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Original Research Article

Pain Prevalence, Characteristics, and Impact Among People with Hemophilia: Findings from the First Portuguese Survey and Implications for Pain Management

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Abstract

Background. Hemophilia is a rare disorder characterized by spontaneous bleeding, with pain being a critical aspect. However, a systematic assessment of hemophilia-related pain in Portugal has never been conducted. **Objective.** To understand the pain experience among Portuguese people with hemophilia (PWH) by describing its prevalence, characteristics, and impact and uncovering intervention needs in the realm of hemophilia-related pain care. **Methods.** A cross-sectional observational survey, with age-adapted versions of questions concerning pain, emotional distress, and quality of life, was answered by 104 adults, 21 children/teenagers (10–17 years), and 19 children (1–9 years). **Results.** Pain was reported by 82 (78.8%) adults, 16 (76.2%) children/teenagers, and 13 (68.4%) children, with 65 (62.5%), 13 (61.9%), and eight (42.1%) of them reporting pain lasting more than three months, respectively. The mean number of pain locations (SD) was 5.23 (3.95) for adults, 4.13 (3.48) for children/teenagers, and 3.15 (1.99) for children age 1–9 years, with lower limbs pain causing the greatest negative impact. More frequent pain-triggering factors were physical effort/movements (61, 74.4%) for adults and hemarthrosis for younger groups (children/teenagers: 14, 87.5%; children: 9, 69.2%). Bleeds yielded the highest mean pain intensity (adults: M [SD] = 5.67 [2.09]; children/teenagers: M [SD] = 5.69 [2.15]). Adults with pain revealed more anxiety (odds ratio [OR] = 1.698, $P = 0.003$) and depression (OR = 1.961, $P = 0.025$) and lower quality of life (OR = 0.928, $P = 0.001$). **Conclusions.** The current findings highlight the high prevalence, duration, and frequency of pain at all ages, its potentially simultaneous acute and chronic nature, its likelihood to affect multiple locations concurrently, and its detrimental impact. Important insights concerning intervention needs are presented, ultimately contributing to the improvement of hemophilia-related pain management and patient care.

Key Words: Hemophilia; Hemarthrosis; Chronic arthropathy; Emotional Distress; Health-Related Quality of Life

Introduction

Hemophilia is an X-chromosomal rare disorder affecting approximately 1 in 10 000 births [1]. It is characterized by deficiency or absence of coagulation factors in the blood, either factor VIII (hemophilia A) or IX (hemophilia B), and is associated with a pattern of spontaneous bleeding, mainly into the joints (hemarthrosis), which is the hallmark of the disease [1–3]. The bleeding rate is influenced by the severity of the hemophilia, determined according to coagulation factor level concentration (mild: 5–40% of normal factor level; moderate: 1–5% of normal; severe: <1% of normal) [4]. The mainstay of treatment for hemophilia is factor replacement therapy, either on demand or prophylactically. Prophylaxis is currently recommended for people with severe hemophilia from an early age, but it was not accessible to patients

who are now in their adult years, who therefore grew up without some form of preventive treatment. In addition, the high cost of this treatment remains a significant obstacle to generalized access, thereby preventing some adult patients from fully benefiting from prophylaxis [2], whereas children have broader access to it. A recent survey showed that access to prophylaxis by Portuguese adults (26–50%) is still below other countries, such as Belgium, Ireland, and the Netherlands, wherein 76–100% of adults have access to prophylaxis [5]. For children and teenagers in Portugal, access to prophylaxis is higher when compared with adults, covering 76–100% of patients. This matches the practices of developed countries like Belgium, Finland, Ireland, and Norway [5].

The potential development of inhibitors to factor replacement, which neutralize the effectiveness of clotting factor concentrates, also needs to be considered as an important complication of treatment [1]. Hemarthrosis is a very painful event, accompanied by swelling, stiffness, and restricted mobility [3,6,7]. Repeated joint bleeds cause the accumulation of intra-articular blood, triggering a series of interdependent biological processes that lead to synovial inflammation. This progressively contributes to irreversible joint degeneration and development of chronic hemophilic arthropathy, characterized by joint deformity, functional limitations, disability, and chronic pain, ultimately requiring surgical intervention [8–10].

Although few studies have addressed the pain characteristics, impact, and management of patients with hemophilia, it is possible to learn from surveys of other countries about its pervasiveness. In one study, 81% of adults with severe hemophilia reported pain, occurring daily in two-thirds of them [11]. Likewise, a survey performed across several countries revealed that 89% of adult people with hemophilia (PWH) experienced pain interfering with daily activities [12]. Specifically concerning children and adolescents, there is limited survey information on this subject [13,14].

Recent figures from the United States [15] found a chronic pain prevalence of 66% among PWH, with 20% complaining of acute pain and 32% experiencing concurrent acute and chronic pain. Interestingly, and beyond the acknowledged relationship between chronic pain and worst psychological functioning and low quality of life [12], the study by Witkop et al. [15] further highlighted that those complaining of both acute and chronic pain were more likely to be depressed and exhibit lower quality of life. Concerning pain in general and psychosocial factors, chronic pain is known to be strongly associated with worst physical and mental health–related quality of life among PWH [16]. Along these lines, it has been suggested that psychological health fully mediates the effect of pain on subsequent functional limitations or disability [17].

Pain is therefore a common and debilitating symptom, whether acute (hemarthrosis) or chronic (hemophilic arthropathy), or even occurring concomitantly within the same individual. This latter feature constitutes an uncommon symptomatic presentation, rendering an additional burden to patients and posing a particular challenge to health care professionals.

Surprisingly, no hemophilia-related pain data have been comprehensively assessed and reported in Portugal, wherein there is an estimated prevalence of approximately 700 cases of hemophilia [18].

Recently, strong calls to action have been made on the need to improve pain assessment and management in the hemophilia field [19,20], as a comprehensive and thorough assessment of pain is the basis for optimal management and treatment. In addition, given the growing emphasis on patient-centered care, the understanding of patients' perspectives is mandatory to identify the most cost-effective hemophilia treatment approaches [21].

Hence, a better understanding of how Portuguese PWH describe pain and cope with it, as well as knowledge of their own perception about pain impact, treatments, and difficulties, is critical to improving the clinical management of hemophilia among Portuguese patients, informing tailored pain management strategies and policy decision-making.

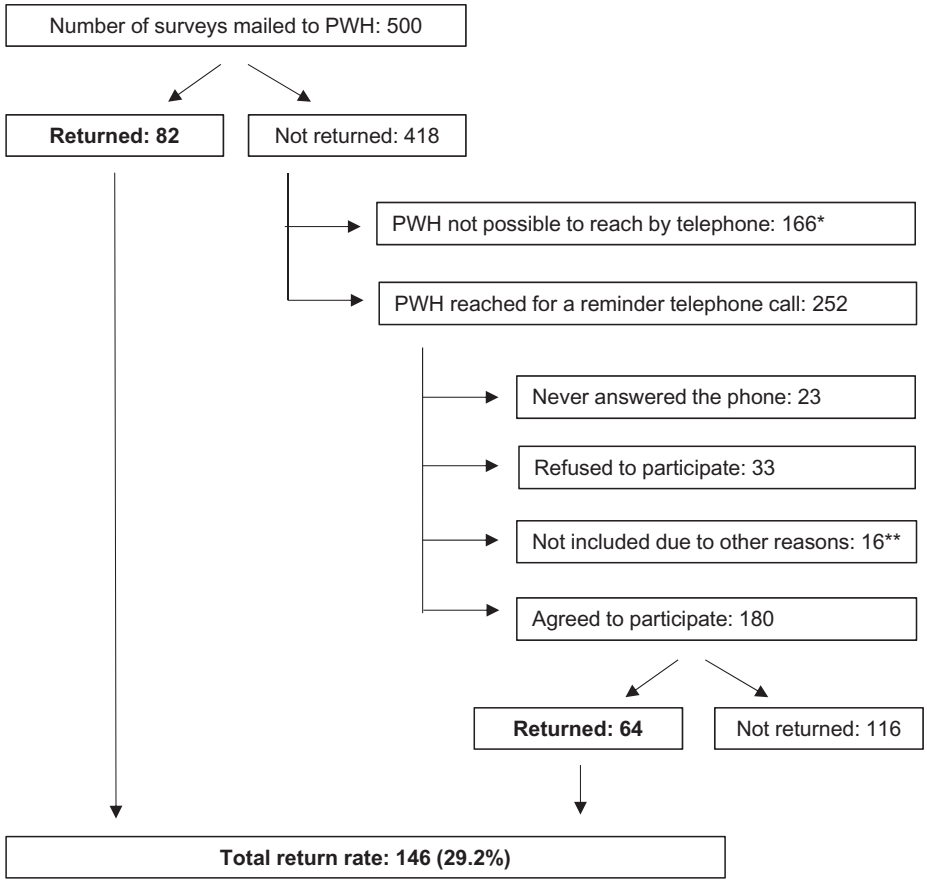
This study aims to understand, for the first time, the pain experience among PWH in Portugal, describing its prevalence, characteristics, and impact and uncovering intervention needs in the realm of hemophilia-related pain care. Given the lack of official information on pain among Portuguese PWH, this study will contribute to improving knowledge about hemophilia patients living in Portugal, thereby pointing to potential critical/problematic areas that can be improved in the Portuguese context.

Methods

Study Design

This was a national, cross-sectional, large observational study performed in the scope of the first Haemophilia National Survey conducted in Portugal, among PWH registered with the Portuguese Haemophilia Association (APH).

An envelope containing an invitation to participate and the description of study objectives, in addition to the informed consent and the questionnaires, was sent by mail to all males registered in APH as having hemophilia, a total of 500 individuals. The surveys were sent in October 2016 and received by May 2017. A telephone call was made to all PWH who had not sent the survey after three months (January 2017), both as a reminder and as a means to clarify possible doubts. Approval for this study was obtained from the Ethical Committee at the University of Minho and the Portuguese Data Protection Agency, and the study is registered at clinicaltrials.gov (NCT02870114). Informed consent was obtained from the participants or legal guardians.



* Reasons for impossibility to reach by phone are: number not listed (n=84) and telephone number wrong or disconnected (n=82).
** Other reasons for non participation are: living abroad (n=6), decease (n=2), unable to answer due to other comorbidities (blindness, cerebral palsy and cognitive impairment) (n=3), bad phone reception (n=3) and increased factor activity level (>40%) due to liver transplant (n=2).

Figure 1. Flowchart of study participants and reasons for nonparticipation.

Participants

Participants included in this survey were male PWH with hemophilia A or B of all ages. Exclusion criteria were inability to read and write or to consent to voluntary participation.

To comprehensively assess PWH of all ages, similar but age-appropriate versions were developed, varying according to target age (adults vs teenagers and children) and mode of response (self-report vs proxy): 1) adults (self-report): age $\geq$18 years; 2) children/teenagers (self-report): age 10–17 years; 3) parents (proxy version): age 0–9 years. From the 146 PWH who returned the survey (29.2% return rate), two were excluded due to missing data on pain measures, leaving 144 participants in the final sample. Figure 1 shows the flow of participants in the survey, including reasons associated with nonparticipation.

Measures

For the purposes of the current study, wherein the focus is the study of the pain prevalence, characteristics, and impact among Portuguese PWH, the analyses exclusively considered pain-related data in all age ranges. Additionally, and apart from demographic and clinical data, further analyses including anxiety, depression, and health-related quality of life in adults were performed. A description of all these measures is below:

1. Sociodemographic Questionnaire: Gathers patients' data concerning age, education, marital status, professional status, etc.
2. Clinical Questionnaire: Collects general clinical information regarding, for instance, hemophilia type and severity, type and regimen of hemophilia treatment, joint bleeding episodes, and comorbidities.
3. Multidimensional Haemophilia Pain Questionnaire (MHPQ; developed by the research team): Includes four initial items aimed at an accurate distinction between acute and chronic pain, followed by nine dimensions concerning hemophilia-related pain experienced in the previous year. If no pain is reported during a one-year time frame, the remaining questions are not answered. These questions are divided in nine dimensions, which are described bellow:
   - Pain locations: Questions about all hemophilia-related pain locations, leading to the establishment of a "number of pain

locations" measure. In addition, participants are asked to choose the "most painful location" and the "pain location that caused the greatest impact."
- The remaining questions should be answered based on the pain that yields the greatest impact.
- Duration: Queries how long ago the pain with greatest impact started.
- Frequency (and temporal pattern): Asks about how often (e.g., daily, weekly, only during bleeds) the pain occurs, along with description of the time of day when pain is most often experienced.
- Pain-triggering factors: Requires the choice, from a list, of perceived triggers related to pain onset, such as bleeds, climbing stairs, effort, or weather changes.
- Intensity: Assessed specifically in relation to six distinct conditions (bleeding episodes; during physical efforts and/or movement; using stairs; after resting or rising from sitting/lying down; during rest, sitting, or lying down; and accidental or "wrong" movements) that are associated with each triggering factor mentioned above. Intensity is rated on a 0–10 numerical rating scale (NRS; 0 = no pain, 10 = worst imaginable pain). This dimension only figures on the self-report versions, showing good Cronbach's alpha coefficients both for adults ($\alpha = 0.88$) and children/teenagers ($\alpha = 0.70$).
- Interference (etrieved from the Brief Pain Inventory [BPI]) [22]: Evaluates interference of hemophilia-related pain in seven domains: general activity, mood, walking ability, normal work, relations with others, sleep, and enjoyment of life. Although in self-report versions the items are measured according to a 0–10 NRS (0 = no interference, 10 = completely interferes), in proxy versions the questions are answered according to a five-point qualitative scale ranging from "no interference" to "total interference," with the additional "does not apply" option, in case the item is not applicable to the child (e.g., walking/crawling ability). Reliability scores for interference items are high for both the adult version ($\alpha = 0.91$) and the age 10–17 version ($\alpha = 0.89$) and adequate ($\alpha = 0.79$) for the proxy version.
- Strategies for pain control: Shows an inventory of several pharmacological and nonpharmacological strategies from which the participants should select the ones they rely on, also pointing the degree of perceived relief on a 0–100% scale.
- Pain specialists or other therapies: Requires the selection, from a list of 11 specialists or therapies (e.g., hemophilia doctors, anesthesiologists, orthopedists, psychologists, or complementary therapies, such as acupuncture or meditation), of those that participants have consulted or would like to consult to manage pain.
- Satisfaction with treatment: Evaluates global satisfaction with pain treatment through a single question, answered on a five-point scale ranging from "very dissatisfied" to "very satisfied."

Finally, each dimension is analyzed separately, and no global pain score is computed for the MHPQ. It can be used with PWH of all ages, but in children from 1–9 years old, it is a proxy version that should be completed by a parent or caregiver, which does not assess pain intensity or degree of relief from pain strategies. To facilitate item understanding, age-appropriate examples are adapted for the items of each version. This questionnaire was originally developed by the research team and has undergone a thorough validation process [23].

- Patient-Reported Outcomes Measurement Information System (PROMIS), anxiety and depression (short forms) [24]: Each form has four items that assess symptoms of anxiety and depression, such as fear (anxiety) or hopelessness (depression). Scores range from 4 to 20, with higher scores indicating more severe symptoms. In the present sample, internal consistency reliability was high both for the anxiety ($\alpha = 0.83$) and depression ($\alpha = 0.92$) subscales.
- A36 Hemofilia-QoL [25]: This is a hemophilia-specific self-report questionnaire assessing health-related quality of life. The 36 items are divided into nine subscales: physical health ($\alpha = 0.89$), daily activities ($\alpha = 0.95$), joints ($\alpha = 0.83$), pain ($\alpha = 0.82$), treatment satisfaction ($\alpha = 0.68$), treatment difficulties ($\alpha = 0.74$), emotional functioning ($\alpha = 0.83$), mental health ($\alpha = 0.82$), and relationships and social activity ($\alpha = 0.92$). A total score ($\alpha = 0.96$) can also be computed.

Statistical Analysis

Statistical analysis was performed with IBM SPSS, version 24 (Chicago, IL, USA). The internal consistency of responses to the questionnaires was assessed using Cronbach's alpha [26]. Categorical data are presented as numbers and percentages, and continuous variables are presented as mean (M) and SD and/or median (Md) and range.

Additionally, a set of predictive hierarchical multivariate logistic regression models was conducted to analyze the psychosocial factors (emotional distress and health-related quality of life) associated with the presence of pain among adult PWH. To adjust for the differences between the pain group and the no pain group, potential confounders were included in the model: in this case, age and hemophilia severity (mild, moderate, severe). No such multivariate analysis was computed for the 10–17 and 1–9 age groups due to small sample size.

P values of <0.05 were considered statistically significant.

Results

Prevalence of Pain Among PWH

The MHPQ was answered by 144 PWH. One-hundred twenty-seven participants (88.2%) reported lifetime pain due to hemophilia, and 111 (77%) reported pain in the previous year. Pain lasting over three months occurred in 86 (59.7%) participants, and 46 (31.9%) reported having pain more than once a week. Table 1 shows the prevalence of pain across age groups.

Sociodemographic and Clinical Characteristics of Study Participants (With and Without Pain in the Previous Year)

Table 2 reveals the sociodemographic and clinical characteristics of the study participants with and without hemophilia-related pain in the previous year. The mean age of adults (SD) was 43.17 (13.00) years for PWH with pain and 45.50 (17.31) years for those without pain. Most adults were married (pain: 46, 57.5%; no pain: 15,

Table 1. Prevalence of pain due to hemophilia among study participants

	Global Sample (N = 144)	Adults Age ≥ 18 y (N = 104)	Children/Teens Age 10–17 y (N = 21)	Children (Proxy) Age 1–9 y (N = 19)
Lifetime pain	127 (88.2%)	93 (89.4%)	19 (90.5%)	15 (78.9%)
In the previous year	111 (77%)	82 (78.8%)	16 (76.2%)	13 (68.4%)
Lasting >3 mo	86 (59.7%)	65 (62.5%)	13 (61.9%)	8 (42.1%)
More than once a week	46 (31.9%)	43 (41.3%)	2 (9.5%)	1 (5.3%)

Table 2. Sociodemographic and clinical information of people with hemophilia with and without pain

	Adults Age ≥ 18 y (N = 104)		Children/Teens Age 10–17 y (N = 21)		Children (proxy) Age 1–9 y (N = 19)	
	Pain (N = 82)*	No Pain (N = 22)*	Pain (N = 16)*	No Pain (N = 5)*	Pain (N = 13)*	No Pain (N = 6)*
Sociodemographic Variables						
Age, y	43.17 ± 13.00 44 (18–74)	45.50 ± 17.31 43.50 (18–72)	13.75 ± 2.30 13.50 (11–17)	14.80 ± 2.78 16 (10–17)	6.38 ± 2.26 7 (2–9)	4.83 ± 2.99 5 (1–9)
Education (completed level)						
Primary school (1st–4th grade)	5 (6.1%)	1 (4.5%)	11 (68.8%)	1 (20%)	–	–
Middle school (5th–9th grade)	16 (19.6%)	9 (40.9%)	5 (31.3%)	4 (80%)	–	–
High school (10th–12th grade)	33 (40.2%)	6 (27.3%)	–	–	–	–
College/postgraduate degree	28 (34.2%)	6 (27.2%)	–	–	–	–
Marital status: married	46 (57.5%) [80]	15 (68.2%)	–	–	–	–
Professional status	[81]					
Student/kindergarten	6 (7.4%)	3 (13.6%)	16 (100%)	5 (100%)	12 (92.3%)	6 (100%)
Full- or part-time job	43 (53.1%)	14 (63.6%)	–	–	–	–
Unemployed	8 (9.9%)	0	–	–	–	–
Retired	22 (27.2%)	5 (22.7%)	–	–	–	–
Medical leave	2 (2.5%)	0	–	–	–	–
If unemployed/retired/medical leave†	N = 32	N = 5	–	–	–	–
Due to hemophilia	20 (62.5%)	0	–	–	–	–
Work/school/kindergarten	N = 48‡	N = 17‡	N = 16	N = 5	N = 12	N = 6
absences due to hemophilia	26 (54.2%)	2 (14.3%) [14]	11 (68.8%)	1 (20%)	10 (83.3%)	4 (66.7%)
Clinical Variables						
Type of hemophilia						
Hemophilia A	73 (89%)	15 (68.2%)	14 (87.5%)	5 (100%)	12 (92.3%)	6 (100%)
Hemophilia B	9 (11%)	7 (31.8%)	2 (12.5%)	0	1 (7.7%)	0
Hemophilia severity						
Mild	7 (8.5%)	5 (22.7%)	3 (18.8%)	1 (20%)	0	1 (16.7%)
Moderate	21 (25.6%)	12 (54.5%)	2 (12.5%)	0	4 (30.8%)	1 (16.7%)
Severe	54 (65.9%)	5 (22.7%)	11 (68.8%)	4 (80%)	9 (69.2%)	4 (66.7%)
Prophylaxis treatment: Yes	31 (37.8%)	3 (13.6%)	12 (75%)	4 (80%)	9 (69.2%)	4 (66.7%)
Urgent hospital visits due to hemophilia¶: Yes	45 (59.2%) [76]	6 (31.6%) [19]	11 (84.6%) [13]	2 (40%)	11 (84.6%)	2 (40%) [5]
Hospitalization due to hemophilia¶: Yes	10 (12.2%)	2 (9.1%)	2 (12.5%)	1 (20%)	4 (30.8%)	0
Bleeding episodes¶: Yes	65 (90.3%) [72]	6 (30%) [20]	12 (80%) [15]	3 (60%)	10 (76.9%) [11]	0
Joint deterioration: Yes	80 (97.6%)	9 (42.9%) [21]	9 (56.3%)	3 (60%)	6 (46.2%)	1 (16.7%)

Continuous variables are presented as mean ± SD and median (range). Categorical variables are presented as No. (%).

*Unless otherwise specified in square brackets.

†Assessed among participants reporting being unemployed, retired, or on medical leave.

‡Assessed among participants who were working or studying.

¶Data reporting to the previous year.

68.2%) and had a full- or part-time job (pain: 43, 53.1%; no pain: 14, 63.6%). Among the adults in the pain group who were unemployed, retired, or on medical leave, 20 (62.5%) reported being in that situation because of hemophilia. In the no pain group, no one attributed that status to hemophilia.

The mean age in the children/teenagers group (SD) was 13.75 (2.30) years among participants with pain and 14.80 (2.78) years in the no pain group. In younger children (age 1–9 years), the mean age was 6.38 (2.26) years in the pain group and 4.83 (2.99) years in the no pain group.

Table 3. Pain characteristics of people with hemophilia

	Adults Age ≥18 y (N = 82)*	Children/Teens Age 10–17 y (N = 16)*	Children (Proxy) Age 1–9 y (N = 13)*
No. of pain locations†	5.23 ± 3.95	4.13 ± 3.48	3.15 ± 1.99
	4 (1–16)	3.50 (1–14)	2 (1–6)
Pain location with more impact†			
Ankle	31 (37.8%)	7 (43.8%)	6 (46.2%)
Knee	30 (36.6%)	2 (12.5%)	3 (23.1%)
Elbow	8 (9.7%)	3 (18.8%)	2 (15.4%)
Hip	5 (6.1%)	0	0
Shoulder	5 (6.1%)	0	0
Other	3 (3.7%)	4 (25%)	2 (15.4%)
Pain duration, mo	137.70 ± 136.46 [63]	28.67 ± 38.03 [15]	16.00 ± 20.79 [7]
	96 (1–612)	6 (1–108)	6 (1–60)
Pain frequency‡			
a) After getting hurt or during bleeds	20 (24.4%)	11 (68.8%)	9 (69.2%)
b) During physical efforts and/or movement	34 (41.5%)	9 (56.3%)	5 (38.5%)
c) Weekly but not daily	17 (20.7%)	1 (6.3%)	0
d) Daily but not constant	15 (18.3%)	0	0
e) Always present, continuous, constant	12 (14.6%)	0	0
Pain temporal pattern‡	[80]		
Morning	15 (18.8%)	1 (6.3%)	1 (7.7%)
Afternoon	5 (6.3%)	0	1 (7.7%)
End of the day	11 (13.8%)	2 (12.5%)	2 (15.4%)
Night	17 (21.3%)	1 (6.3%)	3 (23.1%)
Depends	48 (60%)	12 (75%)	7 (53.8%)
Pain-triggering factors‡			
Bleeding episode	43 (52.4%)	14 (87.5%)	9 (69.2%)
During physical efforts and/or movement	61 (74.4%)	8 (50%)	6 (46.2%)
Using stairs	33 (40.2%)	3 (18.8%)	2 (15.4%)
After resting or rising from sitting/lying down	41 (50%)	2 (12.5%)	0
During rest, sitting, or lying down	18 (22%)	0	0
Accidental or "wrong" movements	45 (54.9%)	10 (62.5%)	1 (7.7%)
Weather changes	34 (41.5%)	4 (25%)	0
Always present, constant	10 (12.2%)	1 (6.3%)	0

Continuous variables are presented as mean ± SD and median (range). Categorical variables are presented as No. (%).

*Unless otherwise specified in square brackets.

†Data reporting to the previous year.

‡More than one response option is possible.

Concerning clinical characteristics, most participants in all age groups had hemophilia A (Table 2). A higher number of participants with pain had severe hemophilia in all groups (age ≥ 18: 54, 65.9%; age 10–17: 11, 68.8%; age 1–9: 9, 69.2%). Table 2 also highlights that urgent hospital visits, hospitalizations, bleeds, and joint deterioration were more often reported among participants with pain.

Pain Characteristics of PWH

Pain Locations

The mean number of pain locations reported (SD) was 5.23 (3.95) for adults, 4.13 (3.48) for children/teenagers, and 3.15 (1.99) for younger children. Pain in the lower limbs was considered by all age groups to cause the greatest negative impact, especially in the ankles (age ≥18: 31, 37.8%; age 10–17: 7, 43.8%; age 1–9: 6, 25%). This was followed by the knees in adults (30, 36.6%) and the 1–9 age group (3, 23.1%), and by the elbows in the 10–17 age group (8, 9.7%) (Table 3).

Pain Duration

The duration of the pain with the greatest impact ranged from 1 to 612 months (51 years) for adults and from 1 to 108 months (9 years) for children/teenagers. Parents reported pain in their children with hemophilia that ranged from 4 to 60 months (five years). The mean (SD) and median (range) values for pain duration are shown in Table 3.

Pain Frequency and Temporal Pattern

Concerning pain frequency, most adults indicated that pain was always present (12, 14.6%), occurring daily (15, 18.3%) or weekly (17, 20.7%). On the other hand, most children/teenagers and parents reported that pain was mostly associated with bleeding episodes (age 10–17: 11, 68.8%; age 1–9: 9, 69.2%) or physical efforts/movements (age 10–17: 9, 56.3%; age 1–9: 5, 38.5%).

Table 3 also highlights that hemophilia-related pain does not present a specific temporal pattern, with most participants from all groups reporting that its onset is

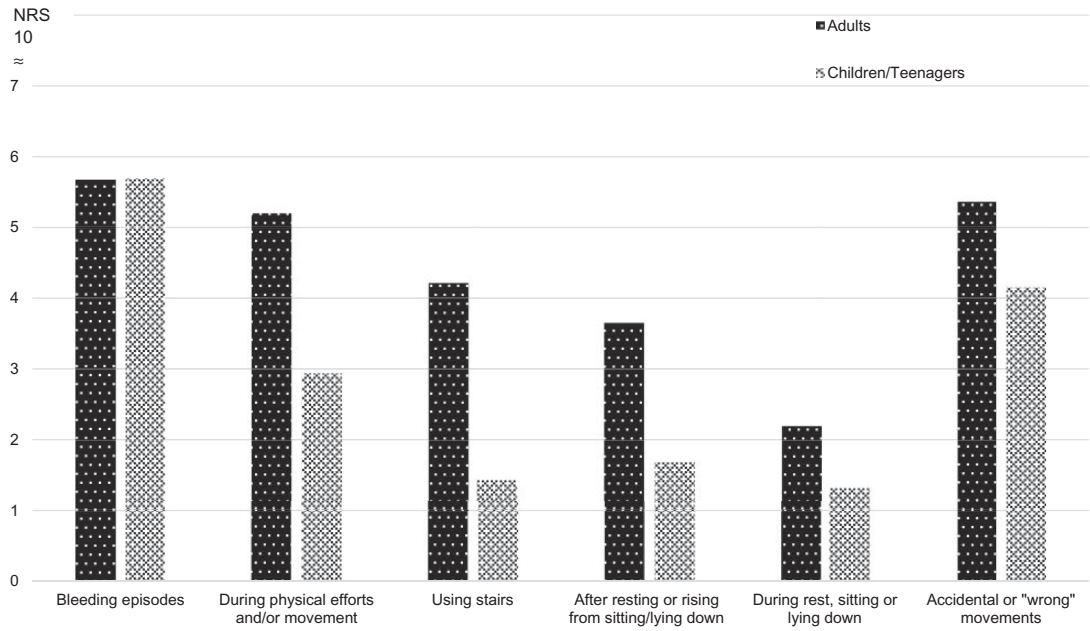


Figure 2. Pain intensity reported by adults (age ≥18 years) and children/teenagers (age 10–17 years) with hemophilia.

variable (depends; age ≥18: 48, 60%; age 10–17: 12, 75%; age 1–9: 7, 53.8%).

Pain-Triggering Factors

The triggering factors for pain most frequently pointed out by adults were physical efforts and/or movements (61, 74.4%). About half the adults also highlighted pain after bleeding episodes (43, 52.4%), after resting or rising from sitting/lying down (41, 50%), and pain due to accidental/"wrong" movements (45, 54.9%). Children and teenagers most frequently reported pain due to hemarthrosis (age 10–17: 14, 87.5%; age 1–9: 9, 69.2%). Table 3 shows a complete description of pain-triggering factors selected by PWH.

Pain Intensity

As previously stated, pain intensity was only assessed on the self-report versions. The highest mean (SD) intensity score was reported for bleeding episodes, both by adults (5.67 [2.09]) and children/teenagers (5.69 [2.15]), followed by accidental or "wrong" movements (age ≥18: 5.35 [2.97]; age 10–17: 4.13 [3.32]). Pain during rest, sitting, or lying down had the lowest intensity score in the adults (2.20 [2.48]) and children/teenagers (1.31 [2.77]) groups (Figure 2).

Pain Interference

Adult PWH revealed the highest mean (SD) pain interference score on "walking ability" (5.65 [3.23]) and "normal work" (4.99 [2.70]), and the lowest on "relations with people" (2.93 [2.79]). In the children/teenagers group, hemophilia-related pain had the highest mean interference score on "general activity" (4.44 [2.56]) and "normal work" (4.13 [2.78]), and the lowest on "enjoyment of life" (2.00 [2.85]) (Figure 3).

Parents of children up 1–9 years old revealed higher interference of their child's pain on "walking/crawling ability," with most reporting severe (4, 30.8%) or total (4, 30.8%) interference. About one-third of parents (30.8%) also pointed to severe or total interference in the "general activity" (severe: 1, 7.7%; total: 3, 23.1%) and "normal (school) work" (severe: 3, 23.1%; total: 1, 7.7%) domains. Around half the parents reported little interference of pain on "sleep" (6, 46.2%) and no interference on "relationship with others" (6, 46.2%). Only four parents (30.8%) reported no interference of hemophilia on the child's mood, with most (8, 61.6%) reporting at least a moderate interference. The lowest interference was found for "enjoyment of life," with 10 (76.9%) parents reporting little or no interference.

Strategies for Pain Control

The top five strategies used for pain management reported by PWH were the same for all groups: ice, rest, factor replacement, pain medication, and elevation. The strategy providing the greatest perception of relief (0–100% scale) was factor replacement (age ≥18: 77.81 [23.09]; age 10–17: 89.87 [16.40]), followed by pain medication (age ≥18: 59.33 [23.67]; age 10–17: 65.36 [24.61]) (Figure 4).

Pain Specialties or Other Therapies

The health care professional most often consulted by the participants in this study was the hemophilia doctor (age ≥18: 71, 86.6%; age 10–17: 14, 87.5%; age 1–9: 13, 100%). The specialist that most PWH "wished to consult" was the acupuncture specialist in the adults

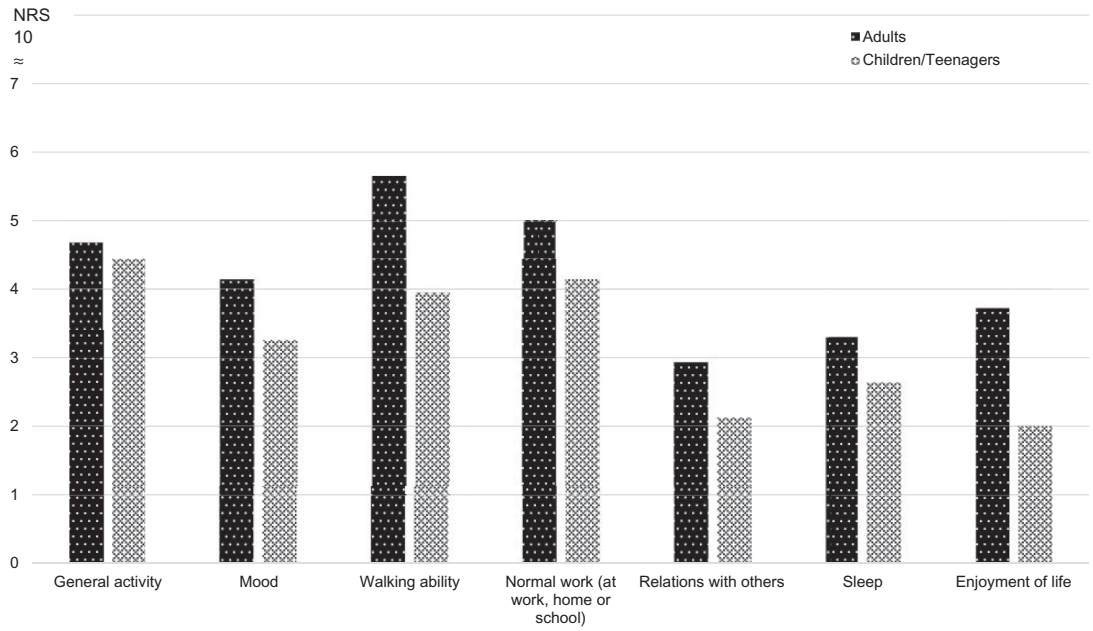


Figure 3. Pain interference reported by adults (age ≥18 years) and children/teenagers (age 10–17 years) with hemophilia.

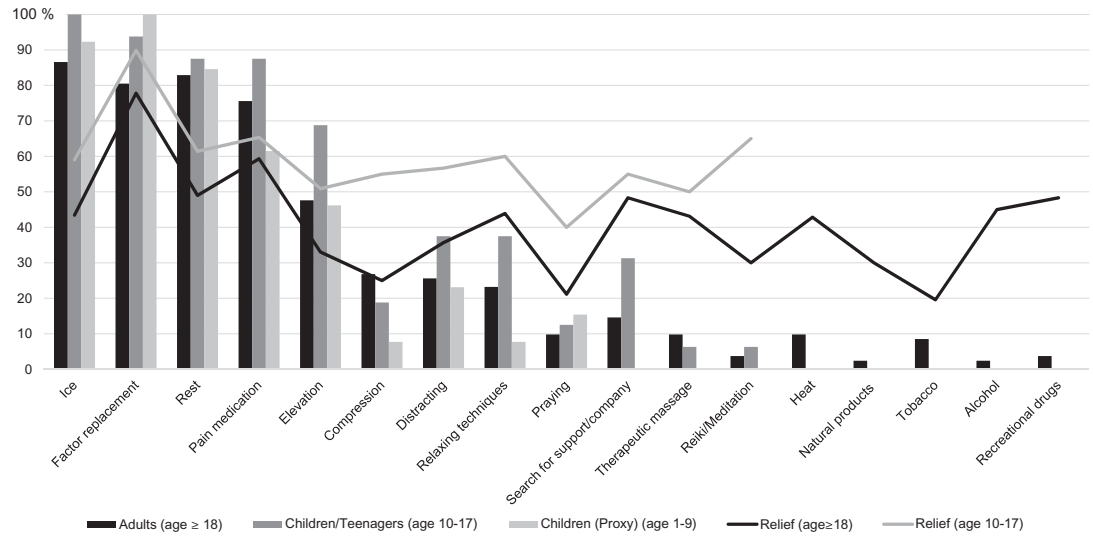


Figure 4. Strategies for pain control (adults, children/teenagers, and proxy version) and perception of relief provided (adults and children/teenagers).

group (9, 11%) and the reiki specialist in the children/teenagers group (3, 18.8%). Parents of 1–9-year-old children highlighted the psychologist (2, 15.4%) and the meditation specialist (2, 15.4%) (Figure 5).

Three adults stated that they had not consulted any specialist to assist in pain management (results not shown).

Satisfaction with Pain Treatment

Twelve (15.4%) adults, but no participants in the children/teenagers group or parent version, reported being dissatisfied (7, 9%) or very dissatisfied (5, 6.4%) with pain treatment. Also, 28 (35.9%) adults, three (18.8%) children/teenagers, and one (7.7%) parent stated that they were neither satisfied nor dissatisfied. The majority of children/teenagers and parents reported being satisfied (age 10–17: 5, 31.3%; age 1–9: 7, 53.8%) or very satisfied (age 10–17: 8, 50%; age 1–9: 5, 38.5%) with pain treatment. In the adults group, 31 (39.7%) were satisfied and seven (9%) very satisfied with pain treatment.

The Detrimental Impact of Pain on Well-being and Health-Related Quality of Life

In terms of what causes emotional distress among PWH, Table 4 shows that, in participants with pain, there was a significantly higher prevalence of anxiety (odds ratio [OR] = 1.698, 95% confidence interval [CI] = 1.190–2.422, $P = 0.003$) and depression (OR = 1.961, 95%

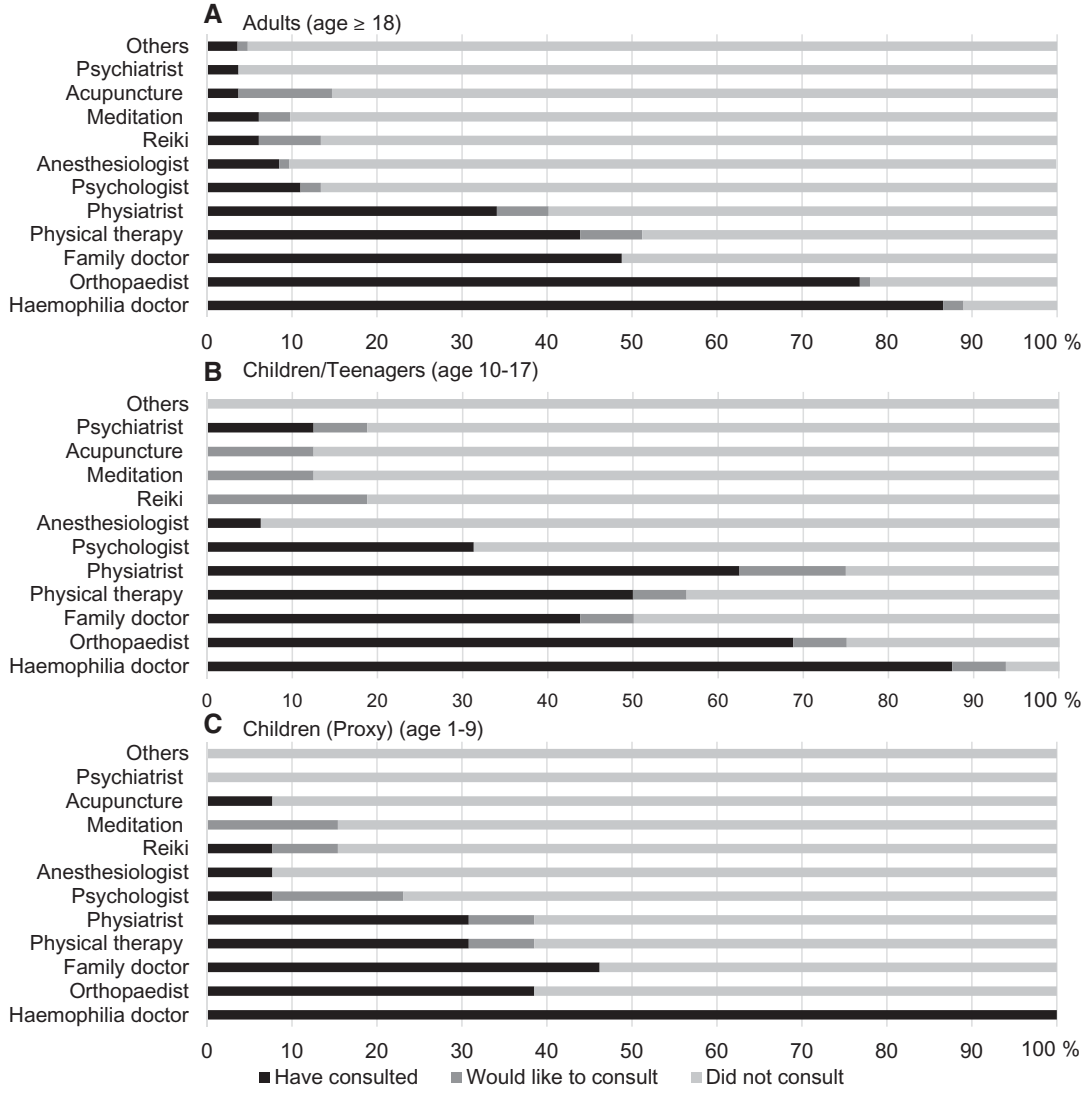


Figure 5. Pain specialties or other therapies that people with hemophilia have consulted or wished to consult.

CI = 1.086–3.541, $P = 0.025$) symptoms, when compared with those participants with hemophilia who did not report hemophilia-related pain.

Regarding health-related quality of life, it was found that PWH with pain had significantly lower levels of global quality of life (OR = 0.928, 95% CI = 0.888–0.970, $P = 0.001$) than PWH without pain. Furthermore, and with the exception of the dimension "treatment difficulties," Table 4 reveals that pain in hemophilia was associated with significantly lower scores of quality of life in all dimensions, such as physical health (OR = 0.651, 95% CI = 0.526–0.806, $P < 0.001$), daily activities (OR = 0.591, 95% CI = 0.447–0.782, $P < 0.001$), joints (OR = 0.484, 95% CI = 0.330–0.712, $P < 0.001$), treatment satisfaction (OR = 0.639, 95% CI = 0.432–0.945, $P = 0.025$), emotional functioning (OR = 0.762, 95% CI = 0.645–0.899, $P = 0.001$), mental health (OR = 0.577, 95% CI = 0.415–0.803, $P = 0.001$), and relationships and social activity (OR = 0.677, 95% CI = 0.517–0.886, $P = 0.005$).

Discussion

This was the first nationwide hemophilia study conducted in Portugal aiming to understand the pain experience among people with hemophilia (PWH), describing its prevalence, characteristics, and impact. The detrimental impact of pain was emphasized across a variety of domains, also clearly showing the association of pain with more emotional distress and poor quality of life, which also increase the burden of the disease.

Findings from this survey provide, for the first time, relevant insights regarding pain among Portuguese patients living with hemophilia, drawing important conclusions concerning intervention needs and targets, and thereby contributing to the improvement of hemophilia-related pain management and patient care.

Pain Prevalence, Characteristics, and Impact

The current findings confirm the high prevalence of pain among PWH, with 77% of the participants reporting

Table 4. Comparison of psychosocial factors between adult people with hemophilia with and without pain: Adjusted analyses

Models (Final Models)*	Pain (N = 82)	No Pain (N = 22)	OR (95% CI)	*P* Value
Emotional Distress–PROMIS				
Anxiety	7.56 ± 3.07	5.29 ± 1.49	1.698 (1.190–2.422)	0.003
Depression	6.77 ± 3.47	4.29 ± 0.78	1.961 (1.086–3.541)	0.025
HQoL–A36 Hemofilia-QoL				
Global HQoL	49.40 ± 25.52	83.87 ± 16.90	0.928 (0.888–0.970)	0.001
Physical health	54.20 ± 25.83	88.76 ± 14.53	0.651 (0.526–0.806)	<0.001
Daily activities	50.23 ± 29.50	91.48 ± 13.63	0.591 (0.447–0.782)	<0.001
Joints	51.72 ± 27.94	89.25 ± 13.94	0.484 (0.330–0.712)	<0.001
Treatment satisfaction	58.50 ± 28.81	72.61 ± 28.78	0.639 (0.432–0.945)	0.025
Treatment difficulties	54.16 ± 32.04	67.72 ± 25.44	0.920 (0.764–1.108)	0.379
Emotional functioning	47.62 ± 31.52	79.29 ± 18.02	0.762 (0.645–0.899)	0.001
Mental health	57.64 ± 27.40	81.90 ± 17.89	0.577 (0.415–0.803)	0.001
Rel. & social activity	52.81 ± 30.64	85.16 ± 21.64	0.677 (0.517–0.886)	0.005

Anxiety: $\chi^2(3) = 23.929$, $P < 0.001$, Nagelkerke $R^2 = 0.328$; final model correctly predicted 82.4% of all participants. Depression: $\chi^2(3) = 22.470$, $P < 0.001$, Nagelkerke $R^2 = 0.310$; final model correctly predicted 80.4% of all participants. Global HQoL: $\chi^2(3) = 54.955$, $P < 0.001$, Nagelkerke $R^2 = 0.416$; final model correctly predicted 87.4% of all participants. Physical health: $\chi^2(3) = 41.810$, $P < 0.001$, Nagelkerke $R^2 = 0.532$; final model correctly predicted 89.0% of all participants. Daily activities: $\chi^2(3) = 40.973$, $P < 0.001$, Nagelkerke $R^2 = 0.516$; final model correctly predicted 89.3% of all participants. Joints: $\chi^2(3) = 35.303$, $P < 0.001$, Nagelkerke $R^2 = 0.466$; final model correctly predicted 83.3% of all participants. Treatment satisfaction: $\chi^2(3) = 16.223$, $P = 0.001$, Nagelkerke $R^2 = 0.248$; final model correctly predicted 83.7% of all participants. Treatment difficulties: $\chi^2(3) = 8.268$, $P = 0.041$, Nagelkerke $R^2 = 0.132$. Emotional functioning: $\chi^2(3) = 25.030$, $P < 0.001$, Nagelkerke $R^2 = 0.345$; final model correctly predicted 80.0% of all participants. Mental health: $\chi^2(3) = 26.629$, $P < 0.001$, Nagelkerke $R^2 = 0.360$; final model correctly predicted 81.4% of all participants. Rel. & social activity: $\chi^2(3) = 25.689$, $P = 0.001$, Nagelkerke $R^2 = 0.368$; final model correctly predicted 86.7% of all participants.

Sample size is not constant due to missing data in the pain group: anxiety (N = 81), depression (N = 81), HQoL total (N = 72), physical health (N = 79), daily activities (N = 82), joints (N = 82), treatment satisfaction (N = 80), treatment difficulties (N = 80), emotional functioning (N = 79), mental health (N = 81), relationships & social activity (N = 79); and in the no pain group: anxiety (N = 21), depression (N = 21), HQoL total (N = 15), physical health (N = 21), daily activities (N = 21), joints (N = 20), treatment satisfaction (N = 18), treatment difficulties (N = 18), emotional functioning (N = 21), mental health (N = 21), relationships & social activity (N = 19).

Continuous variables are presented as mean ± SD.

CI = confidence interval; HQoL = health-related quality of life; PROMIS = Patient-Reported Outcomes Measurement Information System.

*To adjust for the differences between groups, two potential confounders were included in each model as covariates: age and hemophilia severity (mild, moderate, severe).

pain due to hemophilia in the previous year. It is hard to establish comparisons of pain reports across studies given the variety of methods, time frames, and definitions used. For instance, a Dutch survey [11] reported a pain prevalence of 81%, albeit only including severe hemophilia, and an American survey [15] found a prevalence of 85%, though only considering the last six months. Regarding children and adolescents, a German survey showed a prevalence of 66%, though pain was not necessarily related to hemophilia, with another study [14] revealing lower figures (20.8%) despite only considering pain occurrence on the assessment day. Specifically, chronic hemophilia-related pain was reported by 8% of children and 35% of adults in a survey performed across 22 European hemophilia centers [27], and in another survey conducted among 10 countries, general prevalence was 38% [28]. Nevertheless, these studies relied on health professionals' and patients' responses to a single direct question asking about chronic pain. Indeed, PWH experience acute pain during joint bleeds (hemarthrosis), but also chronic pain resulting from hemophilic arthropathy [3]. Witkop et al. [15] considered this distinction, specifying a prevalence of 66% for chronic pain and 20% for acute pain and, interestingly, reported 32% experiencing concurrent acute and chronic pain. However, it is not clear how exactly they distinguished between acute and chronic pain.

With this scope in mind, and in order to accurately classify hemophilia-related pain as chronic, a definition was proposed [27], requiring that pain should be continuous and/or intermittent, lasting over three months and occurring more than once a week.

A clear distinction between acute and chronic pain is of paramount importance, as chronic pain is much more complex, being associated with neurobiological and psychosocial factors that might perpetuate it, with evident implications for treatment strategies. Hence, in the current survey, these guidelines were taken into account, as the pain questionnaire under use carefully considered this distinction. Consequently, it was possible to uncover that among the 77% of PWH reporting pain, 59.7% of them had pain lasting more than three months and 31.9% experienced pain more than once a week. This gives a more accurate insight on pain chronicity, circumventing the limitation of the aforementioned surveys. Together with the information collected through additional questions, it is indisputable that pain is a very significant condition for the majority of Portuguese PWH. Illustrating this is the fact that many adults revealed a high duration and frequency of pain, lasting, in some cases, more than

50 years and occuring on a daily or weekly basis, or even constantly.

The simultaneous occurrence of pain in multiple locations in the same individual, previously reported [11,29], also emphasizes the challenge posed by hemophilia-related pain in terms of management and control. It is particularly demanding to control and cope with pain that can occur simultaneously in five, four, and three locations, as indicated by adults, adolescents, and children, respectively. Furthermore, the ankles and the knees have shown up as the pain locations yielding the highest negative impact among all age groups, corroborating findings from other countries [11,29–31]. Pain in lower limbs entails several limitations to peoples' mobility and general daily activities. It is noteworthy that the greatest pain interference scores were in general activity, walking ability, normal work, and mood, congruent with other findings [30]; these results point to the particular challenges posed by ankle and knee pain, more than pain from upper extremities.

Findings concerning pain characteristics and interference can help explain data on adults' satisfaction with pain treatment, with 15.4% saying they were not satisfied with pain treatment. Comparatively, satisfaction rates are higher among younger patients, which may be due to shorter pain duration and less severe joint complications, attributable to early prophylaxis treatment [2].

Concerning quality of life, this survey also reveals that all its dimensions were substantially more affected in pain participants, matching previous findings [12,15,31], and that the detrimental impact of pain goes beyond the physical domain. Indeed, the current findings clearly demonstrate that anxiety and depression symptoms were much more pronounced among pain patients. Concomitantly, the low scores in the "mental health," "emotional functioning," and "relationships and social activity" domains of the health-related quality of life scale reinforced this conclusion. This is in agreement with other studies, which showed that pain affected the mood of 85% of PWH [29] and that those reporting pain are more likely to be depressed [15], underscoring the need to consider mental health issues when evaluating pain among PWH [33].

Regarding pain intensity, the highest mean intensity was for acute pain (hemarthrosis), both for adults (5.67; 0–10 NRS) and children/teenagers (5.69; 0–10 NRS), which is in agreement with findings (5.95; 0–10 NRS) from the United States [32]. Other studies [15,29] reported pain intensity levels but considered, for instance, worst and average pain, disregarding the acute and chronic pain distinction and thus hampering the likelihood of conceiving and providing effective pain relief strategies tailored to the nature of pain and its triggers. Intensity concerning chronic pain was also gathered in this survey, considering distinct situations, such as pain during movement or rest. This was an important strength of the present survey, as to our knowledge no such accurate and detailed assessment has been conducted among PWH. Reductions in pain intensity translate into improved quality of life. Thus, through such an accurate assessment of pain intensity, according to the specific pain trigger situation, a special focus can then be placed on patients who suffer from high pain intensities that affect their everyday lives.

The Need to Expand Pain Care and Promote Nonpharmacological Strategies

When asked about pain control strategies, most patients stated that they use some elements of the RICE strategy (rest, ice, compression, and elevation), in line with current guidelines for pain management [1,27]. Factor replacement therapy also emerges as one of the most used strategies, and the one providing the greatest perception of relief. In this matter, it should be noted that factor replacement is not recommended to reduce pain, but to stop the bleeding episode, which triggers acute pain. In Portugal, factor replacement is available for all hemophilia patients after hemarthrosis (on demand) to stop bleeding, with a recent survey also describing increasingly greater access to home treatment for Portuguese patients [5].

Concerning specialties or therapies for pain management, an interesting percentage of PWH mentioned nonpharmacological techniques and the wish to consult pain professionals conducting nonpharmacological interventions. Interestingly, this matches the recommendations of international hemophilia guidelines, which state that nonpharmacological treatments, such as psychological interventions, should be considered for pain control [27]. In Portugal, all persons have access to the public National Health System, though access to some specialties, such as psychology, might be hindered by the low number of professionals working in public hospitals. In addition, access to complementary pain therapies (e.g., acupuncture) is limited in public hospitals. Thus, the use of complementary pain therapies is still incipient among Portuguese PWH, despite guidelines and recommendations stating that a combined approach of pharmacological and nonpharmacological strategies (such as psychosocial interventions) is optimal for pain management in hemophilia [27,34]. This fact is indeed corroborated by a survey of hemophilia care in Europe, which reports a decrease in access to social and psychological support by PWH in Portugal [5].

Psychological interventions have been proven to be cost-effective in a broad range of disorders and illnesses [35–39]. Although a few former works have focused on psychological interventions in hemophilia, showing positive and promising results [40–44], it is surprising that there has been a lack of recent works exploring this issue, despite the recommendations and guidelines that emphasize their relevance. In those publications, a blend of

psychological techniques was applied, with particular emphasis on hypnosis [37,38,42,43]. In fact, there is considerable evidence for the effectiveness of hypnosis as an empirically supported clinical intervention in managing symptoms such as pain [22,45–48] and in promoting psychological well-being [49,50]. Among PWH, studies have shown that hypnosis can contribute not only to controlling pain, but also to reducing the frequency and severity of bleeds and factor consumption [37,38,41]. Concurrently, by promoting better disease management, hypnosis can contribute to better coping and less distress [41].

In sum, and despite the shortage of recent studies focused on psychological interventions in hemophilia, these are recognized as complementary nonpharmacologic therapies and should be more often considered as a valuable resource to expand hemophilia care and potentially maximize treatment outcomes, promoting quality of life and emotional well-being and improving symptom management [34,51].

Limitations

This is a cross-sectional study, preventing the establishment of cause–effect associations. The representativeness of the participants could not be controlled, and the low response rate may be responsible for some nonresponse bias. Moreover, there was a small sample size in the 10–17 and 1–9 age groups, stemming from the rarity of this disease, and limiting the use of more accurate statistical procedures. Future research with larger sample sizes and longitudinal assessment of outcomes is thus warranted. This would allow for more robust conclusions concerning which variables might be associated with increased pain and the potential mediating or moderating effect of psychological characteristics between disease variables and outcomes. Another limitation concerns the lack of information regarding pharmacological treatment. Even though this survey included an open question regarding medication intake, we concluded that some of the answers provided were not very clear in terms of the nomenclature used, leaving some doubts about the data, which justified their exclusion from the analysis. A careful assessment of pharmacological treatments and potential substance use disorders among this population should be included in future pain surveys. Finally, it would be of interest to compare PWH with pain and without pain in terms of objectively measured outcomes, such as a clinical/radiological assessment of joint status.

Conclusions

This study has confirmed unequivocally that pain is highly prevalent among Portuguese PWH of all ages, as in other countries. Furthermore, it was clearly demonstrated that pain in hemophilia yields a significant negative impact on peoples' lives and is associated with more emotional distress and poor quality of life, which undoubtedly increases the burden of this disease.

The improvement of evidence-based pain management guidelines and effective practices is therefore imperative and must be a priority in hemophilia care. Three issues are crucial and should be considered: a closer collaboration between hemophilia clinicians and pain specialists; the implementation of effective pain control strategies that include both pharmacological and nonpharmacological approaches, namely psychological strategies; and, finally, the recognition of pain as a critical hemophilia issue by hemophilia health care providers and policy makers.

Definitively, these findings give important clues toward the improvement of health care services and comprehensive hemophilia pain care, also informing the conception and design of more tailored pain management plans.

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