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Joint by Joint Correlations Between Ultrasound HEAD-US Scores and HJHS Joint Scores in Hemophilia A Patients: A National, Multi-Center, Prospective, and Cross-Sectional Study

Hemofili A Hastalarında Ultrason HEAD-US ve HJHS Eklem Skorları Arasındaki Korelasyon: Ulusal, Çok Merkezli, Prospektif ve Kesitsel Bir Çalışma

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ABSTRACT Objective: Hemophilia Joint Health Score (HJHS) and Hemophilia Early Arthropathy Detection with Ultrasound (HEAD-US) Score are indispensable tools for the routine evaluation of joint health in individuals with hemophilia A. This study aims to meticulously evaluate the joint-specific correlations between the HJHS and HEAD-US scoring systems in hemophilia A patients, focusing on the elbow, knee, and ankle joints. **Material and Methods:** A comprehensive national, multicenter, prospective, cross-sectional, non-interventional observational study was conducted across 19 medical centers in Türkiye, involving 192 hemophilia A patients over a two-year duration. The inclusion criteria encompassed patients aged ≥6 years with moderate or severe hemophilia A (FVIII<2%), comprising 63.5% pediatric and 36.5% adult patients. **Results:** In the analysis of 192 patients under prophylactic treatment, a robust correlation was identified between the HJHS and HEAD-US total scores across all age groups. Particularly noteworthy was the finding that adults exhibited a more pronounced correlation than their pediatric counterparts for total scores. When exploring the correlation among the six joints, it became apparent that elbows exhibited the highest correlation *(r: 0.408/0.581)*, while ankles demonstrated the lowest correlation *(r: 0.397/0.311)*. Furthermore, the study uncovered an intriguing insight: a significant difference in correlation rates between children and adults, adding a layer of complexity to the joint evaluation process. **Conclusion:** The HEAD-US and HJHS scoring systems serve as valuable monitoring tools in hemophilia A, offering complementary insights. Our findings highlight varying correlation rates among joints, emphasizing elbows as the most correlated joints.

Keywords: Hemophilia A; joint diseases; ultrasonography; prospective studies; correlation analysis

ÖZET Amaç: Hemofili Eklem Sağlığı Skoru [Hemophilia Joint Health Score (HJHS)] ve Hemofili Erken Artropati Taraması Ultrason [Hemophilia Early Arthropathy Detection with Ultrasound (HEAD-US)] Skoru, rutin uygulamada eklem sağlığını değerlendirmek için vazgeçilmez araçlardır. Bu çalışma, hemofili A hastalarında HJHS ve HEAD-US skorlama sistemlerinin eklem bazında değerlendirmesini yapmayı hedeflemiş olup özellikle dirsek, diz ve ayak bileği eklemlerindeki korelasyonun gücünü değerlendirmiştir. **Gereç ve Yöntemler:** Türkiye genelinde 19 merkezde gerçekleştirilen kapsamlı, ulusal, çok merkezli, prospektif, kesitsel, müdahalesiz gözlemsel bir çalışma olup 192 hemofili A hastasını içeren 2 yıllık bir dönemi kapsamıştır. FVIII<%2 olan orta ve ciddi hemofili A hastalarından, yaşları ≥6 olan hastalar çalışmaya dâhil edilmiş olup, bu hastaların %63,5'i pediatrik ve %36,5'i erişkin hastalardır. **Bulgular:** Profilaktik tedavi almakta olan 192 hastanın analizi, tüm yaş gruplarında HJHS ve HEAD-US toplam skorları arasında önemli korelasyon olduğunu göstermiştir. Özellikle erişkinlerin toplam skorlarında çocuklardan daha güçlü korelasyon gözlemlenmesi dikkat çekicidir. Değerlendirilen altı eklem incelendiğinde, dirsekler en yüksek korelasyonu gösterirken *(r: 0,408/0,581)*, ayak bilekleri en düşük korelasyonu göstermiştir *(r: 0,397/0,311)*. Ayrıca, çocuklar ve erişkinler arasında korelasyon oranlarında belirgin bir fark bulunması, eklem değerlendirme sürecine karmaşıklık katmaktadır. **Sonuç:** HEAD-US ve HJHS skorlama sistemleri, hemofili A'da değerli izleme araçları olarak kullanılmakta ve birbirini tamamlayan bilgiler sunmaktadır. Bulgularımız, eklemler arasında değişen korelasyon oranlarını vurgulayarak dirseklerin en korele eklem olduğunu göstermektedir.

Anahtar Kelimeler: Hemofili A; eklem hastalıkları; ultrasonografi; prospektif çalışma; korelasyon analizi

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The basic point of hemophilia care is to avert hemorrhage by replacing factor concentrates, which serve as substitutions for defective coagulation factors. Administering these factors for prophylaxis and initiating early preventive measures in severe hemophilic children can significantly alleviate the risk of severe bleeding, long-term joint diseases, and resulting disabilities.[1-3]

Evaluating the condition of joints is imperative, serving not only to categorize joint diseases but also to monitor prophylaxis and gauge the outcomes of replacement therapy. The Hemophilia Joint Health Score (HJHS) is widely employed for appraising joint function, albeit necessitating training and experience for its implementation.[4] However, ultrasonography offers several advantages, including cost-effectiveness, availability, repeatability, faster examination, suitability for children without sedation, and the ability to scan multiple joints and dynamically examine them in a single session.[5] In our prior multicenter studies, we consistently observed a general correlation between the Ultrasound-based Hemophilia Early Arthropathy Detection with Ultrasound (HEAD-US) scoring system and HJHS scores.[6,7]

The main focus of our current study is to explore the relationship between HJHS and HEAD-US scores in relation to joint levels.

MATERIAL AND METHODS

PATIENTS

The present investigation was structured as a nationwide, multi-center, prospective, cross-sectional, non-interventional, observational study. A total of 19 healthcare facilities spanning Türkiye were designated, involving 192 individuals diagnosed with hemophilia A (HA). Data collection transpired between October 2021 and August 2022. The study encompassed male participants aged six years or older with moderate or severe HA (factor level <2%). Among the participants, 63.5% belonged to the pediatric group (ages 6 to 18 years), while the remaining 36.5% constituted the adult group (ages 19 to 60 years) (Table 1).

TABLE 1: Demographics of patients with hemophilia A.

	All group	Children (<18 yr)	Adults (>18 yr)
$\bar{X}$+SD	17±10 years	11±4	27±10
Median	15	11	23
Range	6-60 years	6-17	18-60
Total patients	192	122	70
Percentages	100%	63.5%	36.5%

SD: Standard deviation.

Participants experiencing challenges in communication (such as an inability to comprehend or speak Turkish) or cognitive impairments, along with those having inhibitors, were excluded from the study. The study protocol obtained approval from the Clinical Research Ethics Committee of Ege University Faculty of Medicine on September 28, 2021 (no: 21-9.3/1). The study adhered to the principles of the Helsinki Declaration during its implementation.

Final authorization was granted by the Turkish Ministry of Health, Department of Clinical Trials in Ankara, Türkiye. The study's contract research organization (CRO) was Omega-CRO in Ankara, Türkiye, and Pfizer Türkiye sponsored the study. Written informed consent was acquired from either all participants or their legal representatives.

PROCEDURE

After enrolling in the study, patients underwent evaluation during a single visit. At the designated study centers, demographic features and the hemophilia history of patients were documented on records. Comprehensive physical examinations of the elbow, knee, and ankle joints were conducted using the HJHS scoring system at each visit. Additionally, bilateral ultrasonographic examinations of the elbow, ankle, and knee joints were carried out. The results obtained from ultrasonography were analyzed using the HEAD-US scoring system. These assessments were performed by proficient physiotherapists, hematologists, and radiologists at their respective centers.

Recognizing the crucial role of standardized educational programs in ensuring the quality of performance, we implemented training standardization for physiotherapists, hematologists, and radiologists across all 19 centers. Over the past two years, various workshops have been organized for these professionals. Expert radiologists have mentored young ra-

diologists from the centers in the application of the HEAD-US scoring system, while expert physiotherapists have provided educational guidance to young hematologists and physiotherapists for proficiency in the HJHS.

MEASUREMENTS

The HJHS: This system assesses the extent of joint damage in patients with hemophilia (PwH) and is advised for regular follow-up evaluations of joint health. HJHS assesses the six joints most frequently affected in PwH (elbows, knees, and ankles), assigning total scores ranging from 0 to 124, including gaiting. Higher scores indicate greater damage or impairment. Version 2.1 of the scoring system was employed.[4]

The HEAD-US Scoring System: Originating from the work of Martinoli et al., this scoring system centers on three crucial indicators for the primary joints (knees, elbows, and ankles): Synovitis (scored 0-2), Cartilage (scored 0-4), and subchondral bone (scored 0-2), with a maximum of 8 points allotted per joint.[5] Elevated scores denote damage or impairment. Ultrasonography facilitates the identification and quantification of disease activity indicators (such as joint fluid accumulation, synovial hypertrophy) and degenerative changes (like osteochondral alterations). Moreover, it aids in distinguishing inflammatory effusion from hemarthrosis.

SAMPLE SIZE

The sample size of 161 was determined to generate a two-sided 95% confidence interval with a width of 0.200 (+/-0.1) at a sample correlation of 0.600. This sample size was established to evaluate the strength of correlation between HJHS and HEAD-US scores across all six joints.

STATISTICAL ANALYSIS

The data analysis was executed utilizing PASW Statistics for Windows, Version 18.0 (SPSS Inc., Chicago, IL, USA). Descriptive statistics comprised mean, standard deviation, median, minimum-maximum for numerical variables, and number/percentage for categorical variables. To examine correlations, the Spearman's Rho correlation test was applied, with statistical significance established at $p<0.05$.

RESULTS

The study encompassed 192 male HA patients across 19 diverse centers, all of whom received prophylactic treatment for at least one year. Most of the centers (n=16) was pediatric centers and others were adults. The mean age for the entire group was 17 years. Comprehensive details regarding patient characteristics and disease-related information can be found in Table 1.

Correlation analyses were carried out on individual joint scores during patient visits. Across all age groups, a notable correlation emerged between the total scores of HJHS and HEAD-US *(p<0.001)* (Table 2). Notably, adults exhibited a more robust correlation compared to children in terms of total scores.

In terms of correlation strength, a comparison among six different joints revealed the highest correlation in elbow joints and the weakest in ankles (Table 3).

Detailed joint-by-joint evaluations for correlation analysis are presented in Table 4, comprising a total of 1,152 joints. The most correlated joints were right elbow *(r=0.408 and 0.581)* for both adult and children. The lowest correlation rates were in left ankles for both adults and children *(r=0.397 and 0.311)* (Table 4).

TABLE 2: Total HJHS scores and Total HEAD-US scores: Correlation status for ages.

HJHS-total	Parameters	HEAD-US total
Total score	r (correlation coefficient)	0.639
For all groups	p (p value)	<0.001
	n (patient count)	192
<18 yr	**r***	**0.473**
	p	**<0.001**
	n	**122**
>18 yr	**r**	0.622
	p	<0.001
	n	70

*r (correlation co-efficient): 0-0.25: Lower; 0.25-0.50: Moderate; 0.50-0.75: Good; 0.75-1.00: Strong associations; HJHS: Hemophilia Joint Health Score; HEAD-US: Hemophilia Early Arthropathy Detection with Ultrasound.

TABLE 3: Mean and median values in the individual joints for HJHS and HEAD-US scores.

	All patients (n=192)		Children (n=122)		Adults (n=70)	
	HJHS	HEAD-US	HJHS	HEAD-US	HJHS	HEAD-US
	X̄±SD		X̄±SD		X̄±SD	
Joints	Median/Range		Median/Range		Median/Range	
Left elbow	**0.67±1.94**	**1.08±1.94**	**0.22±0.89**	**0.63±1.35**	**1.46±2.8**	**1.87±2.50**
	(0.0)/(0-15)	(0.0)/(0-8)	(0.0)/(0-8)	(0.0)/(0-6)	(0.0)/(0-15)	(1.0)/(0-8)
Right elbow	**0.95±2.24**	**1.06±2.04**	**0.39±1.39**	**0.52±1.24**	**1.93±3.0**	**2.0±2.70**
	(0.0)/(0-12)	(0.0)/(0-8)	(0.0)/(0-9)	(0.0)/(0-6)	(0.0)/(0-12)	(0.0)/(0-8)
Left ankle	**0.70±1.85**	**1.09±1.83**	**0.26±0.9**	**0.51±1.12**	**1.93±3.0**	**2.10±2.3**
	(0.0)/(0-12)	(0.0)/(0-8)	(0.0)/(0-9)	(0.0)/(0-7)	(0.0)/(0-12)	(1.0)/(0-8)
Right ankle	**0.77±2.03**	**1.08±1.84**	**0.39±1.3**	**0.58±1.28**	**1.47±2.6**	**1.94±2.3**
	(0.0)/(0-11)	(0.0)/(0-8)	(0.0)/(0-11)	(1.0)/(0-8)	(0.0)/(0-11)	(1.0)/(0-8)
Left knee	**1.08±2.78**	**0.69±1.64**	**0.43±2.16**	**0.31±0.98**	**2.21±3.3**	**1.34±2.2**
	(0.0)/(0-22)	(0.0)/(0-8)	(0.0)/(0-22)	(0.0)/(0-7)	(0.0)/(0-13)	(0.0)/(0-8)
Right knee	**1.11±2.50**	**0.89±1.87**	**0.52±1.83**	**0.42±1.28**	**2.14±3.1**	**1.7±2.4**
	(0.0)/(0-11)	(0.0)/(0-8)	(0.0)/(0-11)	(0.0)/(0-7)	(1.0)/(0-11)	(0.0)/(0-8)

SD: Standard deviation; HJHS: Hemophilia Joint Health Score; HEAD-US: Hemophilia Early Arthropathy Detection with Ultrasound.

TABLE 4: Joint-Joint evaluations for different age groups in HJHS and HEAD-US scores.

Patients	All group (n=192)		Children (n=120)		Adults (n=72)	
Joints	r*/95%**	p value	r/95%	p value	r/95%	p value
Left ankle	0.410	<0.001	0.249	0.006	0.397	0.001
	(0.285-0.500)		(0.075-0.409)		(0.179-0.578)	
Right ankle	0.382	<0.01	0.283	0.002	0.408	<0.001
	(0.254-0.497)		(0.111-0.439)		(0.191-0.587)	
Left elbow	0.645	<0.001	0.422	<0.001	0.780	<0.001
	(0.554-0.721)		(0.264-0.558)		(0.667-0.858)	
Right elbow	0.649	<0.001	0.581	<0.001	0.666	<0.001
	(0.559-0.724)		(0.450-0.688)		(0.511-0.779)	
Left knee	0.438	<0.001	0.311	<0.001	0.474	<0.001
	(0.316-0.546)		(0.141-0.463)		(0.269-0.638)	
Right knee	0.532	<0.001	0.391	<0.001	0.554	<0.001
	(0.422-0.698)		(0.229-0.532)		(0.367-0.698)	

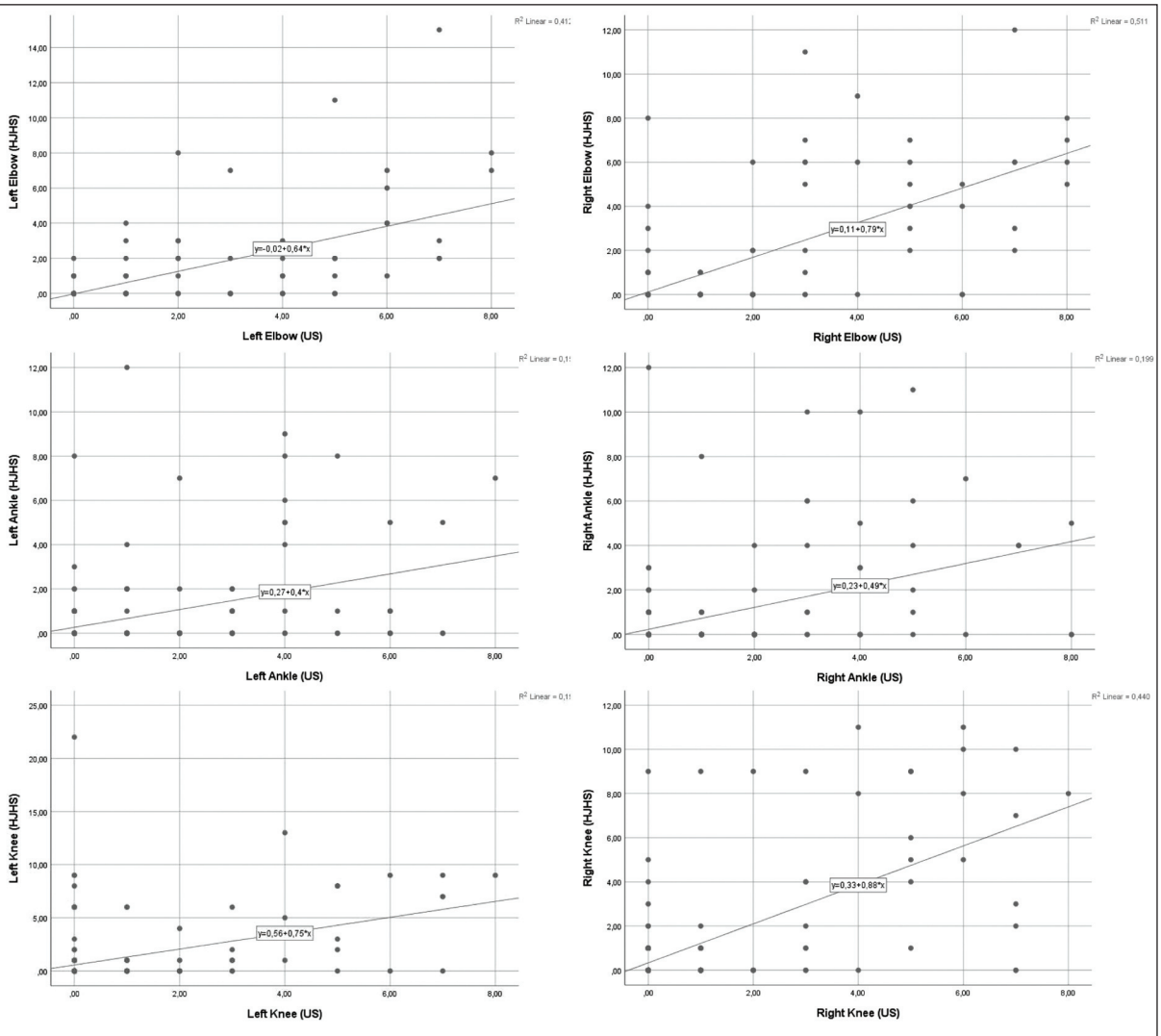
*r (correlation co-efficient): 0-0,25: Lower; 0.25-0.50: Moderate; 0.50-0.75: Good; 0.75-1.00: Strong associations; **95%: 95% confidence intervals for the correlation value.

Both scorring system has 0/0 in 41 patients with children (33%). However this rate is very lower in adults (6 patients and 6%) *(p<0.001)*. Similar scores including 0/0 for both scorring systems were significanly found in 46 children (37%) whereas found in 9 cases (12%). p value was significantly higher *(p<0.001)*. However due to different scorring systems these results did not evaluate as superiority.

Figure 1 visually represents the correlation status across all six joints, illustrating distinct dynamics within each joint.

DISCUSSION

Throughout the monitoring of PwH, the assessment of joint function involves both physical examinations and the widely adopted HJHS scoring system. However, the implementation of HJHS necessitates specialized training and experience.[4,8] Traditional plain radiographs have long served as a means to evaluate the musculoskeletal system. The Pettersson scoring system, a radiological joint assessment tool, yields reliable outcomes when administered by a proficient



Joints	r/p (correlation coefficient/p value)
Left Elbow	**0.645/<0.01**
Right Elbow	**0.649/<0.001**
Left Ankle	0.410/<0.001
Right Ankle	0.382/0.001
Left Knee	**0.438/<0.001**
Right Knee	**0.532/<0.001**

FIGURE 1: Correlation parameters amongst six joints.
DEEP-NOTES of Figure 1.

radiologist.[8] Magnetic resonance imaging (MRI) stands out as a more sensitive imaging modality compared to plain radiograms for joint evaluation. Nonetheless, practical drawbacks such as extended scanning periods, high costs, limited accessibility, and the requirement for sedation in young children

accompany MRI usage. A pressing demand exists for a straightforward, cost-effective, repeatable, efficient, and dependable joint scoring system. Consequently, ultrasonography has gained prominence in recent years as an appealing method for the objective evaluation of joint status and the early detection of changes during routine follow-ups.[7,8]

Ultrasonography presents numerous advantages, including cost-effectiveness, accessibility, expeditious examinations, suitability for children without requiring sedation, and the capability to dynamically assess multiple joints in a single session.[6-10] It enables the identification and quantification of indicators of disease activity (joint fluid accumulation, synovial hypertrophy, etc.) and degenerative changes (osteochondral alterations, etc.), proving beneficial in distinguishing inflammatory effusion from hemarthrosis. As a straightforward and practical tool, ultrasonography stands as a potent candidate to facilitate routine hemophilia care in the near future.[9,10] Various scoring systems have recently been introduced to introduce objectivity to ultrasonographic evaluations. The HEAD-US scoring system holds advantages in that it can be administered by individuals without specialized imaging expertise. Although this scoring system can be executed by non-radiologists following brief training, the speed of the examination is contingent on the sonographer's experience level.[5-7] Additionally, other ultrasound-based scoring systems are available, and reliable outcomes have been reported.[11-14]

Utilizing the HEAD-US scoring system for the assessment of joint status in PwH and examining its correlation with the HJHS has been a focal point in numerous studies in the literature. In a study by Jiménez-Yuste et al., conducted on hemophilia B patients, it was concluded that the routine use of the HEAD-US scoring system provided patients with a superior and objective evaluation, contributing to the personalization of treatment.[15] Notably, in a recent Spanish study involving 66 patients and 203 joints, a strong total score correlation *(r=0.717)* was reported.[16] In this study, while the HJHS identified only 54% of cases with synovitis and 75% of cases with osteochondral damage, the HEAD-US detected several relevant aspects in less than 53% of the cases. HEAD-US demonstrated added value in identifying early changes such as synovitis and osteochondral damage. In another study from China, both knees of 70 patients were evaluated for both scores, revealing a significant correlation between the HEAD-US and HJHS *($p<0.01$)*.[17] Similarly, an intriguing study from Indonesia, involving 120 hemophilic children receiving on-demand treatment, reported a moderate correlation between both scores *($r=0.65/p<0.059$)*.[18]

In a recent report from our research group, a prospective study encompassing all patients indicated a robust correlation *(r=0.842)* between the HEAD-US total scores and the HJHS total score.[6] However, this study solely examined total joint scores, and a joint-by-joint evaluation was not feasible. In the current study, we were able to assess over a thousand joints to evaluate the correlation more comprehensively. Our findings distinctly illustrate that elbow joints exhibit the most significant correlation for both scoring systems. Interestingly, ankles emerged as the most problematic joints, as evident in Table 3. This observation holds true for both children and adults, showcasing a similarly limited correlation for ankles in both age groups (Table 4). The intricate anatomical patterns of ankle joints may contribute to their lower correlation.

Synovitis serves as a fundamental indicator in the assessment of hemophiliac arthropathy and response to therapeutic interventions. A Spanish study, concentrating on synovitis evaluation without ultrasound, highlighted that the ability to detect subclinical synovitis is significantly diminished, particularly in elbows.[19] In our study, among joints exhibiting no swelling, pain, or a history of hemarthrosis, 40% manifested subclinical synovitis upon ultrasound examination. This ratio was notably higher in elbows compared to knees and ankles. The current study observed a similar pattern concerning elbow joints.

The primary advantage of HEAD-US scores over the HJHS system lies in their early detection of joint problems, as demonstrated in our results presented in Table 2, Table 3, and Table 4, as well as in Figure 1.[11-14]

Stephensen et al. reported good repeatability of the HEAD-US protocol when administered by phys-

iotherapists.[20] In our study, we found a moderate correlation between HEAD-US and HJHS for the elbow and ankle joints, and a strong correlation for the knee joint. The discordance between clinics and US examination was 19.3%. In contrast, our present study involved physiotherapists and hematologists for HJHS evaluation, while only radiologists performed ultrasound assessments. Notably, only the left elbow in adults demonstrated a strong association, with most r values indicating a low association in our study. The reduced association in ankle joints in the present study may be linked to lower inter-rater reliability.

Banchev et al. highlighted a robust correlation between the three-year joint bleeding rate and the HEAD-US total score for ankle and knee joints in HA patients undergoing secondary/tertiary prophylaxis.[21] It is noteworthy that these patients may not be representative of those undergoing standard prophylaxis, as observed in our study with Turkish patients. The most recent meta-analysis convincingly demonstrated that ultrasound-based evaluations are more accurate than physical examination by HJHS in clinical practice. This is attributed to the fact that synovial proliferation assessed solely by physical examination tends to be underestimated without the use of a US-based scoring system.[22]

STUDY LIMITATIONS

The assessment of HJHS scores was conducted by physiotherapists and hematologists across 19 centers, while ultrasound evaluations were performed by 27 different radiologists from the same centers, despite comprehensive educational workshops aimed at enhancing standardization among medical staff. Despite these efforts, achieving a perfect correlation rate *(r=1.0)* in certain joints was unattainable, leading to non-universal correlations and occasional discordance observed in specific joints.

CONCLUSION

The HEAD-US and HJHS scoring systems play crucial roles in the continuous monitoring of PwH, offering complementary perspectives on joint health. In everyday clinical practice, both scoring systems prove to be reliable for assessing joint health in hemophilia, demonstrating a robust correlation. Our study findings underscore that a joint-by-joint assessment unveils elbows as the most strongly correlated joints, with ankles exhibiting a relatively lower correlation in this context.

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Conflict of Interest

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Authorship Contributions

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