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ORIGINAL ARTICLE

Assessing joint health in haemophilia patients: The combined value of physical examination and ultrasound imaging

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Abstract

Introduction: Early diagnosis of joint damage is pivotal in haemophilia to prevent the occurrence and progression of haemophilic arthropathy thus providing optimal personalised management. The haemophilia joint health score version 2.1 (HJHS) is based on a physical examination of the mainly affected joints. Musculoskeletal ultrasound has demonstrated the capability to detect early changes in terms of synovitis and osteochondral damage. The haemophilia early detection with ultrasound (HEAD-US) score has been proposed as a simple and reliable evaluation tool.

Aim: This study aims to investigate the correlation between the HJHS and the HEAD-US scores performed by two independent operators (physical therapist and musculoskeletal ultrasound expert) for the evaluation of the joint health status of patients with haemophilia.

Methods: Consecutive adult patients independent of the severity degree were included. Elbows, knees and ankles were evaluated by a physical therapist by HJHS and by a musculoskeletal ultrasound expert following the HEAD-US protocol.

Results: We observed a good positive correlation between HJHS and HEAD-US (Spearman's rho 0.72). The main discrepancy in conceptually similar domains was found between the HJHS swelling and the HEAD-US synovitis (rho 0.17), as ultrasound was able to detect even mild synovitis when HJHS swelling was scored 0 in up to 40% of cases.

Conclusions: The HJHS and HEAD-US correlate well even when performed by two independent operators. Musculoskeletal ultrasound is particularly useful for the early detection of synovitis. The routine assessment of both scores helps clinicians define the stage and extension of joint involvement and set up a personalised treatment.

KEYWORDS
haemophilia, haemophilic arthropathy, joint diseases, physical examination, synovitis, ultrasonography

1 | INTRODUCTION

Haemophilia A and B are rare, inherited X-linked bleeding disorders caused by a complete or partial deficiency of coagulation factors VIII (FVIII) or IX (FIX). In children and adults with severe haemophilia (i.e. plasma FVIII or FIX levels of <1 U/dL), spontaneous joint bleeding (haemarthrosis) is the most frequent clinical manifestation[1] that may also occur in patients with moderate (plasma factor levels of 1–5 UI/dL) or mild disease (plasma factor levels of >5 UI/dL).[2] Repeated joint bleeding, even when subclinical, leads to joint damage, remodelling and subsequent degenerative arthropathy, characterised by a synovial hyperplasia with or without synovial effusion and, in more advanced stages, cartilage loss and subchondral bone sclerosis, which further limit movements and lead to crepitus, pain and deformity.[3] Indeed, chronic arthropathy, which mainly affects ankles, knees and elbows, is the most common complication in patients with haemophilia and causes disability and reduced health-related quality of life (HRQoL).[3] Both physical examination and musculoskeletal ultrasound imaging have demonstrated to be highly useful in evaluating joint health in patients with haemophilia considering different and complementary aspects of haemophilic arthropathy.[4] In addition, point-of-care musculoskeletal ultrasound can help clinicians identify early joint bleeding and differentiate it from synovitis or arthropathic pain.[5,6] As even a single bleeding event can lead to irreversible joint damage, the early detection of joint bleeding, whether symptomatic or subclinical, is pivotal to prevent joint deterioration and disability.[7–9] Therefore, it is relevant to define both clinical and imaging tools that are objective and specific, as part of a routine evaluation of haemophilic patients. Within the physical examination scales, the haemophilia joint health score version 2.1 (HJHS)[10] is a physical examination tool developed by a consensus of experts for joint health assessment initially validated in children and more recently in adults with haemophilia.[11] Among the ultrasound scales, the haemophilia early arthropathy detection with ultrasound (HEAD-US)[12] has proven to be simple and reliable in detecting early changes in joint soft tissues and osteochondral structures, even before these changes are evident during the physical examination.[13]

Both instruments appear to provide complementary data on joint health, which can be useful in tailoring haematological therapy.[14] However, there is little information on the agreement of these assessment tools in patients with different severity of haemophilia and when the two scores are performed by two independent operators.

This study aims to evaluate the correlation between the HJHS, and the HEAD-US scores performed by two independent operators for the joint health status in patients with haemophilia with different severity degrees.

2 | MATERIAL AND METHODS

2.1 | Study design

This is an observational retrospective non-pharmacologic no-profit study. The study was approved by the Milan Area 2 Ethics Committee (No. 199_2021bis) and was carried out in conformity with the 2013 revision of the Declaration of Helsinki and the code of Good Clinical Practice. This study follows the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guidelines for reporting observational study results.[15]

2.2 | Patients

Consecutive adult patients with haemophilia A and B with different severity referring to the outpatient clinic of the Angelo Bianchi Bonomi Hemophilia and Thrombosis Center of Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico in Milan for a routine consultation between March 2021 and December 2021. The HJHS and HEAD-US were performed following physical examination in the same visit by two independent operators blinded to the results of each other.

We collected the following patients' demographic and clinical characteristics: age, type of haemophilia, disease severity, type of treatment and HRQoL as measured by the EQ-5D-5L.[16,17]

2.3 | Physical examination

The HJHS score was performed by a trained physiotherapist (E.B.), with more than 15 years of experience in the evaluation and management of haemophilic patients and currently national coordinator of physiotherapists for the EAHAD. The HJHS is based on the physical examination of six index joints (elbows, knees and ankles) and gait assessment. The items for this scale are scored as follows: swelling (0–3), duration of swelling (0–1), muscular atrophy (0–2), crepitus on motion (0–2), range of motion (flexion loss 0–3, extension loss 0–3), strength (0–4) and joint pain (0–2), for a total score of 0–20 points per joint; in addition, the walking section was scored from 0 to 4. Higher scores indicate poorer joint condition, ranging from 0 to 124 overall.[10] The evaluation was not performed on those joints experiencing an acute bleed within 2 weeks from the examination or previous prosthetic surgery or arthrodesis.[4]

2.4 | Musculoskeletal ultrasound imaging

The HEAD-US was performed on the same six index joints (elbows, knees and ankles) by a rheumatologist with more than 10 years of experience in musculoskeletal ultrasound (R.G.), formally certified by the Italian Society of Ultrasound in Medicine and Biology (SIUMB) and specifically trained under experts in the use of HEAD-US score. The elbows, knees and ankles were evaluated and scored based on synovitis (0–2), articular cartilage damage (0–4) and subchondral bone damage (0–2). Possible scores range from 0 to 8 per joint and therefore the total score ranges from 0 to 48, with higher scores indicating a more severe arthropathy.[12] The ultrasound examination was performed with a Philips Affiniti 50 machine with a 5–12 MHz linear probe. The evaluation was not performed on those joints experiencing an acute bleed

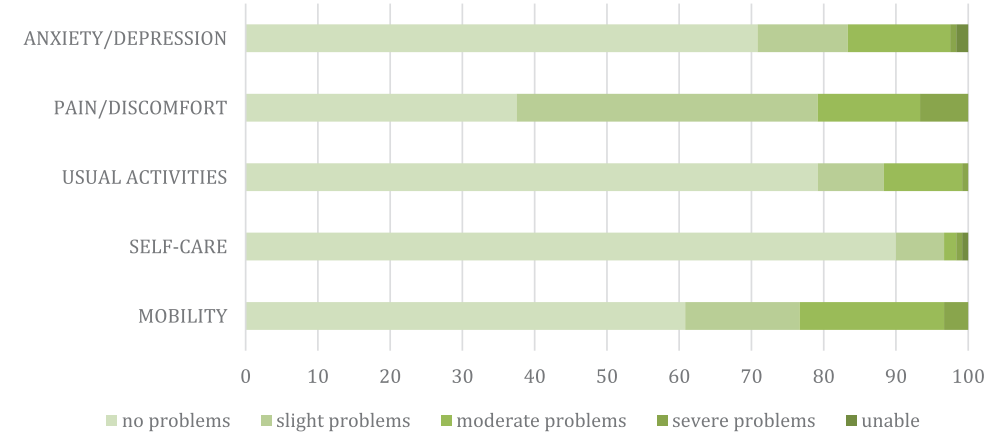


FIGURE 1 The health-related quality of life data of the study population. The figure represents the different domains and results of the EQ-5D-5L questionnaire in the study population.

within 2 weeks from the examination or previous prosthetic surgery or arthrodesis.[4]

2.5 | Statistical analysis

Variables with a normal distribution were expressed as mean and standard deviation (SD), variables with non-normal distribution were expressed as median and interquartile range (IQR). Correlation between variables was assessed by Spearman's rho. The correlation is defined as follows: a Spearman's rho under 0.4 is a weak correlation, 0.40–0.69 is a moderate correlation, a 0.70–0.89 is a good correlation and a 0.90–1.0 is an excellent correlation. The latest version of SPSS was used to perform the analysis (IBM Corp. Released 2020. IBM SPSS Statistics for Windows, Version 27.0. Armonk, NY: IBM Corp) while JMP software was used to create the correlograms (SAS Institute Inc. released 2021, version 'pro 16' for Windows,. SAS Institute Inc., Cary, NC, 1989–2022).

3 | RESULTS

A total of 120 patients affected by haemophilia were included in the study, with a median age of 42 years (IQR 33–56). Haemophilia A patients were 111, of which 84 severe, 13 moderate and 14 mild patients, haemophilia B patients were nine, of which six severe and three moderate patients. Ninety patients were on prophylaxis regimen, in particular, standard half-life (SHL) FVIII products were used by 48 patients, extended half-life (EHL) products by 29 patients and emicizumab by 13 patients (two patients with current inhibitors against FVIII). Twenty patients were on episodic treatment with SHL, three with EHL and seven with desmopressin (DDAVP). Ninety patients reported performing regular physical activity. The HRQoL of patients included in the study is represented in Figure 1. Median general health visual analogue scale was 80 (IQR 70–90).

The median HJHS score was 11 (IQR 5–17), the median HEAD-US score was 11 (IQR 5–19). Thirty-nine knees and 17 ankles were excluded due to prosthetic surgery or arthrodesis.

There was a good linear positive correlation between the HJHS and HEAD-US total scores (rho = 0.72, $p < .001$), as shown in Figure 2. Correlation coefficients between each domain of the HJHS and HEAD-US scores are reported in Table 1. We found a very low correlation (rho = 0.17) between the HJHS swelling domain and the HEAD-US synovitis domain. This finding is consistent with the observation that in 105 patients with an HJHS total swelling domain scoring 0, up to 42 patients (40%) showed the presence of an HEAD-US synovitis domain ≥1.

Furthermore, we observed a moderate to good correlation between the HJHS joint total score and the total HEAD-US synovitis, cartilage and bone damage domains (rho 0.52, 0.73 and 0.66, respectively). The HJHS total pain domain correlated weakly with the HEAD-US cartilage and bone domains (rho 0.33 and 0.30, respectively), and even less with the synovitis domain (rho 0.17).

In 10 subjects with a total HJHS score of 0, the HEAD-US total score was ≥1 in four patients (40%). Of these, four ankles, two knees and two elbows scored ≥1. In addition, out of 14 patients with an HEAD-US total score of 0, eight patients had an HJHS total score ≥1 (57%). In these subjects, the most frequent items scoring ≥1 were those domains not captured by the HEAD-US score, namely extension loss (42.8%), crepitus on motion (35.7%), flexion loss (21.4%) and muscle atrophy (14%). By contrast, swelling, pain and strength loss domains always scored 0.

The colormaps reporting the correlations among the total scores and each domain of the HJHS and HEAD-US scores for elbows, knees and ankles are represented in Figure 3. By analysing each joint, a stronger correlation was found between the HJHS and HEAD-US total scores in elbows (right elbows 0.84, left elbows 0.82), than in knees (right knees 0.56, left knees 0.43) and ankles (right ankles 0.58, left ankles 0.62), as shown in Figure 3. Even in this analysis, a stronger correlation between conceptually similar domains such as HJHS

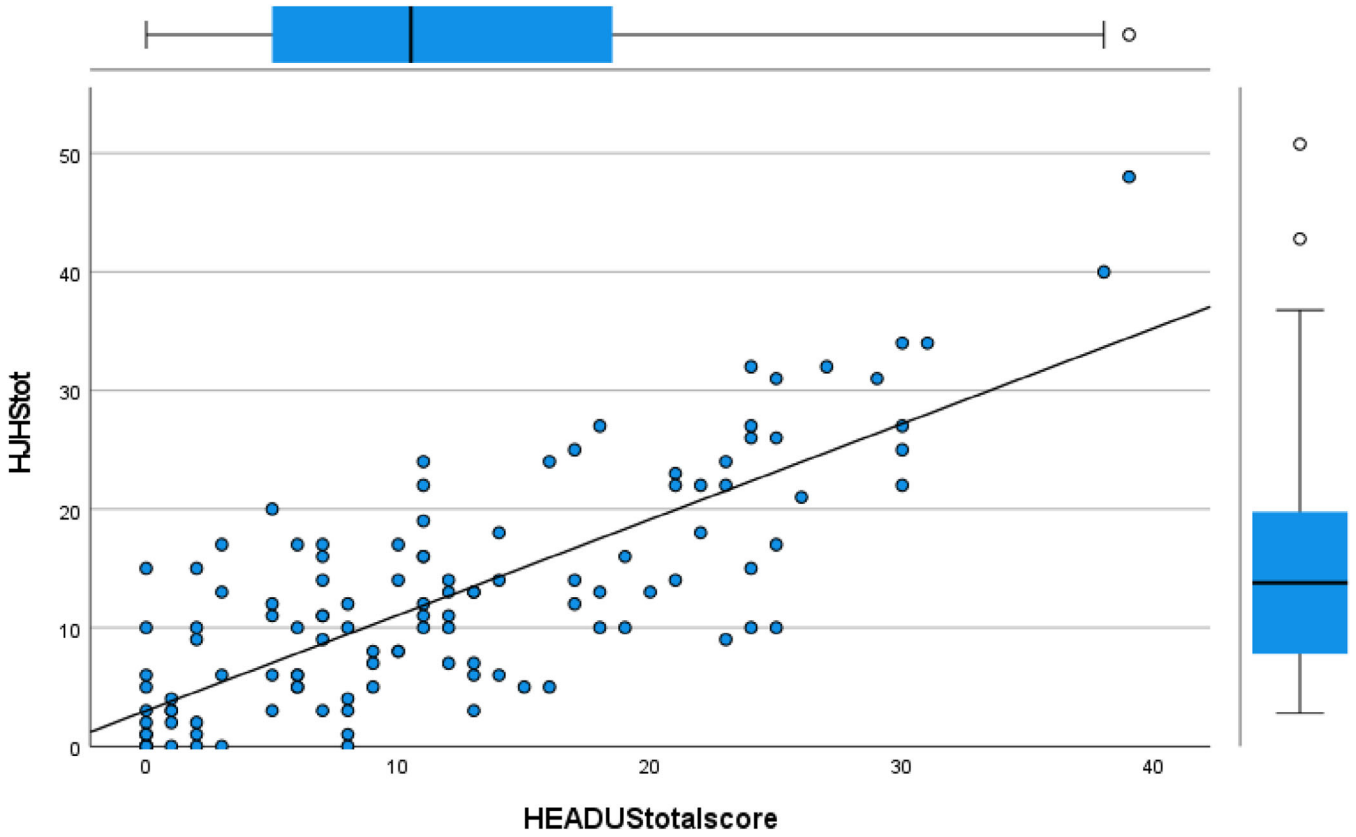


FIGURE 2 The correlation between the haemophilia joint health score version 2.1 (HJHS) and haemophilia early arthropathy detection with ultrasound (HEAD-US) in the study population. The figure represents the scatterplot of the correlation between the HJHS and HEAD-US scores. The box and whiskers on the Y and X axis represent the quartiles and outliers of the HJHS and HEAD-US scores, respectively. HEAD-US, haemophilia early arthropathy detection with ultrasound total score; HJHS, haemophilia joint health score total score.

TABLE 1 Correlation (Spearman's rho) between each domain of the haemophilia joint health score version 2.1 (HJHS) and haemophilia early arthropathy detection with ultrasound (HEAD-US) scores.

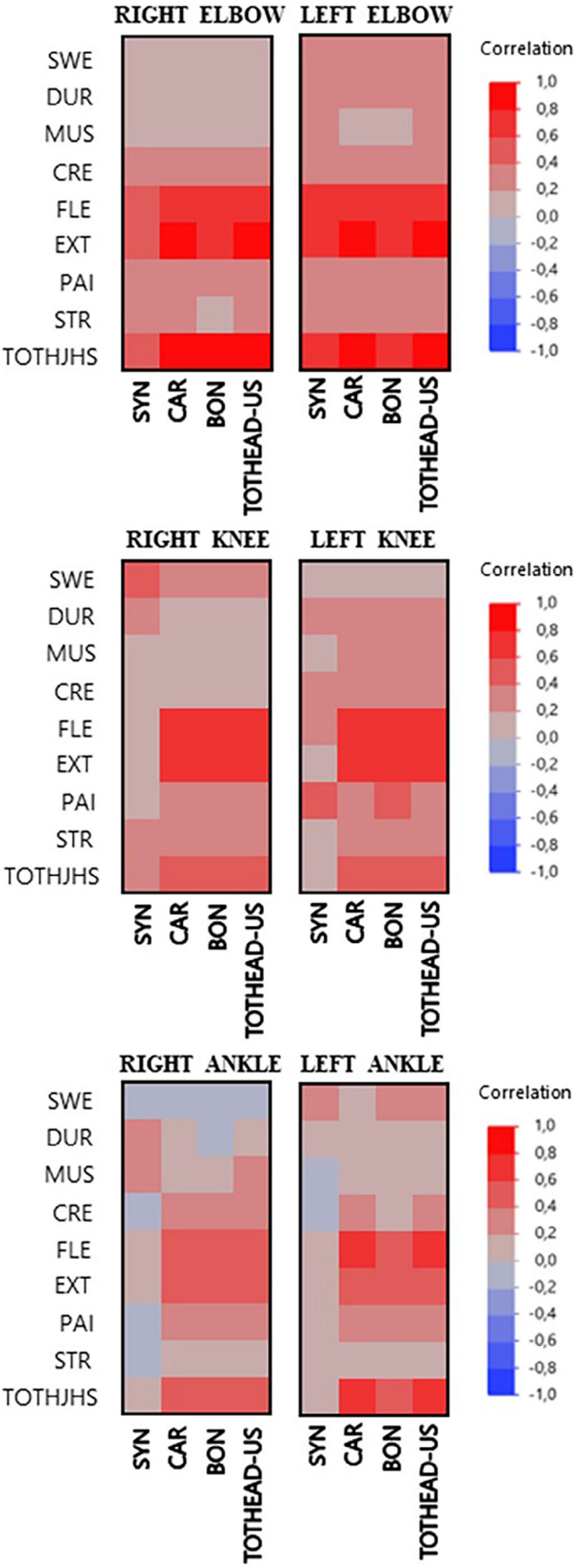
HEAD-US HJHS	Synovitis	Cartilage damage	Bone damage	Total HEAD-US
Swelling	0.17	0.09	0.09	0.10
Duration of swelling	0.23*	0.08	0.02	0.08
Muscle atrophy	0.11	0.16	0.14	0.15
Crepitus on motion	0.30**	0.29**	0.26**	0.29**
Flexion loss	0.55**	0.78**	0.71**	0.77**
Extension loss	0.47**	0.75**	0.69**	0.73**
Joint pain	0.17	0.33**	0.30**	0.31**
Strength	0.22*	0.26**	0.19*	0.24**
Joint total	0.53**	0.75**	0.68**	0.74**
Gait	0.28**	0.48**	0.44**	0.47**
Total HJHS	0.52**	0.74**	0.67**	0.72**

HJHS, haemophilia joint health score version 2.1; HEAD-US, haemophilia early arthropathy detection with ultrasound.
*$p < .05$
**$p < .01$.

flexion and extension loss and HEAD-US cartilage and bone damage was found. The variability of HJHS and HEAD-US domain correlations among elbows, knees and ankles is likely due to a different score in synovitis, cartilage or bone damage, mirroring an early or late stage of arthropathy. In particular, a HEAD-US synovitis domain ≥1 was found more often in elbows (23.4% of total elbows), compared with ankles (6.9%) and knees (6.5%). A HEAD-US cartilage damage domain ≥1 was found more often in ankles (69%) compared with elbows (47%) and knees (18%); a HEAD-US bone damage domain ≥1 was found more often in ankles (67.6%) compared with elbows (42.7%) and knees (15.4%).

4 | DISCUSSION

In the era of major availability of replacement and non-replacement treatments for prophylaxis providing an optimal protection from bleeding, haemophilic arthropathy still has a relevant impact on the HRQoL of haemophilia patients. Considering that even a single episode of bleeding can lead to joint damage, clinicians should consider the possibility that clinical signs and symptoms of recurrent joint bleeding may be blunt, and that subsequent chronic synovitis may be asymptomatic. For these reasons, the use of point-of-care diagnostic tools to



achieve an early diagnosis and prompt an accurate treatment approach are pivotal in preventing the onset and progression of haemophilic arthropathy.[18] Among the tools available to the clinicians, the HJHS and HEAD-US scores are the most widely used to evaluate joint health, even though point-of-care ultrasound evaluation is not always available in haemophilia centres.[14]

In our cohort of adult patients with haemophilia, we found a correlation coefficient of 0.72 between HJHS and HEAD-US, in line with the previous study on European adult patients with haemophilia by De La Corte-Rodriguez et al.,[4] as well as with the studies by Guha et al. and Prasetyo et al. in South-Asian children with haemophilia.[19,20]

Despite this strong correlation, further analysis revealed some discrepancies of interest. Among the different domains of the HEAD-US score, synovitis only demonstrated a minor correlation with the HJHS total score compared with the other domains, namely HEAD-US cartilage and bone damage. This discrepancy is due to the higher sensitivity of musculoskeletal ultrasound to detect synovitis even in the very early stages compared with the physical examination. In line with these findings, up to 40% of patients with an HJHS swelling domain scoring 0 had an HEAD-US synovitis domain ≥1. The magnitude of this finding is far greater than what has been described by Timmer et al. who found only a 18.4% of cases in which the ultrasound evaluation showed the presence of synovitis in the absence of joint swelling at physical examination.[21] The HJHS pain domain did not show any correlation with the synovitis domain of the HEAD-US score, although it showed only a weak correlation with the cartilage and bone domains. This observation further supports the view that synovitis may be subclinical whereas patients often report arthropathic pain due to osteochondral damage.

In addition, the low correlation demonstrated between many HJHS domains such as pain, strength, crepitus and HEAD-US domains could be explained on one hand by the fact that these items might not necessarily be due to haemophilic arthropathy since they are found in other musculoskeletal conditions, on the other hand by the fact that these items explore biomechanical and individual factors that are not necessarily correlated with anatomical modifications of joint explored by ultrasound examination.

Likewise, the strong correlation between the HJHS extension and flexion loss domains and the HEAD-US bone and cartilage damage domains are well explained by the fact that the modifications in the joint range of motion appear only in the late stage of haemophilic

FIGURE 3 The correlograms between the subdomains for each joint of the haemophilia joint health score version 2.1 (HJHS) and haemophilia early arthropathy detection with ultrasound (HEAD-US) scores. Positive correlations are highlighted in red shades, while negative correlations are highlighted in blue shades. Spearman's rho was used in the statistical analysis. BON, HEAD-US bone; CAR, HEAD-US cartilage; CRE, HJHS crepitus; DUR, HJHS duration of swelling; EXT, HJHS extension loss; FLE, HJHS flexion loss; MUS, HJHS muscle atrophy; PAI, HJHS pain; STR, HJHS strength; SWE, HJHS swelling; SYN, HEAD-US synovitis; TOTHEAD-US, HEAD-US total score; TOTHJHS, HJHS total score.

arthropathy, when the repeated intra-articular bleeding has led to irreversible bone and cartilage damage of that joint.

Among the different joints, the elbows showed the highest correlation between the two total scores. The variability of the HJHS and HEAD-US domain correlations among elbows, knees and ankles is likely due to a different score in synovitis, cartilage or bone damage, mirroring an early or late stage of arthropathy. Indeed, ankles are the most frequently affected joints in patients with haemophilia since the infancy, due to their weight-bearing function, thus resulting in earlier and more burdensome damage compared with the knees and elbows. Consequently, the total ultrasound score may underestimate the overall damage, due to the presence of a late-stage fibrotic synovitis that may be less detectable at ultrasound. Moreover, domains such as crepitus on motion are probably less specific indicators of haemophilic arthropathy compared to ultrasound cartilage damage domain. Furthermore, the variations in domains such as strength and pain may arise from the joint specific functions, with ankles being involved in more weight bearing than elbows. On the other side, elbows develop synovitis and osteochondral damage later over the years of growth of the patients and a higher score may be detected in all three ultrasound domains.

Due to the conceptually different domains evaluated by the two scores, it is crucial to consider both tools in the evaluation of haemophilic patients. The HJHS score provides additional information on the physical and biomechanical changes of the affected joint, also guiding the clinician in personalising treatment of patients by specific rehabilitation programs and orthopaedic approaches. The HEAD-US reveals early signs of joint involvement such as synovitis, thus helping clinicians to tackle the onset of haemophilic arthropathy with precise prophylactic therapy management.

Our study has some limitations, in particular only adult patients were included in a single-centre study, thus limiting its generalisability. However, strengths of our study are the large number of patients included in a single-centre study and the fact that the HJHS and HEAD-US were performed by two independent operators blinded to the results of each other, thus reducing the risk of bias in interpreting the two scores.

5 | CONCLUSIONS

Our results confirm a good correlation between the HJHS and HEAD-US scores also confirming that they provide complementary information: in particular, the HEAD-US is more sensitive in detecting synovitis even in early stages of arthropathy, whereas the HJHS includes domains such as muscular atrophy, pain and gait that the HEAD-US does not consider. The combination of physical examination and ultrasound assessment of joints as a point-of-care tool provides complete information regarding anatomical and biomechanical changes in haemophilic arthropathy and informs accurate personalised management.

AUTHOR CONTRIBUTIONS

Roberta Gualtierotti: Design of the study, collection of data, manuscript writing, resources; Andrea Giachi: Statistical analysis, interpretation of data, manuscript writing; Addolorata Truma: Collection of data, first manuscript draft; Sara Arcudi and Alessandro Ciavarella: Collection of data, interpretation of data; Paolo Bucciarelli and Dario Consonni: Statistical analysis and interpretation of data; Elena Boccalandro and Valentina Begnozzi: Collection of data and interpretation of data; Luigi Piero Solimeno and Simona Maria Siboni: collection of data and interpretation of data; Flora Peyvandi: Supervising (study protocol, study design and manuscript), interpretation of data, resources.

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The study was approved by the Ethics Committee of Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico in Milan (No. 199_2021bis) and was carried out in conformity with the 2013 revision of the Declaration of Helsinki and the code of Good Clinical Practice. The study was partially supported by the Italian Ministry of Health—Bando Ricerca Corrente and by the MUSA - Multilayered Urban Sustainability Action - project, funded by the European Union - NextGenerationEU, under the National Recovery and Resilience Plan (NRRP) Mission 4 Component 2 Investment Line 1.5: Strengthening of research structures and creation of R&D "innovation ecosystems", set up of "territorial leaders in R&D". The Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico is member of the European Reference Network (ERN) EuroBloodNet.

CONFLICT OF INTEREST STATEMENT

RG advisory board of Bayer, Roche; speaker bureau/educational meetings Pfizer, SOBI, Takeda, Novo Nordisk; FP advisory board of CSL Behring, Biomarin, Roche, Sanofi, Sobi; speaker bureau/educational meetings Takeda/Spark.

DATA AVAILABILITY STATEMENT

The dataset is available upon reasonable request from the corresponding author.

ETHICS STATEMENT

The present study was approved by the Milan Area 2 Ethics Committee (No. 199_2021bis) and was carried out in conformity with the 2013 revision of the Declaration of Helsinki and the code of Good Clinical Practice; all participants provided written informed consent.

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