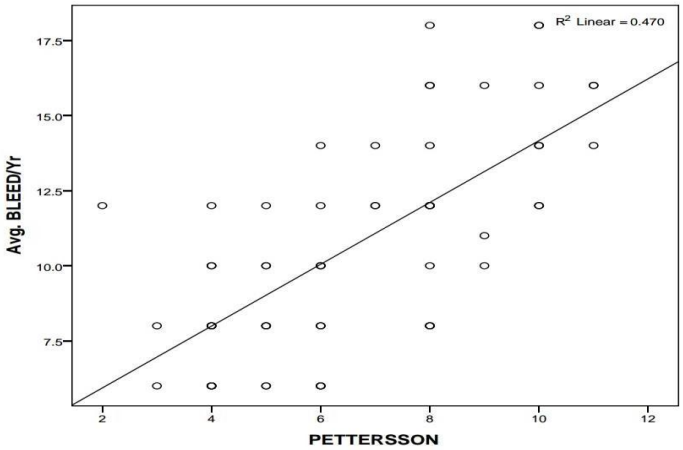

Fig. 22: Correlation of pettersson score with average bleed per year.

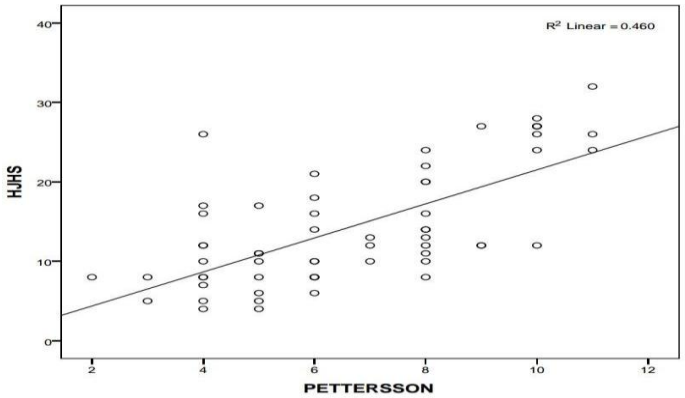

Fig. 23: Correlation of Pettersson score with HJHS 2.1.

P –Value	** Highly Significant at P ≤0.01
P – Value	* Significant at 0.01 < P ≤ 0.05
P – Value	# No Significant at P >0.05

Table 11: Test statistics in patients with severe hemophilia.

	Chi-Square	df	Asymp. Sig.
Age at hemarthrosis	27.915	2	0.0005
Avg. Bleed/Yr	24.381	2	0.0005
Fish total	10.743	2	0.005
Hjhs	8.698	2	0.013

Global gait	1.170	2	0.557
Pettersson	6.606	2	0.037

The above table shows test statistics in patients with severe hemophilia.

The age at hemarthrosis and average bleed per year showed a strong statistically significant correlation with severity of the disease, that is, the age at first hemarthrosis is lower as the factor level declines and they experienced more bleed as compared to moderate and mild diseases. The three scoring system namely, FISH, HJHS 2.1 and Pettersson scoring also showed statistically significant correlation with severity, among which FISH showed the strongest correlation (**p value 0.005**). On the other hand, eventhough Global gait score showed a higher score (higher score being worst) in those withsevere disease, it is has not shown to be statistically significant (p value >0.05).

Table 12: Correlations.

			Avg. Bleed/Yr	Fish total	Hjhs	Pettersson	Globalgait
Spearman's rho	Age at hemarthrosis	Correlation Coefficient	-.343**	.128	-.172	-.105	.079
		Sig. (2- tailed)	0.0005	0.329	0.190	0.423	0.549
		N	60	60	60	60	60
Avg. Bleed/Yr		Correlation Coefficient		-.637**	.678**	.679**	.556**
		Sig. (2- tailed)		0.0005	0.0005	0.0005	0.0005
		N		60	60	60	60
Fish total		Correlation Coefficient			-.755**	-.647**	-.605**
		Sig. (2- tailed)			0.0005	0.0005	0.0005
		N			60	60	60
HJHS		Correlation Coefficient				.649**	.720**
		Sig. (2- tailed)				0.0005	0.0005
		N				60	60
Pettersson		Correlation Coefficient					0.629**
		Sig. (2- tailed)					0.0005
		N					60

There is a statistically significant correlation (**p value <0.05**) between each of the three scoring system and with that of average bleed per year; but not with that of theage of hemarthrosis.

DISCUSSION

The main cause of morbidity in patients with hemophilia is hemophilic arthropathy which is the consequence of repeated bleeding into the joints. The diseased joint is more prone for repeated bleeding which perpetuate the vicious cycle of joint bleed and furtherdestruction of joint, hence arthropathy. This study was carried out to evaluate hemophilic joint clinically, functionally and radiologically using Hemophilic joint health score 2.1(HJHS 2.1), Functional independence score (FISH) and Pettersson scorerespectively. In this study, Hemophilia A comprised of majority of cases (91.7%); 42% had factor activity level <1% of normal. Up to 47% had multiple joint involvements. The most commonly affected joint was Ankle in 40% of cases, Knee in 37%, Elbow in 18.3%, Wrist in 5% which is in agreement with that of Jansen et al.[6] and Abdel Ghanyet al[6] who found that the 3 large joints namely ankle, knee and elbow were the most common joint affected . A study done by Plug et al.[7], Aznar et al.[8] and Molho et al[9] also found the ankle to be the most common affected joint. In children, knee and ankle are weight bearing joint, hence bleed more often. On the other hand, wrist and elbow may be affected in infants when they start crawling as they became weight bearing jointin these age group. Shoulders and hips tend to bleed less due to better support.[10]The age at first hemarthrosis and average number of bleed per year shows statistical significance when compared with severity of disease, which means patients with lowerfactor activity has lower age of first joint bleed and increase in number of joint bleed per year. Similar result was seen in a study done by Abdel Ghany et al[6] The mean ageof first hemarthrosis in severe hemophilia was 1.45 ±1.12 years and range from 0.8 to 8 years. Pollmann et al[11] report that in nearly half of children with severe hemophilia, age of hemarthrosis occurs during first year of life. Fisher et al[12] added that 90% of youngster with severe hemophilia experience atleast one joint bleed before 4.5years of age. The average bleed per year was also significantly increased in patients with severe hemophilia as compared to mild and moderate

hemophilia. Range of motion (ROM) has been the most utilised measurement for evaluating effects of intervention on joint health [13]. ROM limitation increases significantly with more episodes of joint bleed[14] In this study, FISH was significantly lower in patients with severe form of disease.

HJHS 2.1 also showed significant positive correlation with severity of the disease and average bleed per year. Global gait score was also higher with higher number of bleeds.Hassan et al[15] reported a significant positive correlation of Pettersson score with severity of disease. In our study showed similar results. Also, the average bleed per year showed a significant correlation which is in accordance with Van Dijk et al[16]Fisher et al[12] reported that Pettersson score increases by 1 point for every 3 joint bleedoccurring after 5 years of age. Table.12 showed that the three scoring system namely FISH, HJHS 2.1, Pettersson score showed a statistically significant correlation with the average joint bleed per year but not with the age at hemarthrosis. On the contrary, the preceding table (Table 11) showed that there was a significant correlation with severe disease of age at hemarthrosis and the 3 scoring systems. So, the possible explanation for there not being a statistically significant correlation between age of hemarthrosis with the same 3 scoring systems could be due to those proportion with moderate and mild form of disease who seldom experienced spontaneous joint bleed, hence, lesser bleed in contrast to severe disease where bleeding is usually spontaneous. Further, there is a significant positive correlation between the two scoring system namely, HJHS 2.1 and Pettersson score which is in accordance with a study done by P. M. Poonnoose et al.[17] On the other hand, both showed significant negative correlation with FISH. Out of 60 patients, majority (58%) does regular physiotherapy, but its correlation with joint health was not been established. Perhaps in the future, the effect of physiotherapy on joint health could be assessed and stressed on its importance. All patients in the current study received On-demand therapy due to which they experience increase in number of bleeds per year and thus develop more degenerative changes within the joint affecting their functioning and quality of life. This was supported by previous studies.[18] [19]

CONCLUSION

In our study, a significant impairment of joint was demonstrated on the basis of severityof hemophilia using clinical, functional and radiological scoring system. Majority of our patients were having severe form of the disease (factor activity <1% of normal). The most common joint involved were ankle, knee and elbow. All of our patients received On-demand therapy which is inferior to prophylaxis but is the practised method of therapy in our country. Scoring system namely FISH, HJHS 2.1, Pettersson proved to be useful tool for assessing joint health in persons with hemophilia. It can beused for follow up of patients to assess their response to treatment. Although MRI of joint is the preferred method for radiological assessment, in a poor resource country likeIndia, Pettersson score using simple X-ray of the joint can be considered as a cost- effective alternative.

Limitations of the study

The test used some provocative movements which could not be done by some patients. Combination of FISH and HJHS takes long time to administer, approximately 60 minutes for each patient. There was exposure to patient of radiation for the purpose of Pettersson scoring of the joint, but was minimal. The scoring systems were objective, so the possibility of inter-observer variations cannot be dismissed. This study, unlike some does not allot the study population into sub-group for comparison hence, the age at which the patients start showing increased trend of disability was not assessed. Since,it was a cross-sectional study; there is no follow-up of the patients. Larger multicentre trials with more number of subjects are required.

BIBLIOGRAPHY

1. Hoffman textbook of Hematology.
2. Scott JP, Montgomery RR. Hemorrhagic and thrombotic disorder. In: Kliegman RM,Behrman RE, Jenson BF, editors. Nelson's Text Book of Pediatrics. 18 th ed., Vol. 20. Philadelphia: Saunder, 2010; 61-88.
3. Tantawy AAG. Molecular genetics of haemophilia-A:clinical perspectives. Egypt J Med Hum Genet, 2010; 11: 105-114.
4. Poonnoose PM, Thomas R, Bhattacharjee S, Shyamkumar NK, Manigandan C, Srivastava A. Functional Independence Score in Haemophilia (FISH): A new performance based instrument to measure disability. *Haemophilia*, 2005; 11: 598-602.
5. Pettersson H, Ahlberg A, Nilsson IM. A radiologic classification of hemophilic arthropathy. Clin Orthop Relat Res, 1980; 149: 153–153159.
6. Abdel Ghany HM, Hassab HM, El-Noueam KI. Hemophilic arthropathy: clinical, radiologic, and functional evaluation: a single-center experience in a limited resource country. Egypt Rheumatol Rehabil, 2016; 43: 35-4.
7. Plug I, van der Bom JG, Peters M *et al*. Thirty years of haemophilia treatment in the Netherlands, 1972-2001. Blood, 2004; 104: 3494-500.
8. Aznar JA, Magallon M, Querol F, Gorina E, Tussel JM. The orthopaedic status of severe haemophiliacs in Spain. *Haemophilia*, 2000; 6: 170-6.
9. Molho P, Rolland N, Lebrun T et al. Epidemiological survey of the orthopaedic status of severe haemophilia A and B patients in France. The French Study Group secretariat.haemophiles@cch.ap-hop-paris.fr. *Haemophilia*, 2000; 6: 23-32.
10. Stephensen D, Tait RC, Brodie N, Collins P, Cheal R, Keeling D, *et al.*Changing patterns of bleeding in patients with severe haemophilia A. Haemophilia, 2009; 15: 1210–1214.

11. Pollmann H, Richter H, Ringkamp H, Jurgens H. When are children diagnosed as having severe haemophilia and when do they start to bleed? A 10-year single-centre PUP study. Eur J Pediatr, 1999; 158(3): S166–S166S170.
12. Fischer K, van der Bom JG, Mauser-Bunschoten EP, Roosendaal G, Prejs R, de Kleijn P, *et al.* The effects of postponing prophylactic treatmenton long-term outcome in patients with severe hemophilia. Blood, 2002; 99: 2337–2341.
13. Raffini L, Manno C. Modern management of haemophilic arthropathy. Br J Haematol, 2007; 136: 777–787.
14. Soucie JM, Cianfrini C, Janco RL, Kulkarni R, Hambleton J, Evatt B, *et al.* Joint range-of-motion limitations among young males with hemophilia: prevalence and risk factors. Blood, 2004; 103: 2467–2473.
15. Hassan TH, Badr MA, El-Gerby KM. Correlation between musculoskeletal function and radiological joint scores in haemophilia A adolescents. Haemophilia, 2011; 17: 920–925.
16. Van Dijk K, Fischer K, van der Bom JG, Grobbee DE, van den Berg HM. Variability in clinical phenotype of severe haemophilia: the role of the first joint bleed. Haemophilia, 2005; 11: 438–443.
17. Poonnoose, P. M., Hilliard, P., Doria, A. S., Keshava, S. N., Gibikote, S., Kavitha, M. L., Feldman, B. M., Blanchette, V. and Srivastava, A, Correlating clinical and radiological assessment of joints in haemophilia: results of a cross sectional study. Haemophilia, 2016; 22: 925–933. doi:10.1111/hae.13023
18. Hassan TH, Badr MA, El-Gerby KM. Correlation between musculoskeletal function and radiological joint scores in haemophilia A adolescents. Haemophilia, 2011; 17: 920–925.
19. Tlacuilo-Parra A, Villela-Rodriguez J, Garibaldi-Covarrubias R, Soto- Padilla J, Orozco-Alcala J. Functional independence score in hemophilia: a cross-sectional study assessment of Mexican children. Pediatr Blood Cancer, 2010; 54: 394–397.