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Original Article

The Health-Related Quality of Life scores and joint health in children and young adults with hemophilia

Buse Günyel[1], Mesut Bulakçı[2], Gamze Başkent[1], Ayşegül Ünüvar[3]

[1]Department of Pediatrics, İstanbul Faculty of Medicine, İstanbul University, İstanbul; [2]Department of Radiology, İstanbul Faculty of Medicine, İstanbul University, İstanbul; [3]Division of Pediatric Hematology and Oncology, Department of Pediatrics, İstanbul Faculty of Medicine, İstanbul University, İstanbul, Türkiye.

ABSTRACT

Background. Patients with hemophilia should be evaluated for joint health and overall health in their visits. The aims of this study were to evaluate joint health and health-related quality of life (HRQoL) in patients with mild, moderate, and severe hemophilia; determine which patient groups to focus on and whether there are any neglected patient groups.

Methods. This was a single-center, cross-sectional study. Patients were evaluated by ultrasonography (Hemophilia Early Arthropathy Detection with Ultrasound [HEAD-US]), physical examination (Hemophilia Joint Health Score version 2.1 [HJHS-2.1]), and HRQoL scales (EQ-5D/EQ-VAS and Haemo-QoL).

Results. Thirty-nine patients with regular follow-up were evaluated for a total of 234 joints. When hemophilia severity was compared with the HEAD-US and HJHS-2.1, a significant difference was found between severe and non-severe hemophilia. On the other hand, when patients' total HEAD-US scores were compared with total HJHS-2.1 scores, no statistically significant correlations were found; only a statistically significant but negligible correlation was detected when HEAD-US and HJHS-2.1 scores were examined at joint level. No significant difference was found when mild, moderate or severe hemophilia were compared with the HRQoL scores. Also, HEAD-US scores and HRQoL scores were not correlated, showing that the HRQoL score did not change whether the patient has arthropathy or not.

Conclusion. Despite recent advances in treatment options for hemophilia, arthropathy in patients with severe hemophilia remains challenging. For the follow-up of pediatric hemophilia, the HEAD-US and HJHS should be used together because their correlation was weak. Although patients with severe hemophilia are at higher risk in terms of arthropathy, patients with mild/moderate hemophilia should not be ignored because their HRQoL is not different from that of severe hemophilia.

Key words: hemophilia, hemophilic arthropathy, health-related quality of life, HJHS, HEAD-US.

Hemophilia is a congenital bleeding disorder, characterized by a deficiency of coagulation factor VIII, defined as hemophilia A or factor IX, defined as hemophilia B.[1] Although the pathophysiology, distribution of the factor levels, and pharmacokinetic characteristics of infused factors are different, there are no significant differences in expected bleeding between hemophilia A and B.[2,3] The severity of hemophilia is defined by the factor levels. Patients with factor levels below 1% are defined as severe, patients with a factor levels between

✉ Buse Günyel ▪ busegunyel@gmail.com

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1-5% are defined as moderate and patients with factor levels 5-40% are defined as mild hemophilia. Patients with severe hemophilia tend to experience more spontaneous bleeds, especially into their joints, and therefore develop chronic hemophilic arthropathy. When the factor level is higher, it is unlikely to experience spontaneous bleeds and develop complications. The treatment of hemophilia involves the acute treatment of bleeding and prophylactic treatment with regular factor replacement for preventing bleeding and the development of hemophilic arthropathy with regular and continuous factor replacement.[1,4,5] For optimization of follow-up, objective criteria are needed, such as bleeding frequency, physical examination, imaging studies, and health-related quality of life (HRQoL).[6]

This study was undertaken with the aim of examining the joint health and overall health of patients with hemophilia (PwH). We aimed to identify the differences between mild, moderate, and severe hemophilia and thus learn which patients to focus while on ensuring that patients with moderate and mild hemophilia are not neglected, especially in childhood and young adulthood.

Materials and Methods

This study was a single-center, cross-sectional study with 39 PwH over the age of 4 years who were regularly followed in our center (Fig. 1). As part of the clinical follow-up of PwH, joint health assessments were conducted with the Hemophilia Joint Health Score (HJHS) 2.1 and Hemophilia Early Arthropathy Detection with Ultrasound (HEAD-US) together with simultaneous assessments of HRQoL (EQ-5D-3L, EQ-VAS, Haemo-QoL/Haem-A-QoL).

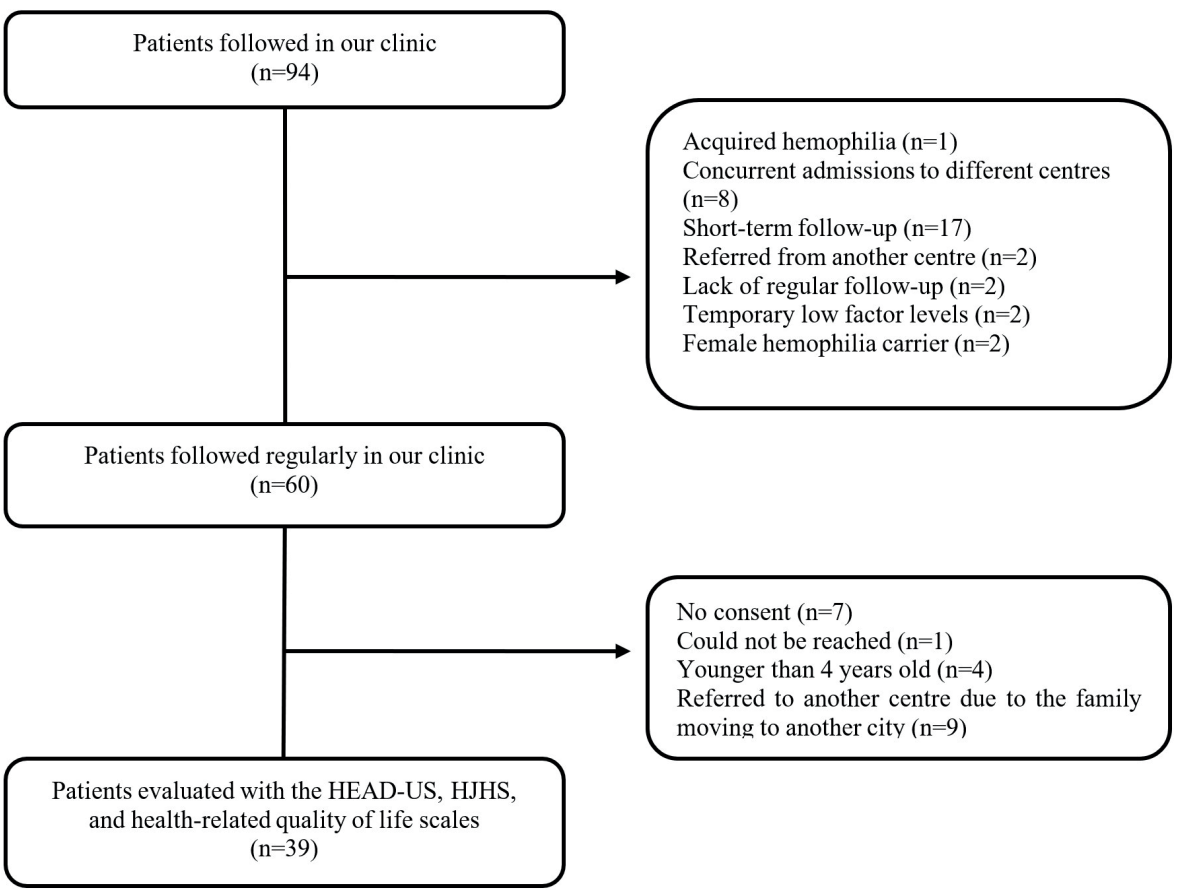

Fig. 1. Flowchart of patient selection.

All procedures were approved by the İstanbul Faculty of Medicine Ethics Committee and complied with the principles of the Declaration of Helsinki and its 2008 amendment. All participants older than 18 years of age and the legal guardians of the patients under 18 years of age were informed of the purpose and content of the research and expressed their informed consent in writing to participate in the study.

The HEAD-US is a scoring system developed by Martinoli et al. that evaluates synovitis, cartilage, and subchondral bone damage in six joints of the elbows, knees, and ankles.[7] The HJHS is a scoring system for clinical evaluation developed by the International Prophylaxis Study Group (IPSG). As part of version 2.1 of the HJHS, the same six joints are evaluated for swelling, duration of swelling, muscle atrophy, crepitus, flexion loss, extension loss, pain, and strength. Additionally, the patient's global gait is evaluated. This scoring system was originally developed for patients between the ages of 4 and 18 years, and it was later validated for use in adults.[8-10] Higher scores are associated with worse joint health for both scoring systems.[7-10]

The EQ-5D is a generic HRQoL metric developed by the EuroQol Group. Proxy versions filled out by parents are used for children between the ages of 4 and 7 years. Five dimensions are assessed: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension is divided into three levels: no problems, some problems, and extreme problems. Patients or their parents are asked to mark points on a visual analogue scale (VAS) ranging between 0 (worst imaginable health state) and 100 (best imaginable health state). If all dimensions show no problems, the individual is said to have a full state of health.[11]

The Haemo-QoL, developed by von Mackensen et al., measures the HRQoL of PwH. There are different versions for different ages, and the scale is completed by interviewing patients between the ages of 4 and 7 years. The total score and each field score can vary between 0 and 100, with higher scores indicating lower HRQoL.[12,13]

Statistical analysis

Descriptive statistics were presented as numbers and percentages for qualitative variables and as medians, minimums, and maximums for quantitative variables. In comparisons of continuous variables, the Mann-Whitney U test was used, while comparisons of more than two groups were performed with the Kruskal-Wallis test. Pairwise comparisons were examined with a post-hoc test with Bonferroni correction. Quantitative variables were examined by Spearman correlation analysis.

IBM SPSS Statistics 21 was used for these analyses, the confidence interval was kept at 95%, and the analysis results were interpreted by comparing them with the $p<0.05$ level of significance.

Results

A total of 39 patients followed at our center, 35 (89.7%) of whom were diagnosed with hemophilia A and 4 (10.3%) of whom were diagnosed with hemophilia B were evaluated. These patients were not currently or previously inhibitor-positive. For severe, moderate, and mild hemophilia; the ages were 12.77 years (4.96-24.15), 7.11 years (4.41-15.95), 15.31 years (11.90-21.89), the factor activity levels were 0.285% (0-0.90), 2.05% (1.00-3.30), 18.00% (8.70-29.30), the median annual bleeding rates (ABR) were 2.5 (0-30), 2 (0-6), 2 (0-40) and the annual joint bleeding rates (AJBR) were 1.5 (0-30), 0 (0-2), 0 (0-2); respectively. All patients received standard half-life factor treatments. The clinical characteristics of the patients are given in Table I.

Patients were evaluated for joint health based on HEAD-US and HJHS-2.1 scores and for HRQoL. The median HEAD-US score of the patients was 0 (0-19), while the median HJHS score was 1 (0-12). The median EQ-VAS score was 90 (50-100) and the median Haemo-QoL score was 22 (6.64-76.19). 43.6% (n=17) of patients reported that they were well in all areas evaluated by the EQ-5D. The median values of HEAD-US,

Table I. Clinical characteristics of the patients (n=39).

	Mild hemophilia (n=7)	Moderate hemophilia (n=8)	Severe hemophilia (n=24)
ABR	2 (0-40)	2 (0-6)	2.50 (0-30)
AJBR	0 (0-2)	0 (0-2)	1.50 (0-30)
Age at time of study, yr	15.31 (11.90-21.89)	7.11 (4.41-15.95)	12.77 (4.96-24.15)
Age at diagnosis, yr	6.70 (1.50-15.01)	1.94 (0.54-8.13)	0.69 (0.02-6.13)
Age at first treatment, yr	9.97 (1.50-14.56)	2.01 (1.18-8.87)	1.07 (0.17-6.34)
Age at prophylaxis (n=26), yr	-	4.32 (2.94-5.70)*	2.90 (0.17-13.82)
Age at first bleeding, yr	2.50 (0-11)	1.28 (0.08-8.86)	0.50 (0.02-6.02)
Factor level (%)	18.00 (8.70-29.30)	2.05 (1.00-3.30)	0.285 (0-0.90)

Data presented as median (min-max).
ABR, annual bleeding rate; AJBR, annual joint bleeding rate; yr, years.
*n=2

Table II. HEAD-US, HJHS-2.1, EQ-VAS, and Haemo-QoL scores of the patients in relation to hemophilia severity (n=39).

	Mild hemophilia (n=7)	Moderate hemophilia (n=8)	Non-severe hemophilia (mild-moderate) (n=15)	Severe hemophilia (n=24)
HEAD-US	All patients had 0 points	0 (0-5)	0 (0-5)	3.50 (0-19)
HJHS-2.1	0 (0-8)	0 (0-4)	0 (0-8)	1.50 (0-12)
EQ-VAS	85 (50-100)	85 (50-100)	85 (50-100)	95 (50-100)
Haemo-QoL	14.29 (6.64-33.44)	23.38 (16.67-76.19)	21.48 (6.64-76.19)	22.78 (6.64-69.05)

Data presented as median (min-max).
EQ-VAS, EuroQoL Visual Analogue Score; Haemo-QoL, Hemophilia Quality of Life Questionnaire; HEAD-US, Hemophilia Early Arthropathy Detection with Ultrasound; HJHS-2.1, Hemophilia Joint Health Score version 2.1.

HJHS-2.1, EQ-VAS, and Haemo-QoL scores according to hemophilia severity are provided in Table II. Haemo-QoL and EQ-5D scores and subscores are shown in Fig. 2 and Table III. The most problematic area was pain in the EQ-5D and family in the Haemo-QoL.

When patients were divided into two groups as severe and non-severe (moderate and mild) hemophilia and compared in terms of the HEAD-US, HJHS-2.1, EQ-VAS, and Haemo-QoL, a significant difference was found only for HEAD-US scores (p=0.001, p=0.598, p=0.309, and p=0.721, respectively). When the patient group was divided as severe, moderate and mild hemophilia; there was a statistically significant difference between the HEAD-US scores of patients diagnosed with mild and severe hemophilia (p=0.006), but no significant difference was detected between mild and moderate (p=1.000) or moderate and severe hemophilia (p=0.052). When the analysis was repeated according to the factor levels of the patients; there was a statistically significant moderate negative correlation between the patients' factor levels and the HEAS-US scores (p=0.001, r=-0.530), and no significant correlation was found between patients' factor levels and the HJHS, EQ-VAS, and Haemo-QoL scores (p=0.874, p=0.431, p=0.451, respectively).

All patients with severe hemophilia (24/24) and two patients with moderate hemophilia (2/8) were on prophylactic treatment, whereas the remaining patients with moderate hemophilia (6/8) and all patients with mild hemophilia (7/7) were managed with on-demand therapy. Two of the patients with moderate hemophilia were receiving prophylaxis due to frequent bleeding (The first patient's factor activity level was 1.60%, aged 12.52, diagnosed at 2.88, started prophylaxis at 2.94 years old. The second patient's factor activity level was 1.80%, aged 8.64, diagnosed at 0.63, started prophylaxis at

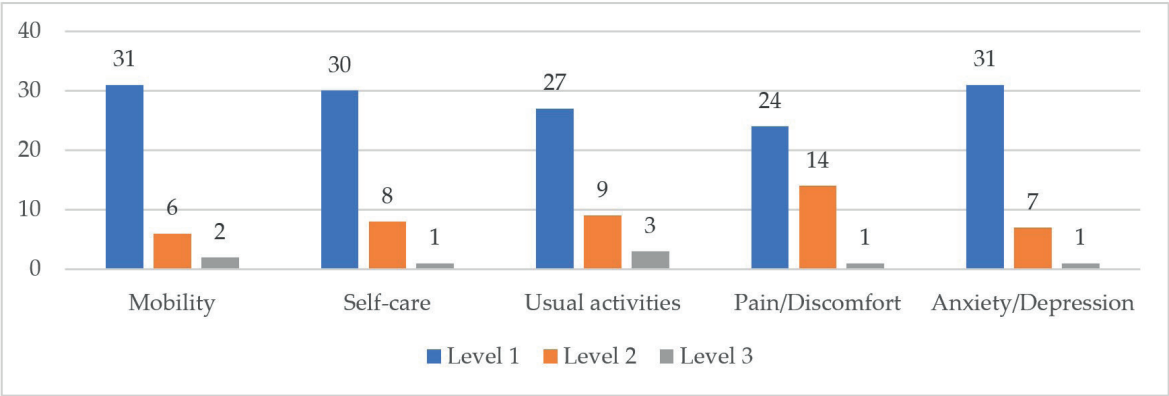

Fig. 2. Distribution of the patients according to the dimensions of the EQ-5D scale.

Table III. EQ-VAS and Haemo-QoL scores and Haemo-QoL subscores.

	n	Median (Range) (%)	Number of patients with the highest score
EQ-VAS	39	90 (50-100)	
Haemo-QoL	39	22 (6.64-76.19)	
Physical health	39	12.5 (0-100)	4
Feelings	39	6.25 (0-83.33)	0
View of yourself	39	16.67 (0-100)	4
Sports	39	27.78 (0-81.25)	6
Treatment	39	25 (0-100)	5
Family	33	45 (12.50-100)	11
Friends	33	25 (0-100)	3
Other people	33	8.33 (0-100)	1
Dealing with hemophilia	32	19.64 (0-100)	2
Perceived support	25	31.25 (0-100)	7
Future	20	22.50 (0-75)	1
Relationships	13	0 (0-62.50)	1
Work	5	6.25 (0-37.50)	0
Family planning	5	0 (0-6.25)	0
Sexuality	6	0 (0-75)	1

EQ-VAS: EuroQoL Visual Analogue Score; Haemo-QoL: Hemophilia Quality of Life Questionnaire

5.70 years old). Because the treatment modality changes according to clinical phenotype; patients were divided into two groups: patients who are receiving prophylaxis and on-demand therapy. Between these two groups, a significant difference was found only for HEAD-US scores (p=0.000). There was no significant difference between HJHS-2.1, EQ-VAS, and Haemo-QoL scores (p=0.546, p=0.489, p=0.872, respectively). When the patients' total HEAD-US scores were compared with their total HJHS-2.1 scores, EQ-VAS scores, and Haemo-QoL scores, no significant correlations were found (p=0.074, p=0.862, and p=0.210, respectively). When the patients who described a state of complete well-being in the EQ-5D and the patients who reported having any problems were compared, no statistically significant difference was detected in HEAD-US, HJHS-2.1, or EQ-VAS scores between the two groups (p=0.082, p=0.564, and p=0.053, respectively), but a statistically significant difference was detected for their Haemo-QoL scores (p=0.001).

When the correlation of the HEAD-US and HJHS-2.1 was examined at the joint level, a statistically significant but negligible correlation was detected ($p<0.001$, $r=0.244$) (Fig. 3). When we looked at the 234 joints to understand why the correlation was negligible, 165 joints with HEAD-US and HJHS-2.1 scores of 0 (165/234, 70.51%), 34 joints (34/199, 17.09%) with a score of 1 or more from the HJHS-2.1 when the HEAD-US was 0, and 21 joints (21/186, 11.29%) with a score of 1 or more from the HEAD-US when the HJHS-2.1 was 0 were observed. Thus, the rate of joints with scores that were incompatible with each other was 23.5% (55/234) among all evaluated joints. When the HJHS-2.1 score was 0, arthropathy was identified by the HEAD-US for 21 joints (synovitis in 18 joints, cartilage damage in 17 joints, bone damage in 6 joints). When the HEAD-US score was 0, among the joints that had scores of >0 from the HJHS-2.1, 25 joints had a non-zero score for crepitation, 1 joint had a non-zero score for loss of extension, and 8 joints had a non-zero score for pain.

Discussion

In the study by Jiménez-Yuste et al., in which the severity, treatment types, and HEAD-US scores of patients with hemophilia B were compared, it was shown that there was a difference between hemophilia severity and HEAD-US scores in most joints when the results were explored at the joint level.[14] In the study by Fang et al. examining knee joints, differences were found between moderate and mild and between severe and mild hemophilia in terms of HEAD-US and HJHS scores, whereas no difference was found between severe and moderate hemophilia. The reason for this was explained as spontaneous bleeding being unusual in cases of mild hemophilia.[15] In this study, we have shown that HEAD-US scores differ statistically between mild and severe hemophilia.

In a study conducted by Xu et al., where the HRQoL of 875 patients was examined with various scales, the Haem-A-QoL was found to be positively correlated with the EQ-5D and negatively correlated with the EQ-VAS.[16] Since there is no threshold value set for the EQ-5D in Türkiye, a relevant comparison could not be made, but when the patients who described themselves as having a state of complete well-being according to the EQ-5D and the patients who reported any problems were examined, there was no statistical difference in EQ-VAS

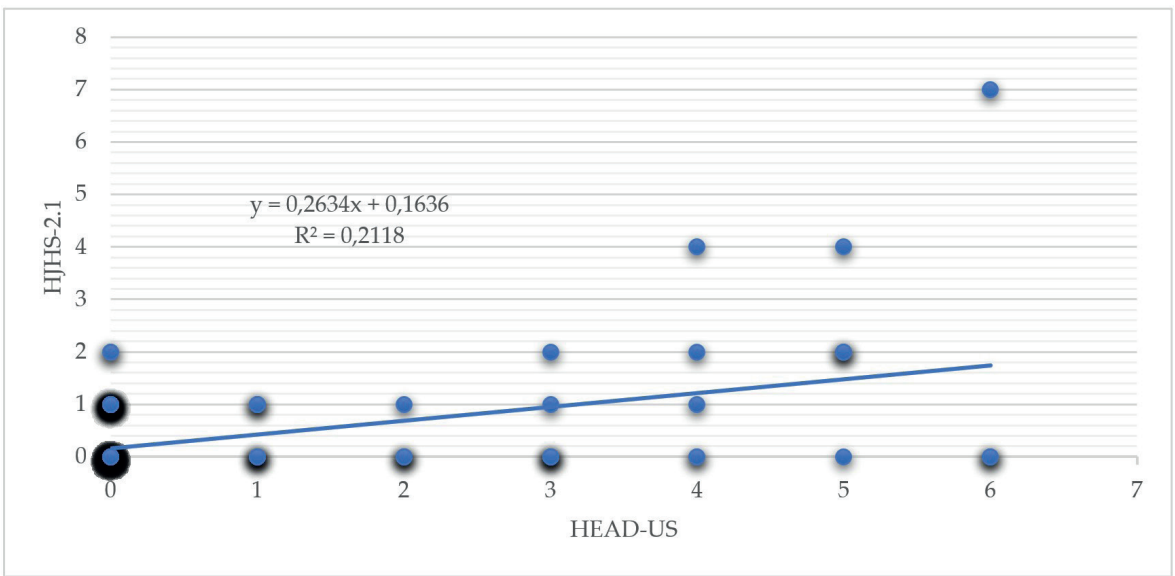

Fig. 3. Scatter plot of HEAD-US and HJHS-2.1 scores at joint level.
HEAD-US, Hemophilia Early Arthropathy Detection with Ultrasound; HJHS-2.1, Hemophilia Joint Health Score version 2.1

scores between the two groups but a statistically significant difference was detected for the Haemo-QoL. In our study, it was seen that the most problematic area of the EQ-5D was pain, while it was family for the Haemo-QoL. Baek et al. showed that the most affected areas for children and adolescents were support, friends, and coping with the disease among patients in Korea with moderate and severe hemophilia.[17] In the study by Oldenburg et al. including patients with severe hemophilia A aged >12 years, the patients received the highest scores in the areas related to sports and the future.[18] In a study in China, patients had the worst scores for the anxiety/depression domain of the EQ-5D-5L, followed by the pain domain; it was observed that the areas where the most problems were reported were pain and then mobility.[16] We believe that the problematic domains may change from culture to culture.

In the PROBE study, the HRQoL scores of patients with moderate and mild hemophilia were found to be significantly lower compared to those of the healthy population.[19] Similar to our study, Cheung et al.[20] showed that HRQoL scores did not change with disease severity. This finding contradicts the results of a study conducted by Daffunchio et al.[21] including patients with mild hemophilia and an average age of 35.9 years, in which it was emphasized that HRQoL was lower among patients with arthropathy. The reason for this difference may be that the median age of the patients in our study was 13 years or that we evaluated patients with all severity levels of hemophilia in our study.

In a study conducted by Foppen et al.[22] that included patients who were diagnosed with severe and moderate hemophilia and receiving prophylaxis, a statistically significant correlation ($p<0.01$, $r=0.700$) was found between HEAD-US and HJHS scores. In our study, no correlation was detected at the patient level ($p=0.074$), while a negligible correlation was detected at the joint level ($p<0.001$, $r=0.244$). The difference in findings on the correlation between the HEAD-US and HJHS-2.1 may be due to the fact that our study was conducted with all hemophilia patients or that more joints were evaluated. In the MoHem study, where HEAD-US and HJHS scores and arthropathy were examined in patients with moderate hemophilia, a statistically significant correlation was found between the HEAD-US and HJHS ($r=0.70$ for elbows, $r=0.60$ for knees, $r=0.65$ for ankles). At the same time, 24% incompatible results were detected. It was observed that when the HJHS score was 0 for 5% of the joints, the HEAD-US scores were 1 or above, and when the HEAD-US score was 0, 26% of the joints received HJHS scores of 1 or above. Crepitus was found to be present in 31% of knees with normal HEAD-US results.[23] In our study, when 234 joints were evaluated, there were 165 joints with 0 points from both the HEAD-US and HJHS-2.1 (165/234, 70.51%), 34 joints (34/199, 17.09%) with a score of ≥1 from the HJHS-2.1 when the HEAD-US score was 0, and 21 joints (21/186, 11.29%) with a score of ≥1 from the HEAD-US when the HJHS-2.1 score was 0. The percentage of joints with scores that were incompatible with each other was 23.5% (55/234) among all joints. Although this is similar to the rate reported by the MoHem study considering discordance among all joints, in our study, the rate of joints with abnormalities detected by the HJHS-2.1 when the HEAD-US score was 0 was found to be lower while the rate of abnormalities detected by the HEAD-US when the HJHS-2.1 score was 0 was found to be higher. The most significant difference between our study and the literature is that the correlation of the HEAD-US and HJHS-2.1 at the joint level varies, but they were found to be less correlated in this study than in the MoHem study.

Since the correlation between the HEAD-US and HJHS-2.1 was found to be lower than previously reported in the literature, an attempt was made to determine which data disrupted that correlation. According to Hilliard et al., when the intraclass correlation of the HJHS was examined, pain and crepitation were found to be the least reliable variables and swelling, muscle atrophy, and walking were found to be

the most reliable.[8] When the subscores of the HJHS-2.1 and HEAD-US were examined in our study, it was observed that the patients scored highest for crepitus and second highest for pain when the HEAD-US score was 0. In this regard, our data are similar to the findings reported in the literature.

The present study is valuable because it emphasizes that HRQoL is not necessarily correlated with patients' arthropathies, since the ways in which children perceive the world differ from those of adults.

Study limitations

The limitations of this study are that it was a cross-sectional design and a limited number of patients were included. More accurate results could be achieved with regular prospective follow-up of patients, the course of their arthropathies, and their HRQoL scores, as well as with studies including larger numbers of patients.

Conclusions

In our study, it was concluded that pediatric patients with hemophilia should be followed with both the HEAD-US and HJHS in terms of arthropathy in childhood because the correlation between them is weak. Additionally, more attention should be paid to patients with severe hemophilia. However, the fact that a patient does not have arthropathy or that a patient has moderate or mild hemophilia does not necessarily mean that the patient's HRQoL scores will be better. In terms of holistic health care, it is necessary to also pay proper attention to patients with moderate and mild hemophilia.

Ethical approval

All procedures were approved by the İstanbul Faculty of Medicine Ethics Committee on 25.11.2022 (meeting no: 21, file no: 2022/1947) and complied with the principles of the Declaration of Helsinki and its 2008 amendment.

Author contribution

The authors confirm contribution to the paper as follows: Study conception and design: AÜ, BG; data collection: BG, MB, GB, AÜ; analysis and interpretation of results: BG, AÜ; draft manuscript preparation: BG, AÜ. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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