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ORIGINAL ARTICLE

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Monitoring recovery of joints after bleeding: Physical examination and ultrasound are complementary

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Abstract

Aim: Traditionally, recovery after a joint bleed in people with bleeding disorders is evaluated by clinical symptoms. Following a bleed, however, asymptomatic joints may still show synovial hypertrophy and effusion on ultrasound. We evaluated the duration of full recovery from a joint bleed. Additionally, we determined how recovery differed when assessed by physical examination and ultrasound.

Methods: In this retrospective cohort study, we investigated joint bleeds in elbows, knees and ankles of people with haemophilia or Von Willebrand disease who attended the Van Creveldkliniek between 2016 and 2021. Physical examination (warmth, swelling, range of motion and gait) and ultrasound (effusion and synovial hypertrophy) were performed within 7 days after the onset of the bleed, 1 week after the first examination and monthly thereafter until patients had recovered fully. Joint bleeds were treated in line with the current international treatment guidelines.

Results: We evaluated 30 joint bleeds in 26 patients. The median recovery time was 1 month (range 0.3-5 months). In 47% of the joint bleeds, the recovery took longer than 1 month. The moment of recovery based on physical examination and ultrasound differed in 27% of bleeds. Both persistent abnormalities at physical examination in joints with normalized ultrasounds and persistent ultrasound findings in clinically recovered joints occurred.

Conclusion: Joint bleed recovery can take long and recovery times differed per bleed. Recovery differed when assessed by physical examination or ultrasound. Therefore, both should be used to closely monitor recovery of joint bleeds and offer personalized care.

KEYWORDS
haemarthrosis, haemophilia, physical examination, ultrasonography

1 | INTRODUCTION

People with haemophilia have a (functional) deficiency in clotting factor VIII or IX resulting in an increased bleeding tendency. Joint bleeds account for up to 80% of all bleeds.[1] People with severe haemophilia still have approximately one joint bleed per year despite prophylactic clotting factor replacement therapy.[2] In people with von Willebrand disease (VWD), the (functional) deficiency in von Willebrand factor

also results in joint bleeds, albeit less frequently.[3] Joint bleeds lead to both acute and long-term pain and disability through subsequent joint damage.[1,4,5] In the acute phase, the intra-articular blood induces chondrocyte apoptosis and triggers synovial inflammation. Concomitant synovial hypertrophy and neo-angiogenesis increases susceptibility to re-bleeding. In the long-term, synovial inflammation damages the cartilage and eventually the underlying bone, resulting in haemophilic arthropathy.[4,5]

The treatment of joint bleeds aims to stop the bleed, to prevent re-bleeding and development of synovitis, and to regain physical functioning.[6,7] Treatment consists of clotting factor replacement therapy and (partial) immobilization of the joint, followed by functional rehabilitation. Inadequate treatment may result in persistent synovial hypertrophy, which is a risk for re-bleeding and chronic synovitis.[6,8]

Traditionally, the treatment effect and start of the physical rehabilitation are based on clinical symptoms, including pain, swelling, warmth and functioning of the joint. Treatment with clotting factor is advised until the bleed has stopped and clinical symptoms decline. However, current international treatment guidelines do not advise on specific follow-up intervals after a joint bleed.[6,7] Joint bleed recovery is often not routinely monitored, since most joint bleeds are home-treated. Furthermore, clinical symptoms do not always adequately represent the current status of the joint.[9,10] Clinical evaluation can be complemented with ultrasound assessment. Ultrasound can accurately assess the synovium, joint effusion, cartilage and joint bleeds.[11–15] In addition, ultrasound can detect synovial hypertrophy in joints without clinical symptoms.[16] Ultrasound is therefore recommended as an additional tool for diagnosing early joint bleeds and monitoring synovitis.[6]

The role of ultrasound in monitoring joint bleed recovery is not well established yet. Two studies followed-up joint bleeds with physical examination (PE) and ultrasound. The first study reported a mean of 13 days for range of motion to recover, while ultrasound findings resolved after a mean of 20 days.[17] The second study reported that painless joints still showed synovial hypertrophy and effusion on ultrasound a week after onset of the bleed.[18] Still, it remains unknown how often subclinical findings on ultrasound occur after a joint bleed and how long it takes for joint bleeds to recover fully.

The aim of this cohort study was twofold. First, we evaluated how long it took for joint bleeds to recover fully. Second, we compared PE and ultrasound findings after a joint bleed to estimate the added value of ultrasound for monitoring joint bleed recovery.

2 | METHODS

2.1 | Study design and study population

In this retrospective cohort study, we followed-up joint bleeds in people with haemophilia or Von Willebrand disease (VWD) who attended the Van Creveldkliniek between April 2016 and April 2021. Patients were included if they had a joint bleed in an ankle, knee or elbow, confirmed by ultrasound. A joint bleed was confirmed by ultrasound when complex intra-articular joint effusion was observed. We only included joint bleeds if patients were examined within 7 days of onset of complaints, and if follow-up was available until full recovery. Patients could be included multiple times with distinct bleeds.

According to the local clinic's protocol, joint bleed recovery was followed-up with both PE and ultrasound examination. Visits were scheduled within 7 days after the onset of the bleed, 1 week after the first examination and monthly thereafter until patients had recovered fully. The study was approved by the institutional Medical Research Ethics Committee (19-665/C).

2.2 | Treatment of joint bleeds

Joint bleeds were treated in line with the World Federation of Haemophilia (WFH) guidelines for management of haemophilia.[6,19] Patients received factor replacement therapy and/or Desmopressin to achieve target peak factor VIII or IX levels of 60% for at least two consecutive days. Subsequently, treatment was adjusted based on clinical signs and ultrasound findings. At the start of treatment, patients were advised to (partially) immobilise the affected joint, then they followed rehabilitation to regain pre-bleed functionality. According to standard care, anti-inflammatory medication was administered in case of persistent synovial hypertrophy.[6]

2.3 | Assessment of joint bleed recovery

Joint bleed recovery was assessed by PE followed by ultrasound examination. Swelling, active range of motion and gait were reported according to the Haemophilia Joint Health Score (HJHS) version 2.1.[20] Warmth of the joint was reported as 'present' or 'absent'. Effusion and synovial hypertrophy were assessed and reported according to the Haemophilia Early Arthropathy Detection with UltraSound (HEAD-US) protocol.[21] All examinations were performed using a single ultrasound scanner (Esaote, MyLab 25 Gold, Genova, Italy) with a 7.5–12 MHz linear transducer. PE and ultrasound were performed by a physiotherapist (MT) or paediatric haematologist (KF), both trained and experienced in using the HJHS and HEAD-US protocol.

2.4 | Outcomes

The primary outcome measure was time to full recovery of the joint bleed. Full recovery was defined as normalisation of all clinical findings (joint swelling, joint warmth, active range of motion, gait) and ultrasound findings (joint effusion and synovial hypertrophy). In joints with pre-existing abnormalities established during previous routine clinical and ultrasound assessment, normalisation to the pre-bleed joint status was considered as full recovery. The secondary outcome was the difference in time to recovery between PE and ultrasound. Full recovery as determined by PE was defined as return to the pre-bleed status of all

clinical findings. Full recovery as determined by ultrasound was defined as return to the pre-bleed status of all ultrasound findings.

2.5 | Data extraction

Extracted patient characteristics from the electronic patient records included bleeding disorder and severity, age, inhibitor status and treatment regimen (prophylaxis or on demand). Joint status prior to the bleed was established by the number of lifetime joint bleeds in the affected joint and the clinical and radiological joint status based on the last reported joint specific HJHS (range 0–20), HEAD-US score (range 0–8) and/or Pettersson score (range 0–13).[22] Joint status was defined as normal if all scores were 0, as minimal-mild haemophilic arthropathy if the scores were <1/3 of the maximum joint score (HJHS <7, HEAD-US <3 and/or Pettersson score <5), or as moderate-severe haemophilic arthropathy if the scores were ≥1/3 of the maximum joint score (HJHS≥7, HEAD-US≥3 and/or Pettersson score was ≥5). When multiple scores were available, the worst score prevailed for grading the severity of haemophilic arthropathy. For each joint bleed, location, cause of bleeding (trauma or unknown), period of bleed-related (altered) clotting factor replacement therapy in days, duration of anti-inflammatory treatment in weeks and physical therapy interventions used (immobilisation, exercise therapy and/or coaching regarding physical activities) were documented. Initial clotting factor replacement therapy was defined as the period in days in which treatment was altered compared to the baseline treatment regimen. Treatment alterations after initial bleed treatment were defined as temporary intensified prophylaxis (intensified dose or frequency of prophylaxis for weeks-months), permanent intensified prophylaxis and switches of regimen or product. During follow-up clinical and ultrasound outcomes were collected at each visit.

2.6 | Analysis

Patient and joint bleed characteristics were reported as medians with ranges, or frequencies with percentages. Time to full recovery of clinical and ultrasound abnormalities was assessed for all bleeding episodes, and were reported as median duration in months with ranges. time to full recovery was summarized in a cumulative incidence curve. The Wilcoxon signed rank test was used to compare recovery as assessed by PE or ultrasound. To investigate differences in recovery as assessed by PE or ultrasound according to recovery time, joint bleeds were divided into three groups based on time to full recovery: recovery <2 weeks, 2 weeks–1 month and >1month. To investigate the influence of disease severity, bleeding cause and joint type, recovery times were compared between people with severe and non-severe haemophilia, between traumatic bleeds and bleeds with unknown cause, and between elbows, knees and ankles, using the Mann-Whitney U test or Kruskal Wallis test. *p*-values of < .05 were considered significant. We created heat maps to search for patterns in the recovery of individual parameters of the PE and ultrasound. All analyses were performed using RStudio (version 1.3.1093).

3 | RESULTS

3.1 | Patient and joint characteristics

Patient and joint characteristics are summarized in Table 1. We identified 30 bleeding episodes in 28 joints of 26 patients who were followed according to our local protocol. Two patients were included twice with two distinct bleeding episodes in one ankle, one patient was included with one bleeding episode in each knee, and one patient was included with an ankle bleed and an elbow bleed. The cohort included 7 adults and the median age at the time of bleeding was 13.8 years (range 2.6–43.1). Half of the patients had mild haemophilia (*n* = 13, 50%), 3 had moderate haemophilia (12%) and 10 had severe haemophilia (38%). All patients with severe haemophilia and one with moderate haemophilia were on prophylaxis.

Overall, joint health status prior to the bleed was good: 14 joints (50%) were healthy without abnormalities prior to the bleed and 3 (11%) had minimal to mild haemophilic arthropathy. For 11 joints (39%), no information regarding the joint status prior to the bleed was available. However, pre-existent joint damage was not expected because these joints recovered without residual abnormalities.

TABLE 1 Patient and joint characteristics.

	Median or *n*	Range or %
A) Patient characteristics (*n* = 26)		
Age (years)	13.8	2.6–43.1
Disease		
Haemophilia A	22	85%
Haemophilia B	3	12%
Von Willebrand Disease	1	4%
Haemophilia severity		
Severe	10	38%
Moderate	2	8%
Mild	13	50%
Prophylactic treatment	11	42%
Positive inhibitor status	1	4%
B) Joint characteristics of affected joints (*n* = 28)		
Baseline joint status[a]		
Normal	14	50%
Minimal–mild HA	3	11%
Moderate–severe HA	0	0%
Not available[b]	11	39%
Lifetime joint bleeds[a]	0	0–4

% might not add up to 100% due to rounding, HA: Haemophilic arthropathy; Normal: HJHS = 0/HEAD-US = 0/Pettersson score = 0; Minimal-mild HA: HJHS < 7/HEAD-US < 3/Pettersson score < 5; Moderate-severe HA: HJHS≥7/HEAD-US≥6/Pettersson score ≥5.

[a]Characteristics on joint level of the joints affected by the joint bleeds (*n* = 28).

[b]All mild haemophilia patients.

3.2 | Joint bleed and treatment characteristics

Characteristics of the joint bleeds and treatment are available in Table 2. Most joint bleeds occurred in ankles ($n = 18$, 60%), followed by knees ($n = 9$, 30%) and elbows ($n = 3$, 10%). Most bleeds had a traumatic origin ($n = 22$, 73%). In 8 joint bleeds, the bleed occurred spontaneously (27%).

Bleeds treated with clotting factor replacement therapy ($n = 29/30$) were treated over a median period of 6 days (range 2–29). The bleed in the patient with VWD was treated with Desmopressin for 2 days. In six bleeds, the initial bleed treatment was followed by temporary intensified prophylaxis (range 1 week to 5 months). After four bleeds, the treatment regimen was permanently altered: 1 patient switched from on demand treatment to prophylaxis, 1 patient switched from recombinant factor VIII to emicizumab prophylaxis, and for 2 patients their prophylaxis was intensified permanently. In nine bleeds, patients received anti-inflammatory treatment with Celecoxib for a median duration of 3.5 weeks (range 1–12). All patients (partly) immobilised the affected joint ($n = 30$, 100%). The immobilisation was followed by coaching regarding physical activities in 28 bleeds (93%) and/or exercise therapy in 18 bleeds (60%).

TABLE 2 Characteristics of joint bleeds and treatment ($n = 30$).

	Median or *n*	Range or %
A) Joint bleeds ($n = 30$)		
Cause		
Trauma	22	73%
Unknown	8	27%
Joint		
Ankle	18	60%
Knee	9	30%
Elbow	3	10%
B) Treatment		
Period of initial clotting factor replacement therapy (days)[a]	6	2–29
Anti-inflammatory treatment	9	30%
Anti-inflammatory treatment duration (weeks)	3.5	1–12
Physical therapy		
(Partial) immobilization	30	100%
Coaching on activities	28	93%
Exercise therapy	18	60%

[a]Period in days in which treatment was altered compared to the baseline treatment regimen, does not correspond to the number of days with administered factor concentrate.

3.3 | Joint bleed recovery

3.3.1 | Duration of joint bleed recovery

The cumulative incidence of fully recovered joint bleeds over time is shown in Figure 1. Joint bleeds recovered in a median of 1 month (range 0.3–5 months). The recovery rate was 10% within 2 weeks, 53% after 1 month and 100% after 5 months. Recovery times were comparable ($p = .48$) when assessed by PE (median 1 month, range 0–5) or ultrasound (median 1 month, range 0.3-5). Duration of full recovery was similar ($p = .37$) in people with severe (median 2 months, range 1–5) and non-severe haemophilia (median 1 month, range 0.3–5). Within the current cohort, we found no difference in the duration of full recovery ($p = .23$) between traumatic bleeds (median 1.5 months, range 0.3–5) and bleeds of unknown cause (median 1 month, range 0.3–3), nor a difference in the duration of full recovery ($p = .20$) between elbows (median 1 month, range 1–1), knees (median 2 months, range 1–5) and ankles (median 1 month, range 0.3–5).

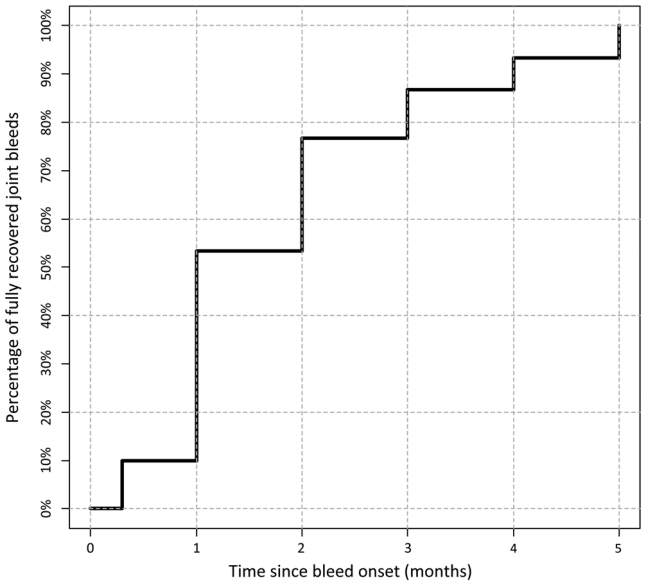

FIGURE 1 The cumulative incidence of full recovery of joint bleeds over time.

3.3.2 | Discrepancies between PE and ultrasound

Recovery of all joint bleeds with distinction between recovery assessed by PE and ultrasound is shown in Figure 2. In the majority of joint bleeds ($n = 22$, 73%), the last clinical symptoms and the last abnormalities on ultrasound recovered simultaneously. In eight joint bleeds however, the last clinical symptoms and abnormalities on ultrasound recovered at different timepoints. An overview of the joint bleeds with discrepancies in recovery according to PE and ultrasound is available in Table 3. In the three bleeds with recovery within 2 weeks clinical symptoms and abnormalities on ultrasound recovered simultaneously. In 1/13 bleeds with recovery between 2 weeks and 1 month synovial hypertrophy on ultrasound persisted while clinical symptoms had already recovered. In 7/14 bleeds with recovery > 1 month, recovery differed when assessed by PE and ultrasound. Abnormalities on ultrasound recovered before clinical symptoms in five bleeds. In these bleeds, active range of motion and gait abnormalities persisted while abnormalities on ultrasound had recovered. Clinical symptoms recovered before abnormalities on ultrasound in two bleeds. In both bleeds, synovial hypertrophy persisted

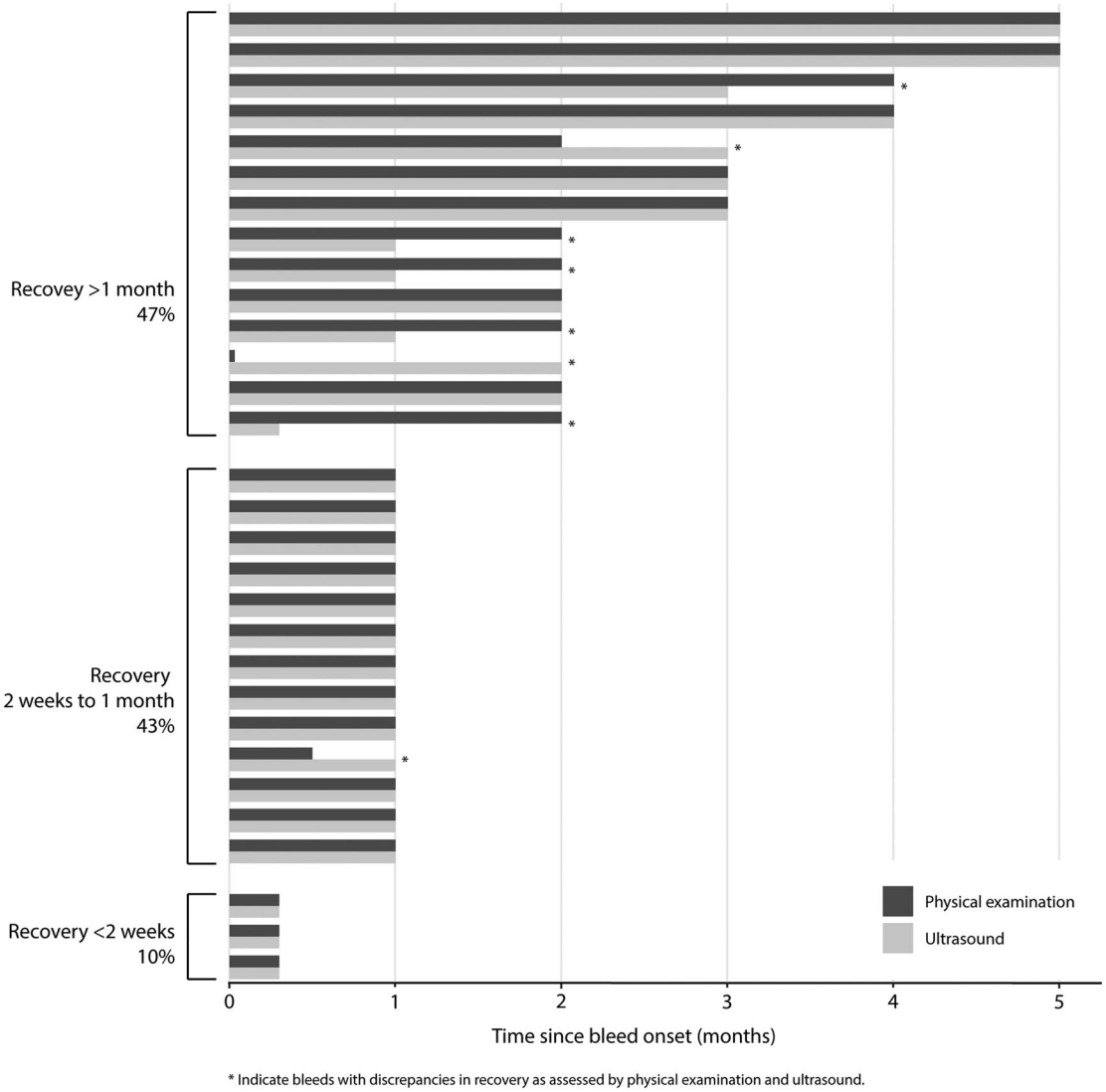

FIGURE 2 Joint bleed recovery per bleed with distinction between recovery assessed by physical examination and ultrasound.

while clinical symptoms had recovered. Figure 3 shows an example of an ankle bleed with discrepancies in recovery when assessed by PE or ultrasound.

3.3.3 | Recovery of individual parameters

Median recovery times of individual parameters of the PE and ultrasound examination are available in Table S1. We did not find a consistent pattern in the order in which the individual parameters of the PE and ultrasound examination recovered. A heat map illustrating the recovery of the individual clinical and ultrasound parameters is available in Figure S1.

4 | DISCUSSION

In this retrospective study, we evaluated the duration of recovery from a joint bleed in people with haemophilia or Von Willebrand disease. Furthermore, we determined the discrepancies between PE and ultrasound when assessing joint bleed recovery. In 47% of the 30 joint bleeds, recovery took longer than one month. In 10% of the bleeds synovial hypertrophy was detected by ultrasound examination in clinically recovered joints, and in 17% of the bleeds clinical abnormalities were detected when ultrasound abnormalities were resolved.

Compared to two previous studies[17,18] we observed longer recovery times after joint bleeds and less discrepancies between PE and ultrasound. These differences may be explained by the use of different definitions for recovery. We defined clinical recovery as absence of warmth, swelling, active range of motion limitations and gait abnormalities, while Aznar et al.[18] defined clinical recovery as absence of pain. Due to our more detailed definition, clinical recovery usually took more than 1 week, which explains why we observed less subclinical synovial hypertrophy and/or effusion. However, the prevalence of synovial hypertrophy and/or effusion 1 week after bleed onset in our study (87%, 95% Confidence interval (CI) 69–96) was comparable to or slightly higher than the prevalence of subclinical synovitis and/or effusion in the study by Aznar et al. (60%, CI 26–88). We observed a

TABLE 3 Joint bleed episodes with discrepancies in clinical recovery and normalization of ultrasound findings.

Patient characteristics		Joint bleed characteristics							
		Joint		Bleeding episode			Recovery		
Age (years)	Haemophilia severity	Joint	Baseline	Cause	Initial clotting factor replacement therapy (days)[1]	Anti-inflammatory treatment (weeks)	Physical examination	Ultrasound	Parameters with delayed recovery
10	Severe	Ankle	HJHS 0 HEAD-US 0	Trauma	3[2]	–	No abnormalities	2 months	Effusion, Synovial hypertrophy
11	Severe	Ankle	HJHS 0	Trauma	2[4]	4	2 months	3 months	Synovial hypertrophy
2	Moderate	Elbow	n.a.	Unknown	5[3]	–	2 weeks[5]	1 month	Synovial hypertrophy
13	Mild	Ankle	n.a.	Unknown	6	3	2 months	1 month	Swelling, warmth, gait
16	Mild	Knee	n.a.	Trauma	10	1	2 months	1 week	AROM, gait
16	Mild	Knee	n.a.	Trauma	22	–	2 months[5]	1 month	AROM, gait[6]
6	Severe	Ankle	HJHS 0	Trauma	11	–	4 months	3 months	Gait
9	Severe	Ankle	HJHS 1	Trauma	6	–	2 months	1 month	Gait

1 = Total duration of the initial treatment, does not correspond with daily treatment; 2 = Patient switched to emicizumab prophylaxis after initial bleed treatment; 3 = Patient started prophylactic treatment after initial bleed treatment; 4 = Prophylaxis was intensified after one month based on findings during follow-up; 5 = Complete gait follow-up unavailable; 6 = Recovery of gait unavailable because of joint bleed in the other knee during follow-up.
Abbreviations: AROM, Active range of motion; HEAD-US, Haemophilia Early Arthropathy Detection with Ultrasound score; HJHS, Haemophilia Joint Health Score; n.a., not available.

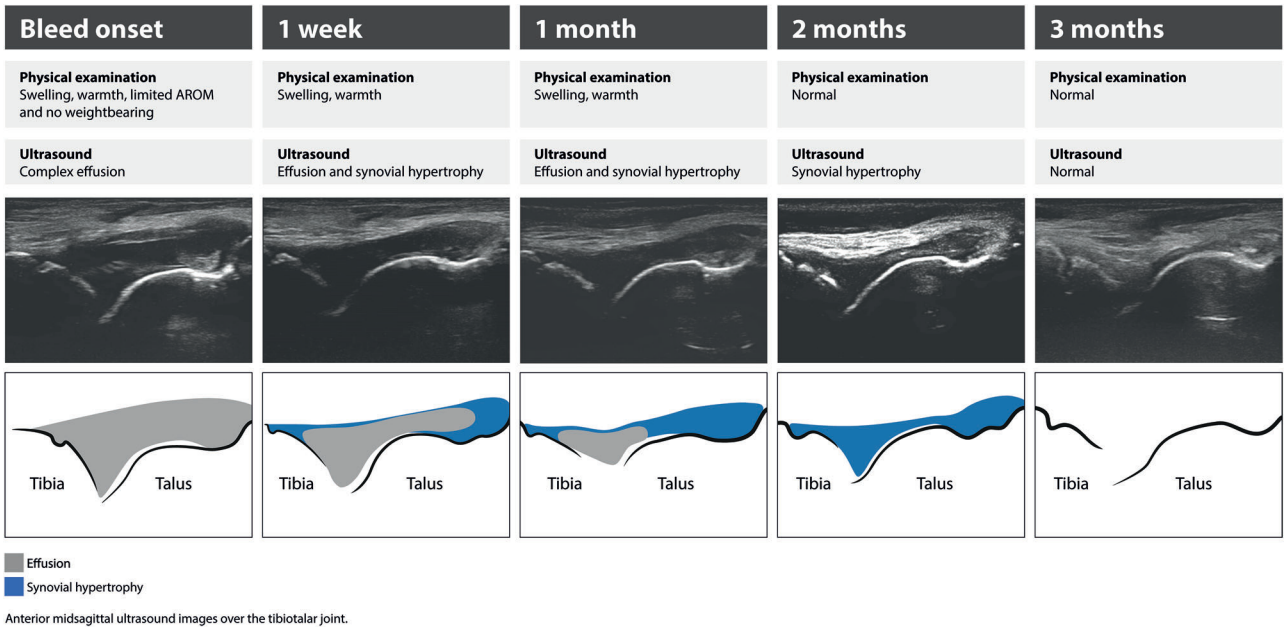

FIGURE 3 Recovery of an ankle bleed in a 11-year-old patient with severe haemophilia A.

longer median recovery time for ultrasound findings (median 1 month) compared to the study by De la Corte-Rodriguez et al.(mean 20 days),[17] which may be due to different definitions as well. We used absence of effusion and synovial hypertrophy to mark ultrasound recovery, while they used absence of bloody effusion. Furthermore, differences in recovery times for range of motion and ultrasound findings between our study and the study by De la Corte-Rodriguez may be due to their weekly follow-up schedule compared to our monthly follow-up.

4.1 | Strengths and limitations

A strength of our study is the standardised follow-up using validated assessment tools, despite the retrospective study design. The follow-up visits were planned at set timepoints, which makes comparison between different bleeds possible and kept missing values to a minimum. The assessments were performed by one haematologist and one physiotherapist. While interobserver variability was minimized by the use of the validated and standardised HJHS score and HEAD-US protocol.[20,23,24]

A limitation of our study might be selection bias. Our study population included predominantly young patients and patients with mild haemophilia. In addition, most patients had a good baseline joint health status. Our selective population can be explained by our retrospective study design and the organisation of haemophilia care in the Netherlands: young people with haemophilia and people with mild haemophilia are usually treated and monitored at the haemophilia care centre when they have a joint bleed. People with severe haemophilia receive home treatment for their bleeds and do not visit the clinic for each bleed.[25] We did not find significant differences in recovery time between people with severe and non-severe haemophilia. Furthermore, clinical symptoms and pathophysiology of joint bleeds can be considered similar between age groups. Hence, we expect that the results can still be generalized to populations with predominantly adults and people with severe haemophilia. However, clinical symptoms and ultrasound findings may differ between arthropathic joints and healthy joints.[9] Therefore, our results might not be completely generalizable to the recovery process in arthropathic joints.

Excluding patients with incomplete follow-ups might have induced selection bias as well. Lost to follow-up might not have occurred randomly yet be related to fast(er) recovery: patients that seemed recovered might have cancelled their follow-up. Therefore, including only patients that were monitored until full recovery might have led to an overestimation of the average recovery time.

Another limitation may be the assumption that the 39% of joints without baseline status were healthy. In the case of unobserved baseline abnormalities, this may have introduced information bias into the recovery times. However, bias from unobserved baseline abnormalities seems negligible as all joints without baseline status recovered without residual abnormalities.

4.2 | Clinical relevance

The current treatment guidelines do not propose an explicit follow-up period after a joint bleed.[6,7] In our study, joint bleeds had long and variable recoveries (range 0.3-5 months). Both PE and ultrasound abnormalities could still be present days to months after onset of the bleed. We therefore recommend to incorporate monitoring the recovery of joint bleeds into regular care. We propose routine follow-up with PE and ultrasound 1 month after bleed onset, since that seems the most effective moment to identify prolonged recovery based on our data. It would give more insight into the course of the recovery process, which could lead to timely detection and treatment of ongoing synovitis or functional abnormalities. Treatment could be individualised based on the findings during follow-up: clotting factor replacement therapy may be intensified until full recovery, additional anti-inflammatory medication may limit synovial inflammation, (partial) immobilisation may be continued, and/or coaching on activities and exercise therapy may be initiated to restore joint function. However, the effectiveness of these treatment alterations still needs to be established.

Discrepancies between PE and ultrasound in the longer recovery processes show the added value of using both because they focus on different aspects of the joint. PE focuses on impairment and functionality,[23] while ultrasound focuses on detection of synovitis.[21] Both examinations provide valuable information to guide treatment decisions and must be seen as complementary.

4.3 | Future research

In our relatively small cohort, we did not find significant differences in recovery time between different bleeding causes, different joints and different haemophilia severities. Future research should focus on larger cohort studies, to enable determining risk factors for prolonged recovery.

In addition, we were unable to investigate the effect of treatment compliance on the recovery time. Treatment compliance is therefore a potential risk factor that remains to be investigated. These risk factors could indicate patients who would benefit from treatment adjustments and/or intensive monitoring. Second, the effectiveness of the proposed routine follow-up visit one month after bleed onset should be established in a prospective study. Third, the optimal treatment adjustments to change the course of the recovery process remain to be established.

5 | CONCLUSIONS

Joint bleed recovery can take long and recovery times differed from bleed to bleed. In 47% of the joint bleeds, the recovery took longer than one month. PE and ultrasound have a different focus and provide complementary information. Therefore, both should be used to monitor joint bleed recovery. Monitoring joint bleeds with PE and ultrasound, for example 1 month after bleed onset, will provide more insight in recovery of the individual joint and enable personalised care.

AUTHOR CONTRIBUTIONS

F.H.P. van Leeuwen—Data analysis, Interpretation of data, Writing—Original Draft. K. Fischer—Data acquisition, Interpretation of data, Writing—Review & Editing, Supervision. W. Foppen—Interpretation of data, Writing—Review & Editing, Supervision. L.F.D. van Vulpen—Data acquisition, Writing—Review & Editing. M.A. Timmer—Conceptualization, Data acquisition, Interpretation of data, Writing—Review & Editing, Supervision, Funding acquisition. The

manuscript has been read and approved for publication by all authors. All authors agree to be accountable for all aspects of the work.

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CONFLICT OF INTEREST STATEMENT

F.L. declares no conflicts of interest. K.F. has received speaker's fees from Bayer, Baxter/Shire, Sobi/Biogen, CSL Behring and Novo Nordisk; has performed consultancy for Bayer, Biogen, CSL Behring, Freeline, Novo Nordisk, Roche and Sobi; and has received research support from Bayer, Baxter/Shire, Novo Nordisk, Pfizer and Biogen; all fees were paid to the institution. W.F. received research grants from Novo Nordisk and Pfizer, which were paid to the institution. L.V. received research grants from CSL Behring and Grifols, and has performed consultancy for Sobi, CSL Behring and Tremeau; all fees were paid to the institution. M.T. received research grants from Novo Nordisk and SOBI and performed consultancy activities for SOBI, all paid to the institution.

DATA AVAILABILITY STATEMENT

Data is available from the senior author (Dr. M.A. Timmer, M.A.Timmer@umcutrecht.nl) upon request.

ETHICS APPROVAL STATEMENT

The study was approved by the Medical Research Ethics Committee of the University Medical Centre Utrecht, The Netherlands (19-665/C).

PATIENT CONSENT STATEMENT

Informed consent was waived by the Medical Research Ethics Committee of the University Medical Centre Utrecht as health care data were used anonymized. Patients that objected to the use of their (anonymized) health care data were excluded.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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