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REVIEW ARTICLE

The good, the bad and the ugly of pain in haemophilia: Recent evidence on the epidemiology, molecular mechanisms and knowledge gaps preventing optimal treatment

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Abstract

Introduction: Haemophilia is an inherited, X-linked blood clotting disorder caused by the deficiency of coagulation factors VIII (FVIII, haemophilia A) or IX (FIX, haemophilia B). Spontaneous bleeds are common in severe forms of haemophilia and can also occur in moderate and mild haemophilia. Severe or repeated bleeding at a joint can evolve into chronic haemophilic arthropathy, with functional damage of the joint, disability, and intense chronic articular pain. Nonetheless, acute and chronic pain may emerge due to secondary conditions related to bleedings.

Aim: This narrative review aims to critically discuss the most recent evidence about pain in haemophilia to give healthcare professionals a clear picture of current knowledge hence favouring the optimisation of clinical management of pain.

Methods: Extensive literature search with the terms 'hemophilia' AND 'pain', focusing on the time window 2021–2023.

Results: Acute and chronic pain is a critical aspect of haemophilia at all ages. It should be considered a multifaceted phenomenon, with a positive role as an early emergency signal of a clinical event (haemarthrosis), and numerous detrimental aspects linked to its burden that heavily affects the health-related quality of life, with psychological and social consequences.

Conclusion: Despite its prevalence and frequency in people with haemophilia, pain is often underestimated by healthcare professionals, leading to insufficient and inadequate treatment, also due to uncertainty linked to the presence of the coagulation disorder or arthritic flares.

KEYWORDS
acute pain, chronic haemophilic arthropathy, chronic pain, haemophilic pain management, pain, quality of life

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1 | INTRODUCTION

According to the Merriam–Webster dictionary, haemophilia is 'a hereditary, sex-linked blood defect occurring almost exclusively in males, that is marked by a delayed clotting of the blood with prolonged or excessive internal or external bleeding after injury or surgery and, in severe cases, by spontaneous bleeding into joints and muscles and that is caused by a deficiency of clotting factors[1]'. However, it is worth noting that this lay definition, although comprehensive and overcoming previous biases such as full gender exclusivity, does not address one crucial and unavoidable aspect of haemophilia syndromes: pain. This may reflect perceptions that might be held by some non-specialists in the field.

The improper blood clotting occurring in haemophilia A and B is caused by the lack or deficiency of the coagulation factor VIII (FVIII) or the coagulation factor IX (FIX), which results in compromised activation of factor X and, consequently, in the underproduction of thrombin in the clotting cascade.[2] Female subjects are mostly heterozygous carriers of one mutated gene on a single X chromosome and may present with a wide range of symptoms of haemophilia.[2]

The severity of haemophilia is defined as severe if the levels of FVIII or FIX are < 1%, moderate if between 1% and 5% and mild if > 5% and < 40% of normal.[3,4] A recent meta-analysis highlighted a prevalence of haemophilia of 17.1 cases (per 100,000 males) for all severities of haemophilia A, 6.0 cases for severe haemophilia A, 3.8 cases for all severities of haemophilia B and 1.1 cases for severe haemophilia B.[4]

Standard of care (SOC) to control severe haemophilia includes prophylactic factor replacement therapy (FRT), aimed at compensating for the deficiency of coagulation factors FVIII or FIX, non-replacement therapies and other treatment perspectives, including gene therapy strategies.[5–7] It is worth noting that last decades have been seeing a progressive improvement in the global care of haemophilia, with the optimisation of the on-demand treatment on one side, and of prophylaxis, by both its fine tailoring and the use of novel pharmacological approaches (e.g. emicizumab), on the other side. According to the impressive results obtained with the abovementioned strategies, the therapeutic target has been changed from the conversion from severe to moderate phenotype, to 0 bleeds. The latter, however, seems to be still a bit too ambitious aim for current clinical practice.[8,9]

Spontaneous bleeds are common in severe forms of haemophilia, while in people with moderate haemophilia, bleeding occurs after minor injuries and spontaneous bleeding is rare.[2]

People with mild haemophilia experience sporadic bleeding because of a trauma, injury or surgery and often remain undiagnosed until a prolonged bleeding occurs.[10] However, a wide variability of bleeding phenotype has been reported, with some moderate patients and a few mild patients reporting frequent and severe bleeding with bleeding-related complications.[11,12] Bleeding episodes in joints and muscles can cause acute pain combined with swelling, warmth and/or decreased range of motion.[13] Severe or repeated joint bleeding can eventually progress to chronic haemophilic arthropathy, triggered by the severe degeneration of cartilage.[2,14,15] In the majority of people with haemophilia (PWH), the joint damage affects bone health, resulting in intense chronic articular pain.[13,16] Despite treatments that could reduce the incidence and severity of bleedings, subclinical episodes and haemophilic arthropathy can occur, and pain may persist.[17,18]

Pain represents a critical aspect of haemophilia at all ages (Table 1).[19,20] According to growing evidence, acute and chronic pain may intertwine with haemophilia and its mechanisms more than previously considered.[13] Pain in haemophilia should be seen as a multifaceted phenomenon, with a positive function as a pathophysiological signal and many detrimental aspects linked to its burden. In point of fact, pain is i) often an early symptom of more or less unexpected, potentially severe or life-threatening medical events (bleeding) consequent to the primal coagulation disorder (the Good); ii) a highly prevalent subjective disturbance, both acute and chronic, related to articular involvement (haemarthrosis and microbleedings, synovitis), likely intensified by alterations in physiological nociceptive pathways and mechanisms, which are still not fully understood (the Bad); iii) a still under-recognised, and hence undertreated, feature of haemophilia, closely related to anxiety and depression, with a relevant burden for patients and caregivers (the Ugly) (Figure 1).

To discuss the most recent evidence emerging about pain in haemophilia, we extensively searched PubMed with the terms 'haemophilia' OR 'hemophilia' AND 'pain', focusing on the time window 2021—2023, identifying 267 papers. This narrative review aims to give healthcare professionals (HCPs) a clear picture of current knowledge, hence favouring the optimisation of clinical management of pain. It is worth noting that the main focus of this narrative review is the evaluation of pain in PWH and not its treatment (read as, available pharmacological and non-pharmacological therapies), which have been recently and widely reviewed elsewhere.[18,21]

2 | THE GOOD—PAIN AS A LIFE (HEALTH)-SAVING SIGNAL

About 70%—80% of bleeding episodes in haemophilia occur into large synovial joints, with ankles, knees and elbows as the most affected sites.[13,19] However, they can also affect intracranial sites, muscles (particularly large muscle groups), oropharyngeal sites, the arms, and the genitourinary and gastrointestinal tracts.[22] Timely recognition of bleeding symptoms in PWH is crucial for prompt medical intervention and to prevent or limit complications, such as drops in haemoglobin level. Intense pain caused by bleeding episodes such as those reported in the recently published cases described below and classified in Table 2, according to their clinical manifestations, outcomes and the treatment required, can serve as a warning signal of a possible acute event, thus playing a positive role, counteracting at least in part its detrimental effects on health-related quality of life (HRQoL).

TABLE 1 Pain prevalence in people with haemophilia.

Study population	Study type	Pain assessment tools	Pain prevalence	Reference
Male adult PWH with haemophilia A or B ($n = 185$)	National cross-sectional survey conducted in Belgium	BPI, EQ-5D-3L, questions about haemophilia	Pain was reported by 86% of patients with severe haemophilia, 71% of patients with moderate haemophilia and 32% of patients with mild haemophilia	Chantrain et al. 2023[20]
Male adult PWH with haemophilia A or B	Systematic review of 13 studies	Self-made surveys, VAS EQ-5D-3L, WFH-score, haemophilia adapted CSQ	Pain was reported by 75% of patients. Chronic pain was reported by 40% of patients, with a greater frequency for moderate pain (61.0%) compared to extreme pain (11.6%)	Ransmann et al. 2022[19]
Male adult PWH with haemophilia A or B ($n = 50$)	National, cross-sectional, observational study conducted in Turkey	MHPQ	Pain was reported by 62% of patients during the last year, with 93.5% of them reporting pain lasting > 3 months	Kurcaloglu and Atay 2023[14]
Male PWH with haemophilia A or B of all ages ($n = 144$)	National, cross-sectional, large observational study conducted in Portugal	MHPQ	Pain was reported by 78.8% of adults, 76.2% of children/teenagers, and 68.4% of children, with 62.5%, 61.9%, and 42.1% of them, respectively, reporting pain lasting > 3 months	Pinto et al. 2020[30]
Male adult PWH with haemophilia A or B of all ages ($n = 599$)	National cross-sectional, non-interventional survey study conducted in the UK	EQ-5D; EQ-VAS	Frequent pain was reported by 59% of patients	Khair et al. 2023[61]

Abbreviations: BPI, Brief Pain Inventory short-form; CSQ, Coping Strategies Questionnaire; EQ-5D-3L, EuroQol-5-Dimensions-3-Levels; MHPQ, Multidimensional Haemophilia Pain Questionnaire; PWH, people with haemophilia; UK, United Kingdom; VAS, Visual Analogue Scale; WFH, World Federation of Haemophilia.

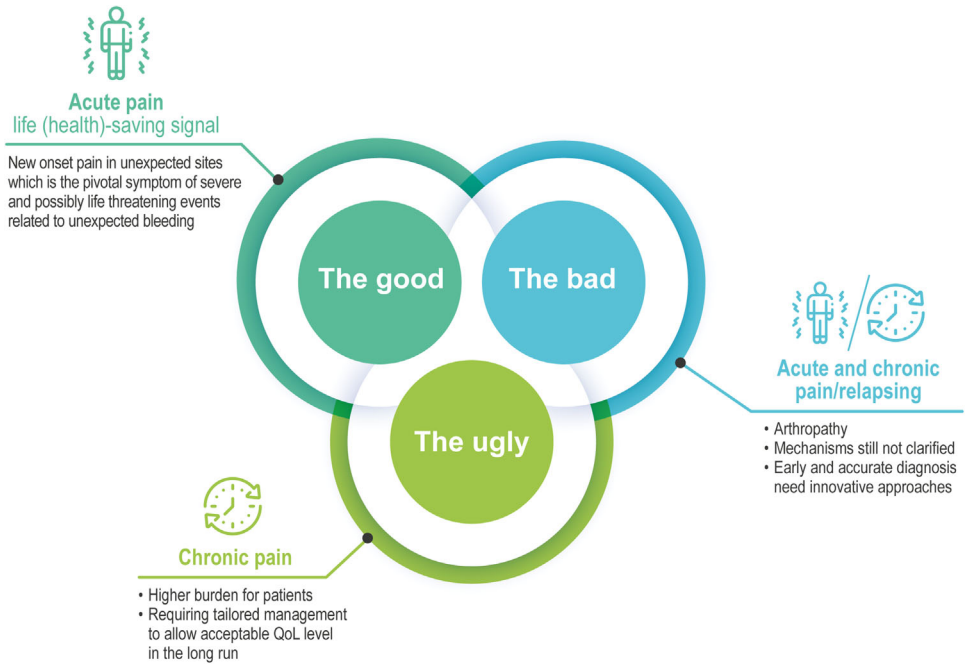

FIGURE 1 Schematic representation of the multifaceted aspects defining pain in haemophilia, highlighting the significance of acute pain and the consequences of chronic recurrent pain.

TABLE 2 Summary of the clinical cases published in the last 2 years emerging with pain symptoms.

Patient history	Clinical manifestations	Treatment needed	Outcome	Reference
24-year-old male with severe haemophilia A, missing three doses of Factor VIII replacement	• Left medial elbow pain, moderate swelling and tenderness to palpation over the medial epicondyle • Pain and paraesthesia in the ring and small fingers • Decreased intrinsic strength • No evidence of compartment syndrome	Surgical decompression (lidocaine with epinephrine to minimise bleeding)	Complete recover of activity at 6-week follow-up Resolution of paraesthesia, Recovered grip strength	Debkowska et al.[23]
27-year-old male with haemophilia B, history of hematomas both spontaneous and post-traumatic, not compliant with follow-ups	• Extremely severe pain in the right scapular region with a sudden start in the previous night • Localised swelling in the same region • Lateral chest wall haematoma • No traumas	Two units of packed red blood cells, along with two units of fresh frozen plasma and recombinant factor IX 100 units/kg	The patient completed his transfusions but left prior to evaluation for interventions (evacuation of hematoma or angiographic embolisation)	Vedire et al.[22]
4-year-old male with severe haemophilia A, high-titre inhibitors	• Intense headache and neck pain • Spinal epidural hematoma	Bypassing agent therapy with recombinant-activated factor VII Emicizumab	No neurological sequelae at 18 months follow-up	Villarreal-Martinez et al.[24]
8-year-old male with a history of haemophilia	• 1-year history of knee pain • Limited range of motion • Ganglion cyst arising from the posterior cruciate ligament by MRI	Arthroscopic decompression of the cyst	Asymptomatic at one-year-follow-up	Vutescu et al.[27]
7-year-old male with no history of haemophilia	First presentation • right hip pain after wrestling • inability to bear weight • small right hip joint effusion/synovitis at MRI Second presentation 7 days after • continued limp and pain • moderate, stable effusion Third presentations 4 days aftersevere pain • large hip hemarthrosis • prolonged PTT (normal during his previous hospital admission)	First presentation Operative aspiration and arthrogram; application of compression Second presentation outpatient paediatric and orthopaedic follow-up Third presentation Morphine for pain control, valium for muscle spasms and tranexamic acid for postoperative bleeding; diagnosis of mild haemophilia B; fresh frozen plasma; 2000 units of recombinant factor IX	Discharged home 4 days after joint aspiration Discharged Pain improved the day after and discharged	Minkowitz et al.[28]
44-year-old male with haemophilia A, history of polyarticular hemarthrosis, hepatitis C and HIV	• Back and hip pain over several months, with pain radiated into the thighs • Chronic headaches and neck pain • Difficult deambulation • Thoracic kyphosis • Enlarged elbow bony prominences	Oxycodone Discontinuation of tenofovir and beginning phosphate vitamin D, and calcium	Rapid improvement after tenofovir discontinuation: walk without assistance, no severe headaches	Woo et al.[26]
74-year-old male with a history of polymyalgia rheumatica, hypertension, Barrett oesophagus, urinary tract infections and haematuria	• Left thigh pain • Ecchymosis concerning haematomas • Low haemoglobin • Haematuria and bleeding gums • Hematomas of the left groin, scrotum, bilateral thighs and back	Blood transfusion Recombinant factor VIIa and rituximab therapy	Improved coagulation factor VIII level within a week	De Paz et al.[29]

2.1 | Recent case reports

Localised acute pain and other associated symptoms can occur when a PWH is not compliant with prophylaxis[23] or when the prophylactic treatment is ineffective and the therapy needs to be adjusted.

A recent report of a diagnosis of lateral chest wall haematoma in a patient with congenital haemophilia B presenting with severe back pain in the absence of any trauma suggests that a high degree of attention should be maintained in PWH, as bleeding can also occur in atypical locations.[22] The importance of a timely and careful evaluation of pain in PWH is also supported by the successfully treated case of spinal

epidural haematoma in a paediatric patient with severe haemophilia A, who presented a sudden onset of intense headache followed by severe neck pain without any previous history of trauma.[24]

Back and joint pain in PWH is not necessarily due to arthropathy, and an accurate differential diagnosis is required, particularly in patients with concomitant diseases and treatments.[25] HCPs should consider a wide range of aetiologies for severe pain in PWH, with an approach that includes an extensive pain and medication history.[26] A case of knee pain in a paediatric patient with haemophilia A caused by the presence of a rare ganglion cyst further confirmed that joint pain is not necessarily due to arthropathy in PWH and that accurate investigations should be performed.[27]

Finally, a sudden intense pain not only serves as a warning signal of a possible acute bleeding event but can also lead to a life-changing diagnosis of haemophilia in the case of no previous medical history, as reported by Minkowitz et al. for a paediatric patient that presented at the emergency department with right hip pain after wrestling.[28] The unexpected bleeding and the large hip haemarthrosis that followed the hip aspiration performed for joint effusion and synovitis led to coagulation testing, revealing a low FIX level (< 17%), consistent with mild haemophilia B. The mild form of this coagulation disorder can often be overlooked for years before the diagnosis, and pain, together with unusual bleeding, can help identify and treat the disease, thus increasing patients' life expectancy. Sudden intense pain can also be a signal of acquired haemophilia (AHA) in older subjects, as reported by de Paz et al. for a 74-year-old male patient with acute thigh pain and haematomas for whom a careful medical evaluation allowed prompt and effective treatment.[29]

3 | THE BAD—PAIN AS AN EPIPHENOMENON OF STILL NOT COMPLETELY UNDERSTOOD ARTICULAR DAMAGE AND, POSSIBLY, PAIN PATHWAYS ALTERATIONS

3.1 | Haemarthrosis and hypertrophic synovium

Haemarthrosis, which represents the most frequent type of bleeding episodes in PWH, is a very painful event accompanied by stiffness, swelling and restricted mobility.[30] Repetitive intra-articular bleedings can lead to synovium hypertrophy due to blood-derived iron deposition and then to hypertrophic synovium (HS), with increased vascular perfusion and the activation of inflammatory pathways.[15,31] Once repetitive bleedings have led to HS, a vicious cycle of bleeding-synovitis-bleeding could emerge due to the profusion and fragility of vessels enriching the synovium. HS should be submitted to enhanced haematological treatment and, if not sufficient to prevent haemarthroses, HS should be corrected with arthroscopic, chemical, radioactive or open synovectomy. If the HS is not corrected, cartilage injury will occur, gradually progressing to fibrotic scar tissue. Haemophilic arthropathy will then become evident, triggering functional damage of the joint, chronic pain and disability.[30] In a recent study, it has been shown that people with severe haemophilia develop gait alterations as a result of changes in mobility of the ankle joint, caused by bleeding and pain, and the compensation mechanisms they induced.[32] The neural control of gait can be abnormal in subjects with haemophilic arthropathy when associated with long years of impairment, more pain and more joint damage.[33] Haemarthrosis should be promptly diagnosed and carefully managed to prevent HS, and a periodic joint screening should be done through imaging techniques to identify subclinical events. It is worth mentioning that, in the last years, ultrasound has undoubtedly gained a primary role, corroborated by increasing evidence.[34] In particular, early haematological prophylaxis and the timely identification of acute intraarticular bleeding in paediatric patients are essential to avoid HS, as the immature musculoskeletal system is more susceptible to the complications of haemophilia.[35] Patients with haemophilia develop acute episodes of joint pain, which may be due to arthritic flares or breakthrough haemarthrosis. Of interest, a symptom-based prediction tool for the diagnosis of haemarthrosis has been recently proposed by Gopal S et al.[36] It consists of 20 questions that are able to differentiate the pain of haemarthrosis from arthritic pain. The sense of fullness within the joint was associated with the highest risk for bleeding; in contrast, symptoms related to arthritic flare included a lack of sponginess with movement. This is of particular relevance as, although clinically similar, haemarthrosis and osteoarthritis show differences in their pathogenesis, and a distinction during diagnosis is relevant to the choice of an adequate therapeutic strategy.[31]

3.2 | Pain sensitivity

Quite surprisingly, patients with severe haemophilia show a lower pain tolerance than healthy control subjects, as suggested by lower pressure pain thresholds in a study analysing gait changes for compensatory mechanisms in the presence of ankle joint alterations due to bleeding.[32] Lower pressure pain threshold and muscle strength have also been detected in patients with severe haemophilia and arthropathy of the knee.[37] Furthermore, the amount of pain perceived by PWH is not always related to the severity of the disease, as shown by studies revealing a lack of association between pain intensity and the structure of the joints in adult PWH.[38,39] A recent cross-sectional study further investigated the factors implicated in the pathophysiology of joint pain in haemophilia, other than structural characteristics, confirming an increased mechanical and thermal pain sensitivity and the presence of psychological factors such as anxiety and depression.[40] Overall, the data suggest alterations of physiological nociceptive pathways that may contribute to joint pain in PWH.

A better comprehension of the mechanisms that regulate the relationship between perceived pain and the severity of joint disease is pivotal to selecting the most appropriate therapeutic interventions, which have been recently reviewed[21] with a specific emphasis on chronic HS.[41]

3.3 | A possible role for oxidative stress

In this setting, some recent studies highlight the role of oxidative stress as a leading contributor to pain in haemophilia, with the mediation

of blood-derived iron accumulated in joints during bleedings.[17] Iron plays multifactorial roles in progression to haemophilic arthropathy: a) the haemoglobin breakdown product haemosiderin is iron-rich and induces the expression of several pro-inflammatory cytokines, ultimately resulting in articular cartilage destruction; b) iron is able to dysregulate the expression of genes involved in synoviocyte proliferation, leading to increased synovial hypertrophy and vascularisation, and to recruitment of inflammatory cells to the area; c) excessive iron levels can damage the cells by increasing the production of reactive oxygen species, with consequent cartilage degeneration.[17] The nervous system is particularly vulnerable to oxidative stress due to its relatively weak antioxidant defence.[42] Consistent literature findings indicate that oxidative stress is intricately linked to and plays a role in the persistence of chronic pain. This contribution can involve both nociceptive and neuropathic pathways, operating through a complex multifactorial mechanism that has been thoroughly described.[17] Among the mechanisms proposed, the combination of oxidative stress, inflammation and cell damage occurring in joints during bleeding may activate peptidergic nociceptors on the nerve fibres with the antidromic release of neuropeptides and the consequent effects, and the prodromic transmission of pain signals.[17] Demonstrating these mechanisms in PWH would allow them to be validated as therapeutic targets.

4 | THE UGLY—PAIN AS AN INAPPROPRIATELY TREATED CLINICAL FEATURE ASSOCIATED WITH ANALGESIC CONSUMPTION, ANXIETY AND DEPRESSION, AND BURDENSOME CONSEQUENCES ON QUALITY OF LIFE

Pain pervasiveness heavily affects the QoL of PWH, with psychological, social and economic consequences. Commonly, chronic pain is much more complex than acute pain for patients, and that is true also in haemophilia, which is associated with psychosocial and neurobiological variables that might perpetuate it, with implications for therapeutic strategies.[30] In the case of chronic pain, issues such as relationship difficulties, mood problems, and substance and alcohol abuse can arise from inappropriate management, and a multidisciplinary approach can be necessary to address them.[13] In addition, adverse events, including mild arthralgia and reactions at the injection site, can be associated with infusions, indicating that not only the disease but also its treatment may cause pain in PWH.[43]

4.1 | Pain burden in PWH

Surveys among PWH and their caregivers can provide a representative measure of the magnitude of pain prevalence and associated anxiety, depression and socioeconomic issues, which can also affect treatment adherence. Indeed, higher depression scores were observed in a cohort of 100 adult PWH compared to patients without haemophilia.[44] Another study summarised that about one-third of patients with severe haemophilia A suffer from anxiety, 64% from depression and 60% from other minor psychological complications.[45] Poor HRQoL has been highlighted in PWH with ankle haemarthropathy in the United Kingdom.[46] A survey including more than 3000 PWH in an 11-year Nordic registry study highlighted that both paediatric and adult PWH used more medications for pain, depression and anxiety compared with a control-matched population, regardless of age, sex or FRT consumption.[47] In particular, data showed a higher opioid use versus controls across all age groups, and this also emerged from a study in the United States,[48] raising concerns related to the risk of addiction among PWH exposed to pain. Of note, chronic pain-related analgesic consumption in PWH may complicate the postoperative analgesia in patients undergoing surgeries with severe postoperative pain due to the higher pain versus non-haemophilic patients.[49]

Some encouraging data arose from a self-reported survey comparing Danish PWH from 16 to 84 years of age versus the Danish general population on selected indicators of HRQoL, which revealed that PWH now resembles the general population in areas such as marriage and education compared with earlier surveys.[50] However, even for young PWH, the disease still imposes poorer levels of employment compared with the general population and a significant burden from arthropathy and pain in extremities and joints.

The severity of haemophilia is a significant predictor of direct medical and societal costs in Europe, and there is also a significant humanistic and economic burden for patients with moderate disease, suggesting greater indirect costs and productivity losses.[51] Another aspect of haemophilia that can increase its psychological burden is the feeling of guilt experienced by mothers of children with haemophilia due to pain during infusions and passing on the affected X chromosome.[52]

4.2 | Medical attention to pain in PWH

Pain is often underestimated by HCPs, leading to insufficient and inadequate therapy, also due to uncertainty linked to the presence of the coagulation disorder.[53] A recent Italian survey confirmed that HCPs could be reluctant to refer PWH to pain specialists, who were involved in only 26.4% of cases.[54] Consistently, PWH reported not being satisfied with their pain control.[55] The majority of PWH participating in a multicentre study indicated no regular use of pain medication despite a high percentage of them reporting chronic pain.[46]

Overall, the data clearly indicate that an increased awareness of pain, anxiety and depression in all severities of haemophilia is needed, together with improved bleed protection and patient care.

5 | DISCUSSION AND CONCLUSION

Pain experience in haemophilia patients is a complex issue influenced by various factors.

Apart from the inherent pain associated with the pathology itself, other contributors, such as those related to therapeutic interventions

for disease management, including pain related to drug administration and orthopaedic surgery, should be taken into account. Although challenging to determine, pain remains a frequent and cardinal symptom in haemophilia, regardless of patients' status or disease severity. Recent meta-analyses highlight the wide prevalence of pain in PWH. Chronic pain was shown to have a pooled prevalence of 46% in an analysis including 11 studies, and similarly, another report including 13 studies found an average prevalence of 40%.[19,56] Chronic pain manifests with considerable heterogeneity among individuals with varying disease severity levels.[56] Hence, the disparities in pain experiences among patient subgroups cannot be solely attributed to haemophilia severity. This points to the presence of additional variables influencing the diversity in pain perception, necessitating focused attention from the research community. Indeed, individual variability and psychosocial factors are potential contributors to pain experience in patients, and the diverse methodologies employed in pain measurement amplify this variability, emphasising the need for careful consideration in research approaches.[56,57]

The emergence of acute pain in a location not previously reported in the patient's medical history should be carefully considered during clinical evaluations, as it could potentially serve as a crucial factor for an emergent additional diagnosis in PWH. In this view, pain can be seen in its traditional physiological protective role, being a burdensome but 'good' signal that prevents the consequences of an untreated disease.

Up to date, in countries with access to therapeutic and high specialty care, it is possible to identify two sub-populations according to pain profile: the previous patients' generation, including patients who have been exposed to new treatment approaches (e.g. prophylaxis) when the disease had already provoked irreversible damages, and the newer generation, who have been protected by infectious risk and exposed to a slower development of articular alterations. Accordingly, patients belonging to the two generations may be extremely different regarding their pain experience and not only for age reasons. About the latter, it is worth noting that pain perception and its reporting can be influenced by the patient's age, with children experiencing a lower pain threshold compared to adults.[58] A study examining pain perception in relation to age suggests a potential heightened sensitivity in children compared to adolescents and adults. This variation could stem from differences in the development of neural transmission pathways.[59] However, it is crucial to note that this observation requires additional, comprehensive studies to establish a robust scientific foundation.[60]

Pain management in PWH is still unsatisfactory.[61] Since the underlying mechanisms have not been fully clarified, the therapeutic approaches are limited, not supported by population-specific evidence, and likely to be biased by plausible but theoretical hypotheses about possible interactions between the disease and analgesic drug mechanisms. Therefore, there are currently no specific recommendations for the treatment of pain in PWH, which should be managed on a case-by-case basis. Chronic pain management mainly focuses on multidisciplinary interventions, including maintaining coagulation control, pharmacological pain treatment, and physical and psychological care.[53] Specific recommendations are available for young patients, given the peculiarity of their physiology (haemostatic and neural systems in development, higher metabolic activity, lower threshold of pain perception).[53] A Delphi consensus supported using a personalised treatment approach for pain management in paediatric and adult PWH based on multimodal pharmacological and non-pharmacological therapies delivered by a multidisciplinary team. The panel of clinicians recommended continuous monitoring and assessment of pain and its effects on QoL, with an adequate adjustment of treatment.[18] A similar multimodal approach, including not only different types of analgesia but also physical and rehabilitation medicine and psychological strategies, has been suggested with particular reference to managing musculoskeletal haemophilic pain in children and young adults.[16] Consistently, a meta-analysis of 15 trials highlighted that physical therapy is effective in reducing pain in PWH, enhancing joint health and increasing joint range of motion.[62]

Assessing the mechanisms underlying pain onset is central to identifying therapeutic interventions. The potential role of inflammation and oxidative stress, common responses to bleeding, is worth investigating[17,63]; neuroinflammatory mechanisms may also have a role, although still to be clarified.[64] Exploring inflammation involvement and interaction with pain receptors in the context of haemophilia could provide valuable insights into the intricate pathways contributing to pain perception in this condition.[65]

Prophylaxis in PWH is a pillar to prevent bleeding and, hence, pain. Standard FRT has been shown to be inadequate for complete protection against bleeding and arthropathy,[66] and an optimisation of prophylaxis, also including newer therapeutic approaches, would likely lead to better pain control,[67] which is of particular significance for elderly patients who have additional sources of pain.[68]

Haemophilia-related pain is often underestimated in clinical practice, and its quantitative measurement is not always performed.[53] This lack of knowledge and appropriate tools for pain assessment contributes to an insufficient utilisation of pain therapy options[18,54] and points out the need for more awareness for both HCPs and patients. In particular, HCPs should receive specific education on the investigation, prevention and treatment of treat pain in this population of patients.[18,54]

Overall data highlight the need to maintain a critical mindset when thinking about pain in haemophilia and to further investigate the pathogenesis of pain in haemophilia, identify potential specific therapeutic targets and develop patient-centred initiatives to improve the wellness of PWH.

AUTHOR CONTRIBUTIONS

All authors conceived the work, analysed the literature and drafted and edited the manuscript. All authors approved the final version for submission.

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CONFLICT OF INTEREST STATEMENT

Silvia Benemei is Pfizer employee.

Consalvo Mattia has acted as a paid consultant to SOBI, Pfizer, Roche and Viatris.

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Data sharing not applicable to this article, as no datasets were generated or analysed during the current study.

ETHICS STATEMENT

Not applicable.

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REFERENCES

1. Merriam-Webster.com Dictionary. Hemophilia. [cited October 1, 2023]. https://bit.ly/3F4sMJP
2. Berntorp E, Fischer K, Hart DP, et al. Haemophilia. *Nat Rev Dis Primers*. 2021;7(1):45.
3. Blanchette VS, Key NS, Ljung LR, et al. Definitions in hemophilia: communication from the SSC of the ISTH. *J Thromb Haemost*. 2014;12(11):1935-1939.
4. Iorio A, Stonebraker JS, Chambost H, et al. Establishing the prevalence and prevalence at birth of hemophilia in males: a meta-analytic approach using national registries. *Ann Intern Med*. 2019;171(8):540-546.
5. Pipe SW, Leebeek FWG, Recht M, et al. Gene therapy with etranacogene dezaparvovec for hemophilia B. *N Engl J Med*. 2023;388(8):706-718.
6. Chou SC, Hsu YC, Lin SW. Gene therapy for hemophilia, a clinical viewpoint. *J Formos Med Assoc*. 2023;122(11):1101-1110.
7. Yamaguti-Hayakawa GG, Ozelo MC. Gene therapy for hemophilia: looking beyond factor expression. *Exp Biol Med (Maywood)*. 2022;247(24):2223-2232.
8. Adramerina A, Teli A, Symeonidis S, Nianiu A, Economou M. Is zero bleeds a realistic goal for hemophilia patients in the real world setting? [abstract]. *Res Pract Thromb Haemost*. 2021;5(Suppl 2). Accessed on March 20, 2024. https://abstracts.isth.org/abstract/is-zero-bleeds-a-realistic-goal-for-hemophilia-patients-in-the-real-world-setting/
9. Giordano P, Pollio B, Sottilotta G, et al. Pattern of use and clinical outcomes with rIX-FP in pediatric/adolescent patients with haemophilia B in Italy: results from IDEAL real-world study. *Eur J Haematol*. 2024. doi:10.1111/ejh.14168
10. Daffunchio C, Landro ME, Galatro G, et al. How mild is mild haemophilia? *Haemophilia*. 2023;29(2):530-537.
11. Castaman G, Peyvandi F, De Cristofaro R, Pollio B, Di Minno DMN. Mild and moderate hemophilia A: neglected conditions, still with unmet needs. *J Clin Med*. 2023;12(4):1368.
12. Di Minno MN, Ambrosino P, Franchini M, Coppola A, Di Minno G. Arthropathy in patients with moderate hemophilia a: a systematic review of the literature. *Semin Thromb Hemost*. 2013;39(7):723-731.
13. Auerswald G, Dolan G, Duffy A, et al. Pain and pain management in haemophilia. *Blood Coagul Fibrinolysis*. 2016;27(8):845-854.
14. Kurcaloglu M, Atay MH. Pain: a neglected symptom in hemophilia. *Ann Hematol*. 2023;102(4):947-953.
15. Calcaterra I, Iannuzzo G, Dell'Aquila F, Di Minno MND. Pathophysiological role of synovitis in hemophilic arthropathy development: a two-hit hypothesis. *Front Physiol*. 2020;11:541.
16. Rodriguez-Merchan EC, De la Corte-Rodriguez H. Pain management in people with hemophilia in childhood and young adulthood. *Expert Rev Hematol*. 2021;14(6):525-535.
17. Fouda R, Argueta DA, Gupta K. Pain in hemophilia: unexplored role of oxidative stress. *Antioxidants (Basel)*. 2022;11(6):1113.
18. Santoro C, Di Minno MND, Corcione A, et al. Improving assessment and management of pain in hemophilia: an Italian Delphi consensus statement. *Blood Rev*. 2022;51:100885.
19. Ransmann P, Kruger S, Hilberg T, Hagedorn T, Roussel N. Prevalence of pain in adult patients with moderate to severe haemophilia: a systematic review. *Scand J Pain*. 2022;22(3):436-444.
20. Chantrain VA, Lambert C, De Smet P, et al. Pain interferes with daily activities, emotions and sleep in adults with severe, moderate and mild haemophilia: a national cross-sectional survey. *Haemophilia*. 2023;29(2):521-529.
21. Gualtierotti R, Tafuri F, Arcudi S, et al. Current and emerging approaches for pain management in hemophilic arthropathy. *Pain Ther*. 2022;11(1):1-15.
22. Vedire A, Upadrasta G, Imburgio S, Johal AS, Hossain MA. Hemophilia B: a pain in the back. *Cureus*. 2023;15(3):e36577.
23. Debkowska MP, Cotterell IH, Riley AJ. Case report: acute cubital tunnel syndrome in a hemophiliac patient. *SAGE Open Med Case Rep*. 2019;7:2050313×18824814.
24. Villarreal-Martinez L, Sepulveda-Orozco MDC, Garcia-Viera DA, et al. Spinal epidural hematoma in a child with hemophilia A with high titer inhibitors and follow-up with prophylactic emicizumab: case report and literature review. *Blood Coagul Fibrinolysis*. 2021;32(6):418-422.
25. Ceponis A, Wong-Sefidan I, Glass CS, von Drygalski A. Rapid musculoskeletal ultrasound for painful episodes in adult haemophilia patients. *Haemophilia*. 2013;19(5):790-798.
26. Woo E, Kumbhare D, Winston P. Incapacitating pain from tenofovir induced hypophosphatemic osteomalacia in a hemophilia patient—a case report. *Can J Pain*. 2020;4(1):287-291.
27. Vutescu ES, Strada N. Symptomatic posterior cruciate ligament ganglion cyst in a child with hemophilia: a case report. *JBJS Case Connect*. 2020;10(4). e20 00351.
28. Minkowitz B, Lillie E, Ristic JR. Unmasking hemophilia B after hip aspiration: a case report. *JBJS Case Connect*. 2019;9(2):e0275.
29. De Paz N, Belaunzaran MA, Cabrera R, Macias T, Lacaille S, Guida C. An unusual case of zero percent coagulopathic factor in a patient with polymyalgia rheumatica. *Cureus*. 2023;15(1):e33414.
30. Pinto PR, Paredes AC, Almeida A. Pain prevalence, characteristics, and impact among people with hemophilia: findings from the first Portuguese survey and implications for pain management. *Pain Med*. 2020;21(3):458-471.
31. Kalebota N, Salai G, Peric P, et al. ADAMTS-4 as a possible distinguishing indicator between osteoarthritis and haemophilic arthropathy. *Haemophilia*. 2022;28(4):656-662.
32. Hmida J, Hilberg T, Koob S, et al. Peak pressure during gait in patients with severe haemophilia: a controlled cross-sectional study. *Gait Posture*. 2022;93:26-31.
33. Cruz-Montecinos C, Maas H, Cerda M, Perez-Alenda S. Altered neural control of gait and its association with pain and joint impairment in adults with haemophilic arthropathy: clinical and methodological implications. *Haemophilia*. 2022;28(3):497-504.
34. van Leeuwen FHP, Timmer MA, de Jong PA, Fischer K, Foppen W. Screening for subclinical synovial proliferation in haemophilia:

a systematic review and meta-analysis comparing physical examination and ultrasound. *Haemophilia*. 2023;29(2):445-455.
35. Rodriguez-Merchan EC. Synovitis in hemophilia: preventing, detecting, and treating joint bleeds. *Expert Rev Hematol*. 2023;16(7):525-534.
36. Gopal S, Barnes RFW, Volland LM, Page D, von Drygalski A. Patient-derived assessment tool using musculoskeletal ultrasound for validation of haemarthrosis. *Haemophilia*. 2022;28(5):842-848.
37. Villalon-Gonzalez M, Fernandez de Luco-Santamaria I, Cuesta-Barriuso R, Lopez-Pina JA, Perez-Llanes R. Hemophilic arthropathy of the knee and its association with reduced muscle strength and activation and the pressure pain threshold: a case-control study. *J Clin Med*. 2023;12(9).
38. Roussel NA, Chantrain VA, Foubert A, et al. Gaining more insight into ankle pain in haemophilia: a study exploring pain, structural and functional evaluation of the ankle joint. *Haemophilia*. 2022;28(3):480-490.
39. Chantrain VA, Guillaume S, Foubert A, et al. Discordance between joint pain and imagery severity in the ankle joint and contributors of lower limb activity limitations in adults with haemophilia: a cross-sectional study. *Haemophilia*. 2023;29(2):648-657.
40. Foubert A, Chantrain VA, Meeus M, et al. Psychophysical assessment of pain in adults with moderate and severe haemophilia: a cross-sectional study. *Haemophilia*. 2023;29(5):1243-1258.
41. Di Minno MND, Napolitano M, Giuffrida AC, et al. Diagnosis and treatment of chronic synovitis in patients with haemophilia: consensus statements from the Italian Association of Haemophilia Centres. *Br J Haematol*. 2022;196(4):871-883.
42. Tauffenberger A, Magistretti PJ. Reactive oxygen species: beyond their reactive behavior. *Neurochem Res*. 2021;46(1):77-87.
43. Wei L, Tian Y, Chen X, et al. Data mining and analysis for emicizumab adverse event signals based on the Food and Drug Administration Adverse Event Reporting System database. *Int J Clin Pharm*. 2023;45(3):622-629.
44. Jimenez-Cebrian AM, Palomo-Lopez P, Becerro-de-Bengoa Vallejo R, et al. Impact of depression on patients with hemophilia: a retrospective case-control research. *Front Psychiatry*. 2022;13:892321.
45. Asad F, Jahangarad S, Dorgalaleh A. Psychological complications among patients with congenital bleeding disorders. *Blood Coagul Fibrinolysis*. 2023;34(3):138-143.
46. Wilkins RA, Siddle HJ, Chapman GJ, Horn E, Walwyn R, Redmond AC. Decline in health-related quality of life and foot and ankle patient reported outcomes measures in patients with haemophilia and ankle haemarthropathy. *J Foot Ankle Res*. 2023;16(1):12.
47. Steen Carlsson K, Winding B, Astermark J, et al. High use of pain, depression, and anxiety drugs in hemophilia: more than 3000 people with hemophilia in an 11-year Nordic registry study. *Res Pract Thromb Haemost*. 2023;7(2):100061.
48. Peltier SJ, Mazepa MA, Freese RL, Nelson SF, Kearney SL, Reding MT. Opioid exposure in haemophilia patients is common and underreported. *Haemophilia*. 2020;26(2):251-256.
49. Canbolat N, Dinc T, Koltka K, et al. Comparison of analgesic consumption of hemophilic and non-hemophilic patients in knee arthroplasty. *Ulus Travma Acil Cerrahi Derg*. 2022;28(11):1616-1621.
50. Schnohr C, Ekholm O, Poulsen LH, et al. Health and quality of life of patients with haemophilia: a national study of 124 Danish men. *Haemophilia*. 2023;29(2):538-544.
51. Rodriguez-Santana I, DasMahapatra P, Burke T, et al. Differential humanistic and economic burden of mild, moderate and severe haemophilia in European adults: a regression analysis of the CHESS II study. *Orphanet J Rare Dis*. 2022;17(1):148.
52. Sheridan N, Thompson B, Lichten L, Coleman K. The emotional experience of mothers of children with haemophilia: maternal guilt, effective coping strategies and resilience within the haemophilia community. *Haemophilia*. 2023;29(2):513-520.
53. Stromer W, Pabinger I, Ay C, et al. Pain management in hemophilia: expert recommendations. *Wien Klin Wochenschr*. 2021;133(19-20):1042-1056.
54. Di Minno MND, Santoro C, Corcione A, et al. Pain assessment and management in Italian Haemophilia Centres. *Blood Transfus*. 2021;19(4):335-342.
55. Kalnins W, Schelle G, Jost K, Eberl W, Tiede A. Pain therapy in haemophilia in Germany. Patient survey (BESTH study). *Hamostaseologie*. 2015;35(2):167-173.
56. Paredes AC, Teixeira P, Almeida A, Pinto PR. Prevalence and interference of chronic pain among people with hemophilia: a systematic review and meta-analysis. *J Pain*. 2021;22(10):1134-1145.
57. Palareti L, Melotti G, Cassis F, Nevitt SJ, Iorio A. Psychological interventions for people with hemophilia. *Cochrane Database Syst Rev*. 2020;3(3):CD010215.
58. Etzweiler D, Albisetti M, Meichtry A, Huber EO. The effect of age on the pressure pain threshold of asymptomatic ankles and knees in young individuals with haemophilia. *Haemophilia*. 2021;27(4):683-689.
59. Blankenburg M, Boekens H, Hechler T, et al. Reference values for quantitative sensory testing in children and adolescents: developmental and gender differences of somatosensory perception. *Pain*. 2010;149(1):76-88.
60. El Tumi H, Johnson MI, Dantas PBF, Maynard MJ, Tashani OA. Age-related changes in pain sensitivity in healthy humans: a systematic review with meta-analysis. *Eur J Pain*. 2017;21(6):955-964.
61. Khair K, McLaughlin P, Roussel N, Boyton M, Holland M. Prevalence and perceptions of pain in people with haemophilia: a UK study. *Haemophilia*. 2023;29(6):1509-1518.
62. Chen CM, Lin CH, Kung KY. Effects of physical therapy on joint pain, joint range of motion, joint health, strength, and mobility in patients with hemophilia: a systematic review and meta-analysis. *Am J Phys Med Rehabil*. 2023;102(7):577-587.
63. Knowles LM, Wolter C, Menger MD, et al. Activation of the acute-phase response in hemophilia. *Thromb Haemost*. 2023;123(9):867-879.
64. Wehmeier UF, Orth V, Hoppe V, Valentino LA, Hilberg T. Neuroinflammatory markers in patients with haemophilia and healthy controls: where are the differences? *Haemophilia*. 2023;29(6):1539-1546.
65. Seifert O, Baerwald C. Interaction of pain and chronic inflammation. *Z Rheumatol*. 2021;80(3):205-213.
66. Manco-Johnson MJ, Warren BB. Long-term prophylaxis: what are our options and how to define success? *Hematology Am Soc Hematol Educ Program*. 2022;2022(1):579-585.
67. Malec L, Matino D. Targeting higher factor VIII levels for prophylaxis in haemophilia A: a narrative review. *Haemophilia*. 2023;29(6):1419-1429.
68. Chantrain VA, Foubert A, Meeus M, et al. Joint status, pain and quality of life in elderly people with haemophilia: a case-control study. *Haemophilia*. 2023;29(6):1621-1632.

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