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Assessment of quality of life by functional independence score in hemophilic patients: a single-center experience

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Abstract

Background: Hemophilia is an inherited condition that is caused by the deficiency of clotting factors in the blood. The most common presentations of hemophilia are hemarthrosis and muscle hemorrhage. The severity of the bleeding episodes can vary from mild to severe resulting in pain and swelling of the joints and the muscles. Repeated musculoskeletal bleeding can result in hemophilic arthropathies with subsequent joint degeneration and deformity. Our study aims to clinically assess the quality of life in hemophilic patients in terms of disease severity and morbidity in our community using the Functional Independence Score for Hemophilia (FISH).

Results: Our cross-sectional study which involved 64 hemophilia patients revealed that the most affected joints were the weight-bearing large joints (knees, elbows, ankles) and this was associated with a lower FISH score. While the total FISH score showed a significant positive correlation with the factor activity level, the average FISH score was 21.11 ± 4.5, and the score was slightly lower in severe hemophilia compared to mild-moderate disease.

Conclusion: We concluded that there is a significant decline in the functional ability of hemophilia patients having disease affecting the knee and elbow joints. Moreover, squatting was significantly reduced in patients with severe hemophilia. The quality of patients' life can be improved by early and regular physiotherapy and regular administration of the prophylactic factor.

Keywords: Hemophilia, Hemarthrosis, FISH score

Introduction

Hemophilia is the most common severe hereditary hemorrhagic disorder [1]. Hemophilia A results from factor VIII deficiency while hemophilia B results from factor IX deficiency. There is a less common form of hemophilia that occurs due to deficiency of clotting factor XI, it is known as hemophilia C. Hemophilia is characterized by prolonged and excessive bleeding after minor trauma or even spontaneously [2, 3].

The epidemiology of hemophilia worldwide shows equal distribution among all ethnic groups. A recent meta-analysis showed that more than 1,125,000 around the world have the inherited bleeding disorder; 418,000 of those have a severe version of the mostly undiagnosed disease. Previously, only 400,000 people globally were estimated to have hemophilia. The study found that, per 100,000, there are 17.1 cases for all severities of hemophilia A, 6 cases for severe hemophilia A, 3.8 cases for all severities of hemophilia B, 1.1 cases for severe hemophilia B [4].

Hemophilia is inherited via an X-linked recessive pattern. Female carrier mothers have a 50% chance of having affected males and a 50% chance of having carrier

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females. Females could also be affected if there is a complete inactivation of chromosome X through lyonization, compound heterozygosity, partial, or complete absence of chromosome X such as in Turner syndrome or if both parents carry the abnormal gene [5].

Hemophilia is diagnosed if the clotting factor activity is less than 40% of normal factor activity. Molecular genotyping should then be offered to confirm the diagnosis and to help prediction of the disease severity. Bleeding in hemophilia often correlates with the degree of residual factor level which in turn classifies the disease into mild with factor level (5–40%) moderate with factor level (1–4%) severe with factor level < 1%. Hemophilic arthropathies are caused by repeated joint bleeding. Knees, elbows, ankles, shoulders, wrists, and hips are the most typically affected joints [6]. Management of hemophilia includes replacement with clotting factor concentrate (CFC) of factor VIII or IX in case of acute bleeding and for prophylaxis [7]. Prevention of musculoskeletal morbidity is an important objective in the treatment of hemophilia. Two commonly used and established standardized measures to evaluate joint status are the World Federation of Hemophilia Physical Examination (WFH-PE) scale and the Functional Independence Score for Hemophilia (FISH). Patients with hemophilia and their therapists were asked to indicate activities that could be impaired by hemophilia, which were then categorized according to the International Classification of Functioning (ICF), Disability, and Health, which was employed in our study [8].

Methods

Our study design is a cross-sectional study that was performed in Assiut University Hospitals including 64 patients. The patients were subjected to full history taking, thorough clinical examination, and focused lab work (complete blood count, prothrombin time and concentration, activated partial thromboplastin time, factor VIII and IX levels). Clinical scoring by FISH Score from 1 to 4 according to the following:

1. The subject is either unable to conduct the task or need entire assistance to do so.
2. The subject needs partial assistance/aids/modified instruments/modified environment to perform the activity.
3. The subject can perform the activity without aids or assistance, but with slight discomfort (not the same as his/her healthy peers).
4. The subject can perform the activity without any difficulty like other healthy peers.

There are seven activities included in the score (eating/grooming, bathing, dressing, chair, squatting, walking, step climbing) a score from 1 to 4 was assigned for each activity according to the assistance required, thus gives total score from 7 to 28.

Inclusion/exclusion criteria

Patient aged ≥ 18 years with hemophilia A and B were included. Contrarily, those with comorbidities affecting joint activity (SLE, RA, OA, and other connective tissue diseases)/affecting general performance (severe heart disease) and those with bleeding tendencies (VWB disease) were excluded.

Statistical analysis

Data were analyzed using the statistical package SPSS (Statistical Package for the Social Sciences) version 25. Data were summarized using mean, median, minimum, and maximum in quantitative data and using frequency (count) and relative frequency (percentage) for categorical data in the different components of the questionnaire. A comparison of quantitative variables was done. Pearson correlation between quantitative variables was done. A *P* value less than 0.05 was considered significant.

Results

We studied 64 hemophilic patients, 61 (95.3%) were males and 3 (4.7%) were females. Their ages ranged from 18 to 65 years with a mean of 29.22 ± 9.43 years. Of the 64 patients, 36 (56.3%) patients were hemophilia A, 27 (42.2%) were hemophilia B, and 1 patient (1.5%) was combined A and B as shown in Fig. 1.

The affected joints in the studied patients are summarized in Fig. 2 where the most affected joints were the

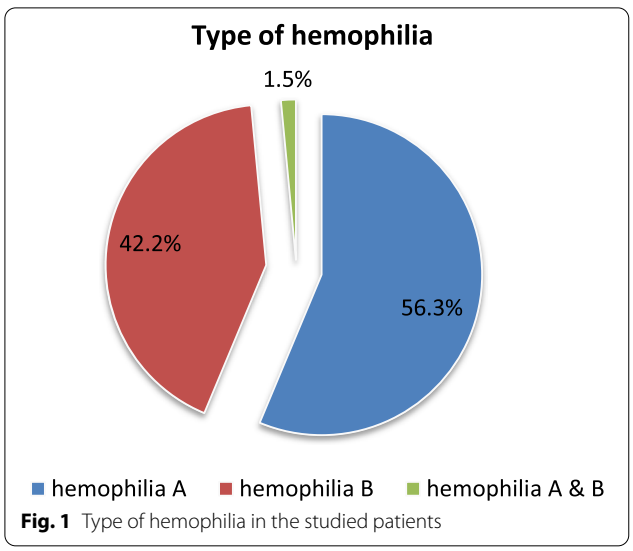

Fig. 1 Type of hemophilia in the studied patients

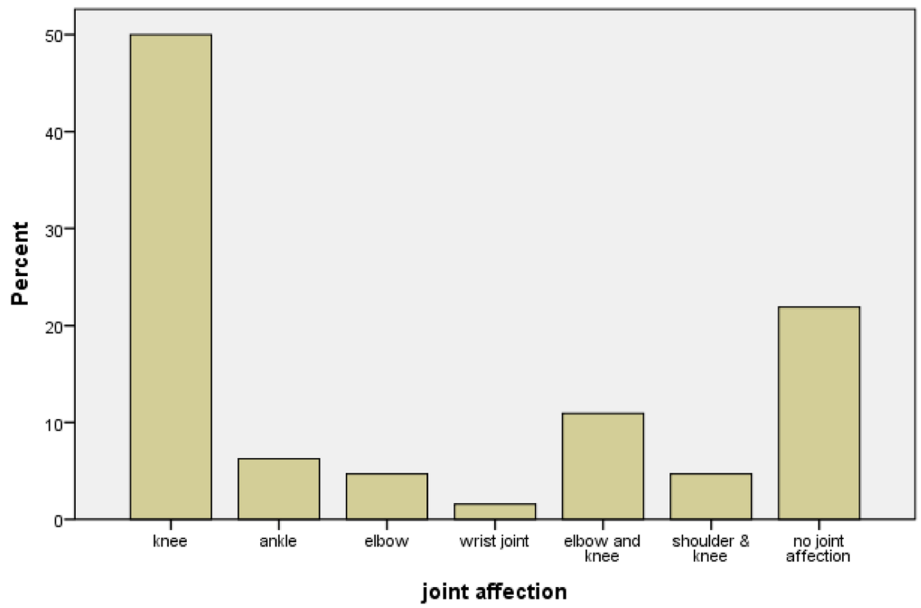

Fig. 2 The affected joints in the studied patients

knees by 50%. Also, one-fifth of cases (20%) did not have affected joints.

The lab work showed a mean activated partial thromboplastin time (APTT) of 78.3 ± 35.11 s and a mean factor level of 3.98 ± 4.4. The results are shown in Figs. 3 and 4.

The mean total FISH was 21.11 ± 4.5 ranging from 12 to 28. Table 1 shows the score obtained for each of the activities requested. Squatting and chair transfers were the tasks with the lowest scores. Regarding squatting, 56.2% of the patients needed assistance with either partial 24 (37.5%) or complete assistance 12 (18.7%).

When the scores of functional independence were analyzed according to the severity of hemophilia: the median FISH score for mild was 21.5 (19–28), moderate was 21 (20–22), and severe cases was 19 (16–21), results showed that there were no significant differences between severity groups in total FISH score, but the squatting score was significantly lower in patients with severe hemophilia (p value = 0.018) (Fig. 5).

On the one hand, there was no statistical significance regarding the type of hemophilia, age, or gender in the total FISH score (p value > 0.05), but on the other hand, the total FISH score was significantly lower in patients with elbow and knee affection (p value < 0.001) as shown in Fig. 6.

Additionally, there was a significantly negative correlation between APTT and total FISH score, i.e., increase in the level of APTT was associated with decrease in the FISH score (Fig. 7A), and a significantly positive correlation between factor level and total FISH, i.e., increase in the factor level was associated with increase in the FISH score (p values < 0.05) as shown in Fig. 7B, C.

The variables (joint affection, APTT, factor level) which significantly correlated with the total FISH scale were entered into the multiple linear regression model and shown in Fig. 8. It was found that joint affection, APTT, and factor level accounted for 40.4% of the variability in FISH score ($R^2 = 0.404$, $p < 0.01$).

Discussion

Despite the improvement in the long-term survival of patients with hemophilia, joint damage still represents a critical issue in the management of these patients. Thus, the assessment of joint functionality has been one of the most important targets of hemophilia management [9].

In this study, FISH was used to objectively measure functional disability in Egyptian patients with hemophilia presenting to a tertiary care center.

The study included 64 patients; their mean age was 29 ± 9.4 years. It was found that people with hemophilia can present at any age. At the end of the 1960s and before the introduction of substitution therapy, hemophilia often resulted in severe disability at a young age and premature death [4]. However, in a study by Yang et al. [10] that included 1149 hemophilia patients, they discovered that patients survived longer, with 25 of the 1149 participants in their study being beyond 45 years old. Also, Hermans et al. and Zimmermann et al. [11, 12] revealed that there are many more elderly people with hemophilia than in

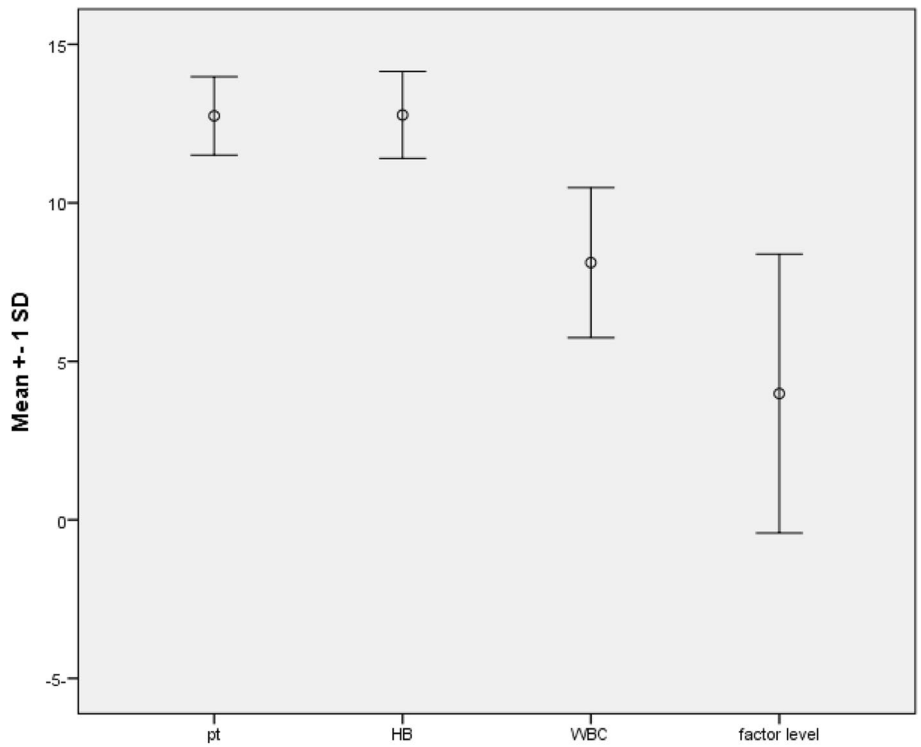

Fig. 3 Clinical investigations (PT, HB, WBC, and factor level) in the studied patients

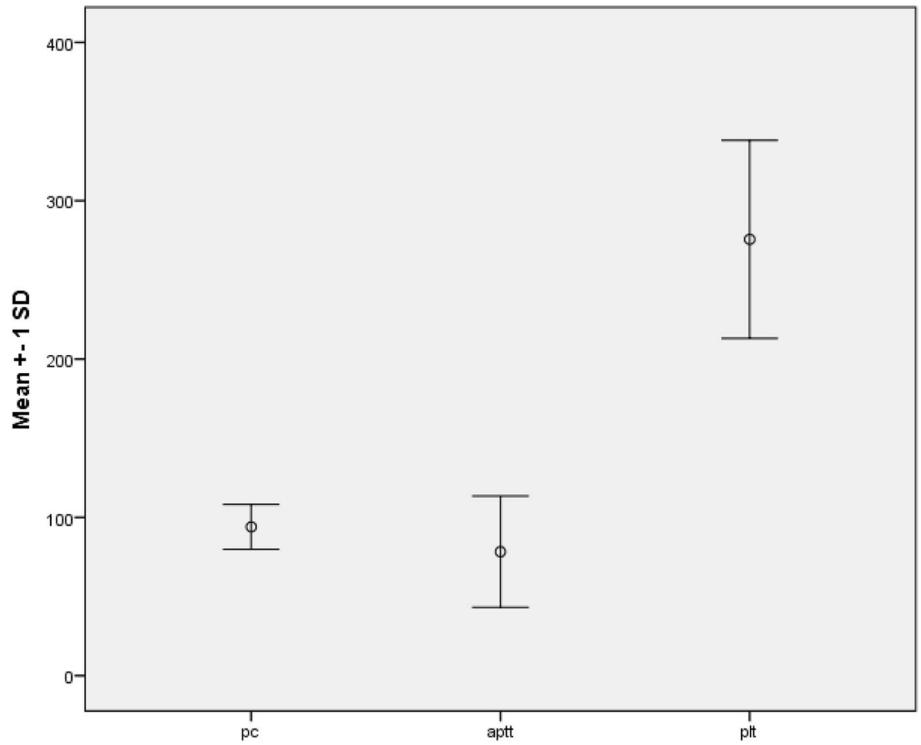

Fig. 4 Clinical investigations (PC, APTT, and platelet) in the studied patients

Table 1 The functional independence score in hemophilia (FISH)

	No.(%)			
	Unable	**Needs partial assistance**	**Able but discomfort**	**Able**
Eating and grooming	0 (0%)	3 (4.7%)	30 (46.9%)	31 (48.4%)
Bathing	0 (0%)	6 (9.4%)	40 (62.5%)	18 (28.1%)
Dressing	0 (0%)	7 (10.9%)	41 (64.1%)	16 (25%)
Chair	4 (6.2%)	17 (26.6%)	24 (37.5%)	19 (29.7%)
Squatting	12 (18.7%)	24 (37.5%)	11 (17.2%)	17 (26.6%)
Moving	0 (0%)	21 (32.8%)	26 (40.6%)	17 (26.6%)
Step climbing	0 (0%)	18 (28.1%)	29 (45.3%)	17 (26.6%)
Total FISH	21.5 (19–28)	21 (20–22)	19 (16-21)	

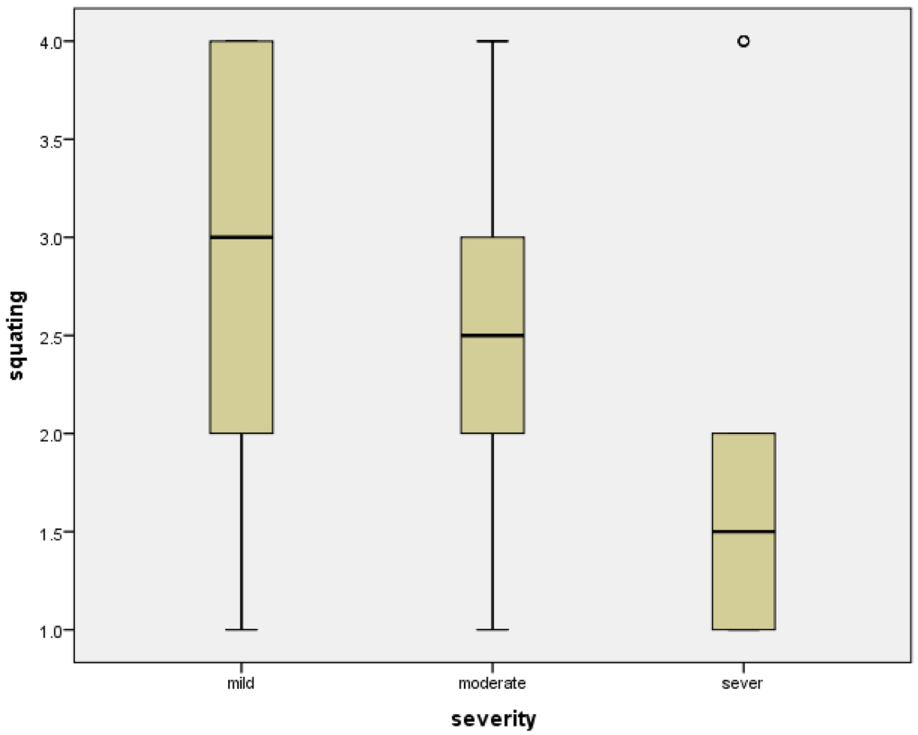

Fig. 5 Squatting score according to severity of hemophilia

the previous generations. Life expectancy for people with hemophilia has improved and approached that of the general population. In our study, the age of the included patients ranged from 18 to 65. Factors contributing to improvement included high quality factor concentrate, insights into the management of hemophilia arthropathy, improved medical management provided by specialized hemophilic treatment centers.

The most commonly affected joints in the present study were the knee joint in 32 patients (50%) followed by the elbow in 10 patients (15.5%) and the ankle in 4 patients (6.3%). This coincides with other previous studies that showed more common affection of the three large joints, namely the knee, elbow, and ankle [13, 14]. In the study conducted by Abdel Ghany et al. [13], they included 30 boys with hemophilia and a history of previous joint bleeding. The knee was the most affected joint in 22 patients (73.3%) patients followed by the ankle in 5 (16.7%) and the elbow in 2 (6.7%) patients. This could be explained by the weight-bearing function of the knee and ankle that led to more often bleeding. Shoulders and hips are better supported and thus bleed less [15].

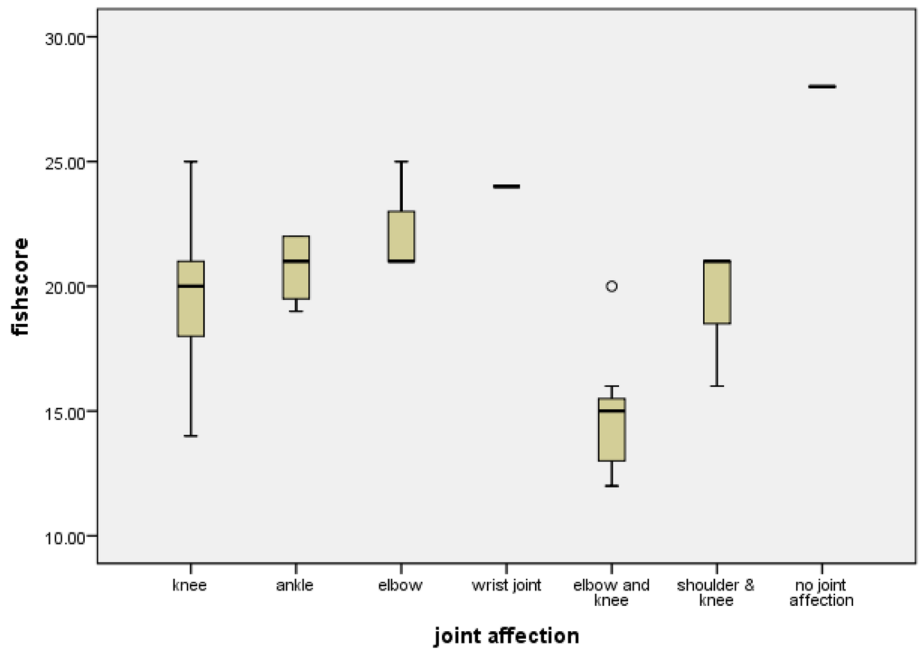

Fig. 6 FISH score according to joint affection

In our study, the mean total FISH score was 21.5, 21, and 19 in patients with mild, moderate, and severe hemophilia respectively, with an overall mean of 21.11 ± 4.5. These scores were a little bit lower than that reported by Shamoon et al. [16], whose study revealed a mean FISH formild, moderate, and severe hemophilia of 29.5, 28.3, and 26, and an overall mean of 28. Additionally, Choudhary et al. [17] reported higher scores than ours despite including more cases of severe disease (52%) compared to ours (28%). This could be attributed to different management plans, e.g., less availability of coagulation factor replacement in our setting and use of prophylactic versus episodic treatment. This explanation was supported by the results of a previous Egyptian study that demonstrated that FISH scores were significantly higher in patients receiving regular factor VIII replacement than those receiving either irregular factor VIII replacement or fresh frozen plasma Badr et al. [18].

In our study, we noted that the FISH score did not differ significantly between mild, moderate, or severe cases. This was in contrast to a study by Tlacuilo'Parra et al. [9] which revealedsignificantly higher score in patients with mild hemophilia (28 ± 0) than patients with moderate (26.2 ± 2.5; $P = 0.004$) or severe hemophilia (24.0 ± 4.7; $P = 0.0006$). Moreover, the study conducted by Badr et al. [18] showed no difference in the FISH score between healthy control and patients with mild hemophilia.

Moreover, the FISH score was significantly lower in those with moderate and severe hemophilia when compared to mild hemophilia. These differences might be attributed to lack of awareness about the disease severity (those with mild disease ignore seeking medical advice leading to advancement of disease while those with moderate/severe states seek medical advice and received treatment) that leads to insignificant difference in FISH scores between grades of severity in our study. Overall, the most difficult activity was squatting as 56.2% of the patients needed assistance either partial in 24 patients (37.5%) or complete in 12 patients (18.7%). The squatting score was significantly lower in severe cases. Tlacuilo-Parra et al. [9] also revealed that the most commonly affected activities were squatting, walking, and step climbing which were affected in nearly one-third of patients with moderate or severe hemophilia. These activities are characterized by weight-bearing demands. This also goes hand in hand with our finding of the significantly lower FISH score in the case of knee and elbow disease compared to other joints. Additionally, Badr et al. [18] showed that squatting, walking, and step climbing were the most commonly affected activities. Although there was improvement in patient's care from 2010 till now, several factors contributed to that the outcome of disease still the same, i.e., worsening of SES of patients that leads to neglect of follow-up and regular treatment, in line with the lack of awareness about disease severity.

There was no significant correlation between the age and total FISH score. However, a significant positive correlation was found between factor activity level and total

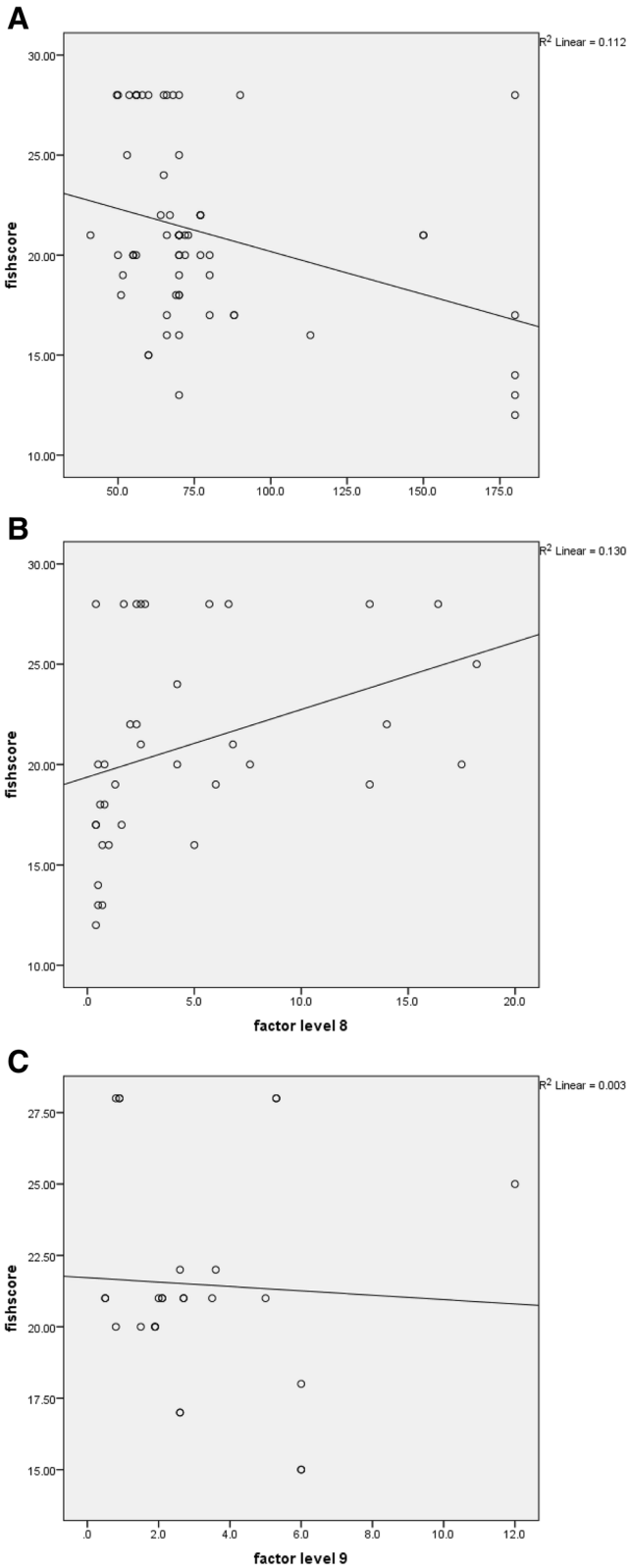

Fig. 7 **A** Correlation between APTT and total FISH score. **B** Correlation between factor level 8 and total FISH score. **C** Correlation between factor level 9 and total FISH score

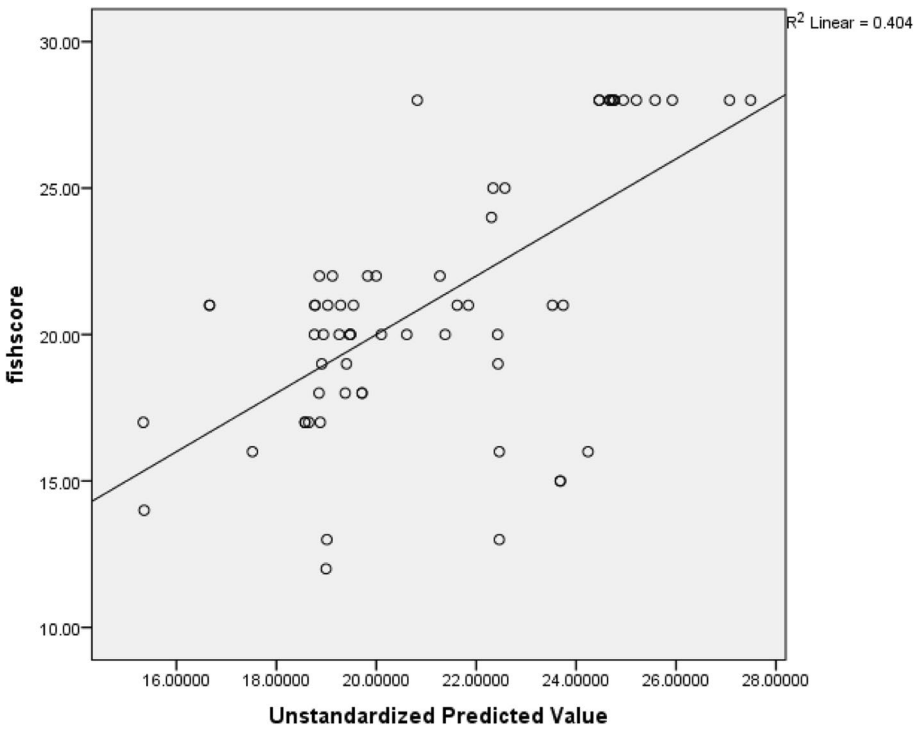

Fig. 8 Actual total FISH score versus predicted values based on the multiple regression model

FISH score. This matches with the study performed by Abdel Ghany et al. [13] who reported that the FISH score had a significant positive correlation with factor activity level ($r = 0.6$, $p < 0.001$).

Although the FISH score is less sensitive to the early joint damage in contrast to the radiologic and physiometric methods, it has more value in resource-limited settings where coagulation factor replacement is less available and more joint disease is expected to be encountered at a relatively earlier age.

Conclusion

A significant decline in the functional ability was observed in hemophilia patients having disease affecting the knee and elbow joints. The squatting was significantly reduced in patients with severe hemophilia.

Recommendations

We recommend prophylactic factor administration regularly to improve the quality of life of patients with hemophilia.

Abbreviations

APTT: Activated partial thromboplastin time; CFC: Clotting factor concentrate; FISH: Functional Independence Score in Hemophilia; Hb: Hemoglobin; ICF: International Classification of Functioning; PC: Prothrombin concentration; PT: Prothrombin time; PTT: Partial thromboplastin time; SD: Standard deviation; SPSS: Statistical Package for the Social Sciences; WBCs: White blood cells; WFH-PE: World Federation of Hemophilia Physical Examination.

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None

Authors' contributions

OAI, AFT, SST, and SMM contributed to the study design, analysis, and interpretation of the data. SMM, AFT, SST, and KM contributed to the writing and preparation of the manuscript. OAI, AFT, and SMM revised, edited, and approved the final manuscript. All authors have read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

There was no risk during the application of the research. Privacy and confidentiality were maintained during all stages of assessment. Every patient subjected to this study was informed about the results of the research. The work is approved by Ethical Committee of Faculty of Medicine of Assiut University (approval number IRB no 17101082). Consent (verbal) was obtained from all patients who participated in this study. Refusal would not affect medical services which are usually offered. Verbal consent is approved by the ethics committee.

Consent for publication

Consent (verbal) was obtained from all patients. Verbal consent is approved by the ethics committee.

Competing interests
The authors declare that they have no competing interests.

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