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Title page

Mental, emotional and social dimensions of quality of life and their relationship with physical and functional status in adults with haemophilia.

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The authors stated that they had no interests which might be perceived as posing a conflict or bias.

Ethics approval statement

The study was approved by Ethics Committee of the University and Polytechnic Hospital La Fe (nº 2019/0250).

Patient consent statement

All participants voluntarily signed a written informed consent form after being informed of the aims of the study and after any doubts had been clarified.

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Abstract:

Introduction: A comprehensive treatment for patients with haemophilia (PwH) should focus on how the disease interferes with their mental, emotional and social environment to analyse if all the therapeutic efforts invested in their physical status have positive impact on a life worth living.

Aim: To analyse the correlation between the physical status of a cohort of adults with haemophilia and their mental, emotional and social states regarding their treatment modality; Also, to investigate which variables are most related to quality of life (QoL), joint health and emotional, mental and social states.

Methods: In this cross-sectional, 102 adults with haemophilia divided into a prophylactic group (G1, n=77) and on-demand group (G2, n=25) were included. Demographic and clinical characteristics, health joint (HJHS), presence of synovitis with ultrasound, self-perceived functionality (HAL) and QoL (A36-HaemoQoL), were analysed.

Results: In G1 all the variables that defined the physical status correlated (rho: 0.33 to 0.72) to the mental and social spheres. The emotional state correlated with the self-perceived ones. In G2 physical status did not correlate with the three states. According to the regression models, HAL was the variable that most influenced the QoL (together with the bleedings in the last year, R^2=.61), emotional (R^2=.16), mental (together with HJHS, R^2=.41) and social states (R^2=.39). In addition, the HJHS was influenced by synovitis, HAL, mental health, age and the bleeding history (R^2=.83).

Conclusion: Emotional, mental and social states of PwH in prophylaxis are correlated to their physical status, being the self-perceived functionality the variable that most influenced in their QoL.

Key words: Haemophilia, hemarthrosis, health status, ultrasound, blood coagulation factor, quality of life, assessment patient outcome.

Introduction

Haemophilia is an inherited disease characterised by a deficiency of coagulation factors VIII (haemophilia A) and IX (haemophilia B) with a significant impact on the musculoskeletal health, especially in patients with severe haemophilia[1]. The joint health of people with haemophilia (PwH) depends on the severity of the disease, as well as access and adherence to pharmacological treatment, in prophylactic or on-demand regimen. Despite prophylaxis, clinical and subclinical bleeds are still possible[2] and haemophilic arthropathy continues to be one of the most important and disabling sequels of the disease. Its main clinical manifestations (i.e., chronic pain, decreased joint range of movement, loss of strength, and functional disability) have a substantial impact on health-related quality of life (HRQoL) in this population [3–5]. Joint health, together with the difficulties and impairments found by PwH in their daily live (i.e., frequent hospital visits, frequent intra-venous injections, limited participation in social or sport activities) may lead to stress, social isolation and depression[6], affecting their HRQoL.

The multidisciplinary efforts for the prevention, early detection, monitoring and treatment of bleeds and management of complications of PwH are well known, being the clinical and ultrasound examination (i.e. Point-of-care ultrasound) crucial in regular standardized examination[1,7–9]. Additionally, to provide and integral and optimal care is also very important to focus on know how patients feel as a consequence of the disease, that is, how they self-perceive the disease and how it interferes with their mental, emotional and social environment. [10,11]

Therefore, for a full understanding of the influence of this chronic health condition on PwH is essential to analyse if all the health professional-patient therapeutic efforts invested in their physical status have positive impact on a life worth living from a mental, emotional and social point of view.[10]

So that, the main objective of this study is to analyse, in a cohort of adult PwH, to what extent their physical and functional status are related to their mental, emotional and social states regarding their treatment modality (on demand or prophylaxis). Secondarily, to investigate which variables are most related to quality of life, emotional state, mental state, social state and the joint health.

METHODS

Study design and setting

This is a cross-sectional, open-label and single-centre study of a population of PwH carried out at the Haemostasis and Thrombosis Unit (HTU) of the University and Polytechnic Hospital La Fe (Valencia, Spain). The data for the study were collected from January 2019 to December 2022 and are part of a longitudinal study. The study was approved by the Ethics Committee of the University and Polytechnic Hospital La Fe (nº 2019/0250) and conformed to the principles outlined in the Declaration of Helsinki. The study followed the STROBE guidelines for the reporting of observational studies[12].

Participants

The patients were recruited among PwH who attended the physiotherapist's office in the hospital's HTU, to carry out their periodic monitoring and assessment (annual control in severe or moderate patients and biannual in mild patients). The eligibility criteria were patients: a) ≥ 18 years of age, b) with haemophilia A or B, c) with any type of severity of haemophilia, d) who had received approval from both the haematologist and the physiotherapist for being in adequate condition to participate in the study, e) who were not being monitored for a traumatic or post-surgical event, and f) agreed to participate in the study. All participants gave written informed consent.

Outcome measures

Demographic data (age, body mass index; BMI) and clinical data: type of haemophilia (A/B), severity (mild, moderate, severe), age of diagnosis (at birth, before one year, after one year), total number of joint bleedings throughout their life and target joint (one in which 20 lifetime bleeding episodes have occurred), annual bleeding join rate in the last year (ABJR), inhibitors development and comorbidities (HIV or HCV infection), haemostatic agents [plasma factors, standard half-life recombinant factors, extended half-life recombinant factors, other haemostatic agents as FIXa-FX bi-specific antibodies or emicizumab, bypass agents, vasopressin analogues (with indication in haemophilia A; desmopressin) and antifibrinolytics], and modality of treatment (demand, primary prophylaxis, secondary or tertiary) were obtained from each patient from the medical records and clinical interview.

The physical status was evaluated through the Haemophilia Joint Health Score (HJHS v 2.0)[13] along with an ultrasonographic protocol,[7,14] the self-perceived functionality (measured with the Haemophilia Activity List – HAL)[15] and the physical health, daily activities, joints and pain dimensions of the A36-HaemoQoL questionnaire[16].

The HJHS is a clinical scale that measures 9 different items in elbows, knees and ankles: Swelling, duration swelling, muscle atrophy, crepitus on movement, loss of flexion/extension, joint pain and strength. A punctuation from 0-4 is added regarding the item global gait. The maximum score per joint is 20 points and total maximum score is 124 points (sum of elbows, knees, ankles and global gait). The higher the score, the worse the joint health. Psychometric characteristics showed good values in terms of reliability (internal consistency α = 0.83–0.84) and convergent validity (Petterson Score)[13]. Complementarily, elbows, knees and ankles were examined by ultrasound (Canon, Viamo sv7, multi-frequency 1.5-12 MHz linear array-transducer) to detect the presence of effusion or synovial hypertrophy. The ultrasound examination protocol consisted of: (a) For elbows, examination of the posterior olecranon recess; (b) The anterior knee was examined with the transducer placed in the mid longitudinal plane using as reference the upper pole of the patellar and insertion of the quadriceps tendon; (c) For ankles, examination of the anterior recess (tibio-talar joint)[7,14].All the clinical and ultrasound examinations were performed by two physiotherapists with more than 5 years of experience with haemophilic patients.

The self-perceived functionality was measured with the Haemophilia Activity List (HAL)[15], that assesses self-reported limitations in activities and participation in PwH. It contains 42 multiple choice questions in 7 domains. Domains, component scores and sum scores are converted to a normalized domain score ranging from 0 (worst possible functional abilities) to 100 (best possible functional abilities). The HAL demonstrates good test-retest reliability with an intraclass correlation coefficient value >0.90[17]. The average smallest detectable change value for the normalized HAL sum score was 10.2[18]. The internal consistency for the seven domains of the HAL was good (Cronbach's α=0.61–0.96). The internal consistency of the three components was also good (α=0.93–0.95).

HRQoL was measured with the Spanish version of the Haemophilia-specific HRQoL, A36-haemophilia-QoL® (A36-haemoQoL). This questionnaire consists of 36 items divided into 9 domains. The maximum score is 144 and the higher the score the lower is the influence of haemophilia disease on their quality of life. The internal consistency of the total questionnaire is α = 0.95. In addition to obtaining the global QoL score, we analyse the items related to physical status ["physical health" (8 items; α= 0.88), 'daily activities' (4 items; α = 0.88), 'joints' (3 items; α= 0.79), and 'pain' (2 items; α= 0.78)] and mental, emotional and social status ["emotional functioning' (5 items; α = 0.74), 'mental health' (3 items; α= 0.74) and 'relationships and social activity' (5 items; α= 0.85)][16,19].

The primary outcome is the correlation analysis between the mental, emotional, and social dimensions of the QoL and the physical and functional status- related variables.

Data analysis

All analyses were performed with the SPSS Statistics software for Windows (Version 26.0; IBM Corp, Armonk, NY, USA). Kolmogorov-Smirnov test was used to check the normality of the continuous data. Participants were divided into two groups regarding their treatment modality (G1: Prophylaxis; G2: On demand) in order to perform the comparison analyses. Descriptive measures are presented as mean (standard deviation), median (25-75th percentile) or frequencies (percentage), as appropriate. To compare clinical, demographic, and quality of life variables between G1 and G2, the t-test or the Wilcoxon test were used depending on the normality. The effect size was interpreted as small (d >= 0.2), medium (d >= 0.5), and large (d >= 0.8).

The correlation between physical status and the emotional, mental and social status in G1 and G2 were assessed using Pearson's or Spearman's correlation depending on the data normality. Additionally, the correlation analysis was performed in two subgroups of G1: patients receiving EHL treatment and patients receiving SHL treatment. Correlation coefficients were interpreted as small (0.1-0.3), medium (0.3-0.5) and large (0.5-1.0)[20].

Stepwise multiple linear regression analyses were used to investigate which variables of all those analysed were most related to total quality of life, emotional state, mental state, social activity and HJHS of the whole participants. For QoL models total, emotional, mental and social state, HJHS, age, IMC, severity, total historic bleedings, ABJR, HAL, total effusion, total synovitis as well as start of treatment was included as the independent variables. For HJHS model, the same variables except HJHS were included as the independent variables. Statistical significance was set at $p < 0.05$.

An a priori sample size calculation for a Spearman correlation (primary outcome) was determined using G*Power version 3.1.9.7 (Heinrich-Heine-Universität, Düsseldorf, Germany). Assuming an alpha of 0.05, a power of 0.80, and a medium-large correlation value (rho = 0.5) for a two-tailed test, the required minimum sample size was determined to be 29.

RESULTS

Study population

Of a total of 400 patients who regularly attend the hospital's UHT, 192 visited the physiotherapist. Of them, 74 were excluded (under 18 years), 12 declined to participate and 4 did not complete the questionnaires. Finally, 102 patients participated in the study (Figure 1).

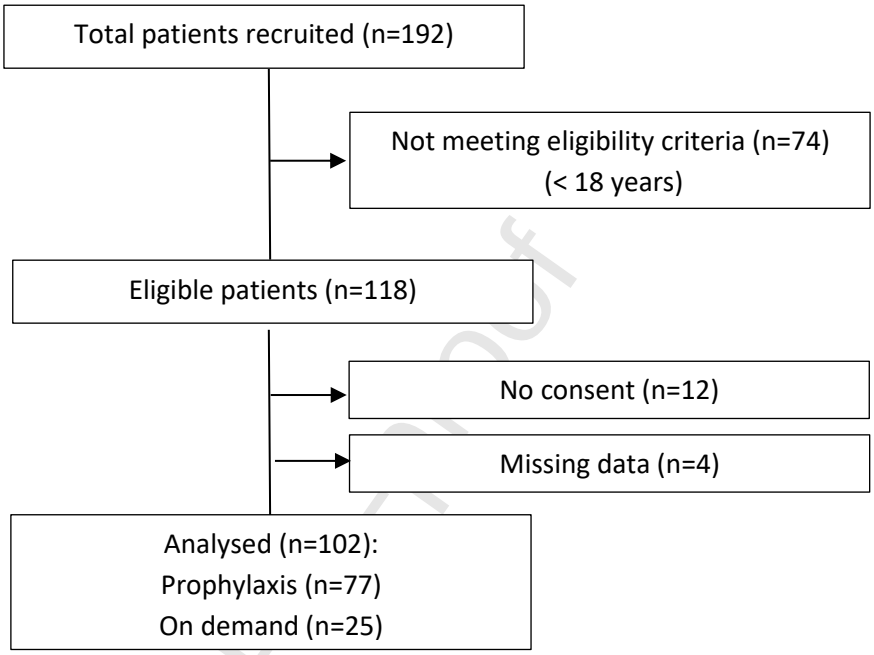

Figure 1. Flow chart of patient enrolment

Demographic and clinical characteristics

Table 1 shows descriptive and clinical characteristics of participants. The mean age of participants receiving prophylaxis treatment (G1) was 36.58 years (SD 12.00) and that of those receiving on-demand treatment (G2) was 38.48 years (SD 13.92). In both groups, about 90% were type A. As expected, most of the participants in G1 had severe haemophilia (90.91%), while those in the G2 had mild (76%) and moderate (20%) haemophilia. In this group, there was one participant with severe haemophilia.

Physical status

Table 2 shows the physical status of the two groups. The G1 had a much higher punctuation in the HJHS [median, range 23.00 (6.00-37.00)] than G2 [median, range 3.00 (1.00-5.50)] ($p<0.001$; $d = 0.96$) being the ankles the joints more affected [median, range 8.00 (1.00-13.00)], followed by the elbows [median, range 5.00 (0.00-12.50)]. Regarding ultrasonographic examination, there were no differences between groups in the presence of joint effusion. However, there were differences in the presence of synovitis, with 81.80% of patients

presenting between 1 and 6 joints with synovitis in the G1, and 72% with none in the G2 ($p<0.001$; d= 1.11).

The median (range) of the Haemophilia Activity List's total score in the G1 was 79.00 (66.90–96.65), while in the G2 was significantly higher 97.10 (91.45-99.75) ($p= 0.002$; d= 0.66), in the same way that in all dimensions of the questionnaire ($p<0.05$; d between 0.43 and 0.66). Most affected dimension in the G1 was 'functions of the legs' [66.67 (50.00-100.00)] and 'complex lower extremity component'. Participants in G1 perceived their physical health significantly worst [25.00 (19.00-29.00)] that the G2 [29.00 (25.50-30.50)] ($p=0.003$; d= 0.56). They also felt that the haemophilia affected their daily activities [11.00 (5.50-16.00)] significantly more than the G2 [14.00 (12.00-16.00)] ($p=0.006$; d= 0.45). Moreover, pain had a greater impact on the QoL of the participants receiving prophylaxis treatment [5.00 (3.00-7.00)] than in the G2 [6.00 (6.00-7.00)] ($p=0.037$; d= 0.42). However, there were no statistically significant differences in relation to the impact of the state of their joints on their QoL [G1 [9.00 (7.50-10.00)], G2 [10.00 (9.00-10.00)] ($p = 0.1$).

Quality of life, emotional, mental and social status

Regarding QoL, the median (range) of the A36-Haemophilia QoL's total score in the G2 was 114.00 (107.50-119.00), while in the G1 was 100.00 (78.00-116.00), being statistically significant the difference between both groups ($p=0.003$; d=0.63) (Table 3). There were no statistically significant differences between G1-G2 regarding their emotional functioning total score, although the item "Feeling that everything is going well" was significantly best scored in the G2 ($p=0.028$; d=0.44). There were also no statistically significant differences between G1-G2 regarding their mental health total score, but the item "To feel limited in their personal growth" was significantly best scored in the G2 ($p=0.024$; d =0.44). Finally, G2 presented a statistically higher punctuation in the relationships and social activity total score [20.00 (18.00-20.00)] ($p=0.004$; d =0.58) as well as in four of the five items evaluated ("Family", "Friendships", "Love life" and "Social activity") ($p<0.05$; d between 0.38 and 0.57).

Relationship between physical status and emotional, mental and social status

According to the correlation analyses (Table 4), in G1, the mental and social states showed a negative correlation with HJHS and synovitis (rho between -0.33 and -0.43; $p<0.05$) and a positive correlation with the remaining variables related to physical status (rho between 0.32 and 0.72; $p<0.05$). The emotional state showed positive correlations with all variables (rho between 0.31 and 0.49; $p<0.05$), except for HJHS (rho = -0.19; $p = 0.11$) and synovitis (rho= -

0.14 p=0.23). Comparing the prophylaxis EHL and SHL subgroups, results showed that the EHL group presented 17 significant correlations (rho between -0.52 and -0.43, as well as between 0.44 and 0.75; p<0.05), while the SHL group presented only 7 (rho between 0.48 and 0.70; p<0.05). In G2, the emotional, mental and social states presented low correlations with the analysed variables related to physical status, except for the emotional state with daily activities (rho=0.52; p=0.007), and the social state with joints (rho=0.54; p= 0.005).

Variables most related to total QoL, emotional, mental and social states and the joint health.

Results of the stepwise multiple regression models are shown in Table 5. For the total QoL model, regression analysis revealed that the HAL questionnaire was positively associated and ABJR is negatively related with the QoL. Together, these variables explained the 61% of the variance. For emotional and social QoL domains, only HAL variable was retained by the model (positively associated), explaining the 16% and 39% of the variance, respectively. For mental domain, HAL and HJHS were retained (both positively related), explaining the 41% of the model variance. Regarding the HJHS model, synovitis, HAL, mental health, age and historic of bleedings explained the 83% of the variance. Of these independent variables, synovitis was the most important since it explained 77% of the HJHS variance. HAL questionnaire was negatively related while the rest of variables were positively associated with the HJHS.

DISCUSSION

According to our knowledge, this is the first observational study that analyses the relationship between the physical status and the emotional, mental and social dimensions in adult PwH in relation to their treatment modality (i.e., prophylaxis or on-demand). The results showed that in the prophylaxis group the emotional, mental and social states of the participants were significantly correlated with all the variables that defined their physical status (e.g., joint health, perception of daily activities, pain and self-perceived functionality), being the correlations higher in the subgroup of patients in prophylaxis with EHL products. However, in the on-demand group the correlation was only partially established. That is, patients in prophylaxis, especially patients treated with EHL products, as they self-perceived better in their physical state, they self-perceived better in their mental and social environment. Furthermore, to have a higher score on the HJHS (more arthropathy) or to have a greater presence of synovitis in their joints, also negatively correlated to their mental and social status. It should be noted that, in contrast to other studies that state PwH experience poor mental health (e.g., anxiety, depression) at least in part due to pain and functional impairment[21], our patients in G1 did not present differences with the G2 in their mental state total score,

therefore, they did not self-perceived themselves discouraged, disable or weak more often than those in G2. However, patients in G1 felt the haemophilia limited their personal growth. This may be due to their physical limitations, dependency or emotional challenges. Therefore, it is important to continue providing appropriate support and promoting haemophilia education and awareness to help people cope with these challenges and develop a positive self-image.

Regarding the QoL and to their relationships and social state, the G2 felt that haemophilia did not affect their family relationships, friendships, love life and social activity at all, but those of G1 mostly answered that they felt a little affected in these social areas, these differences being statistically significant. These results are in line with studies that show the haemophilia has a large impact on the family and personal life[22]. In fact, joint pain and impairment limit the daily life of people with severe haemophilia. These physical problems limit the type and amount of time they spend on activities and jobs they would like to do. Moreover, haemophilia also affects their ability to develop close relationships[23], which has consequences on their QoL[24]. In addition, the social dimension of QoL was the worst self-perceived compared to the G2. Maybe the reason why the results in the G1 were not worse in the social domain was that it has been stated that many PwH choose to hide the diagnosis of haemophilia from friends, social contacts and employers[25].

On the other hand, the emotional state of the G1 and in the subgroup of patients in prophylaxis with EHL correlated only with the physical status' self-perceived variables (with the exception of joint in EHL subgroup) and not with the HJHS score or the presence of synovitis in the ultrasound scan, which can be interpreted as the real clinical situation of their joints due to the haemophilia did not make them feel overwhelmed, different, with an uncertain future or annoyed by the people lack of knowledge about the disease. In this sense, it should be noted that overall, these participants, comparatively with the G2, did no show differences in the emotional state, although they felt significantly less optimistic about their future.

All these results are consistent with the fact that in G1, 90.91% of the participants were severe, diagnosed mostly at birth, with a high number of joint bleeds during their lifetime, with haemophilic arthropathy, presence of synovitis in up to 6 joints, with comorbidities such as VHC (48.05%) and HIV (36.36%) and receiving mostly tertiary prophylaxis (61.04%). Overall higher HJHS and more patients with ankle as a target joint were reported for the ankle joint compared with the knee and elbow in G1 as in previous research, suggesting that the ankle joint is the most severely compromised joint in PwH[26]. The classical goals of haemophilia

treatment are to prevent bleeds, minimise the risk of long-term complications associated with joint damage and improve QoL by maintaining appropriate factor levels[27]. Prophylaxis with new treatments (i.e., extended half-life treatment and Emicizumab) has also demonstrated the reduction of the frequency of haemarthrosis[28,29]. In our sample, 90.91% of severe patients are in prophylaxis (53.3% use new treatments: 45.50% extended half-life treatment and 7.80% Emicizumab) and 74.03% of them with cero bleeding in the previous year. However, only 18.20% of them did not present synovitis in any joint explored by ultrasound, that raises suspicion of the existence of repeated subclinical bleeding[30]. Synovitis is the major cause for haemophiliac arthropathy, so that synovitis prevention is key to protect joints from long-term irreversible structural damage. By one hand, patients with synovitis need more frequent musculoskeletal assessment than patients without synovitis, specially by ultrasound due to clinical assessment tool as HJHS is not sensitive enough to detect synovitis. On the other hand, treatment tailoring and prophylaxis intensification with factor replacement is needed in the presence of synovitis plus conservative treatments (i.e., anti-inflammatory drugs, physiotherapy) and for chronic synovitis resistant synoviorthesis, arthroscopic/surgical synovectomy or selective arterial embolization are recommended[31]. Prophylaxis do not seem to be the unique and definitive solution. It is necessary to improve the physical health of these patients in order to have a dignified life in all its spheres. Finally, the greater presence of comorbidities (i.e., HCV and HIV) in the G1 may also partly explain the lower QoL of the patients, especially in the social sphere as HRQoL is impaired by co-infections[32].

All these factors seemed to be self-perceived as determinants for their functionality, measured with the HAL questionnaire, which presented significantly lower scores in G1 than G2 in all dimensions, mainly in those related to the functioning of the legs, congruently with the ankles being reported as most affected joints, and matching other studies regarding functionality[33]. Besides, for their self-perceived physical health, daily activities and pain, whose scores were significantly worse compared to in the G2. Considering that they were young adulthood (less than 40 years), we have been able to verify that their physical condition clearly influenced their emotional, mental and social states.

Although recent advances have led to substantial improvements in patient outcomes, PwH continue to experience joint and functional impairment, acute and chronic pain, and poor mental health, all of which should have a negative impact on HRQoL[34]. However, surprisingly participants in our study presented high scores in the A36-HaemoQoL (G1: 100 [78.00:116.00]; G2: 114 [107.50:119:00] what could be explained by the disability paradox[35], as in other studies with similar results. The essence of this paradox lies in the fact that many people with

disabilities report levels of satisfaction and QoL similar to or even higher than those without disabilities, despite facing significant challenges in terms of access, mobility, and participation in society[36].

Our secondary objective was to investigate which of all the analysed variables could better explain the QoL, the emotional, mental and social state, and the joint health of all the participants. The results showed that the self-perceived functionality was the variable that most influenced all these aspects. Therefore, incorporating personalized rehabilitation programs aimed at improving muscular strength, mobility, and joint function together with the adherence to the prophylaxis treatment can help to prevent recurrent bleeding and enhance emotional, mental and social environment of PwH.

The novelty of our study lies in its ability to provide a more nuanced understanding of the needs of patients with haemophilia, which extend beyond clinical indicators. Our results emphasize the importance of addressing the broader psychosocial aspects of the disease, including its social, mental, and emotional impacts on daily life. This multidimensional approach underscores the need for healthcare teams to routinely assess not only physical status but also quality of life and functionality, fostering a more collaborative and patient-centered approach to care. By involving patients in discussions about issues such as social isolation, depression, and anxiety, we can enhance adherence to treatment and physiotherapy, ultimately optimizing outcomes and enabling patients to lead fuller lives despite their condition.

Limitations

This study has some limitations that should be addressed. First, our sample is solely composed of adult PwH from a single centre, therefore the results cannot be extrapolated to the general haemophilia population. Second, this is a cross-sectional observational study, so changes in the variables of interest over time cannot be analysed. Finally, other factors that can potentially influence QoL such as socioeconomic factors (educational level, employment status and economic levels/monetary income) have not been included in the study. Therefore, future studies should include the follow-up of a greater number of patients from multiple centres to confirm and expand the results obtained.

CONCLUSIONS

Emotional, mental and social states of PwH in prophylaxis are correlated to their physical status, being the self-perceived functionality the variable that most influenced in their QoL. Then, QoL should be routinely monitored in clinical practice as part of patient care, allowing for the complementation of objective clinical evaluation with the patient's perspective. Emotional, mental, and especially social health should be established as a priority in improving health status and QoL in PwH. In this regard, healthcare teams should be multidisciplinary, contributing to a comprehensive disease management plan that results in improved joint health and patient functionality. Providing emotional support and promoting education and awareness about haemophilia are important in helping individuals confront these challenges and develop a positive self-image.

AUTHOR CONTRIBUTIONS

SPA, FQF and SB conceived and designed the study. SB and JEMV provided participants. MAR and ACH conducted the evaluation sessions. JJC and ACH analysed the data. SPA, MAR, ACH and JJC drafted the manuscript. All authors reviewed and approved the final version of the paper.

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Table 1. Descriptive and clinical characteristics of participants.

	TOTAL (102)	G1: Prophylaxis (77)	G2: On demand (25)	p; d
DEMOGRAPHIC DATA				
Age, years (mean, SD)	37.05 (12.46)	36.58 (12.00)	38.48 (13.92)	.51
BMI, kg/m^2 (mean, SD)	24.95 (3.88)	24.81 (3.92)	25.38 (3.80)	.53
CLINICAL DATA				
Type haemophilia (n, %)				
A	93 (91.18)	70 (90.91)	23 (92)	-
B	9 (8.82)	7 (9.09)	2 (8)	
Severity (n. %):				
Mild	19 (18.63)	0	19 (76)	
Moderate	12 (11.76)	7 (9.09)	5 (20)	-
Severe	71 (69.61)	70 (90.91)	1 (4)	
Age of diagnosis (n, %):				
At birth	45 (44.12)	36 (46.75)	9 (36)	
Before one year	15(14.71)	15 (19.48)	0	-
After one year	42 (41.18)	26 (33.77)	16 (64)	
Target joint (n, %):				
Right elbow/Left elbow	10 (9.80)/ 9 (8.82)	10 (12.98)/ 8		
Right knee/Left knee	12 (11.76)/ 10	(10.38)	0 / 1 (4)	-
Right ankle/left ankle	(9.80)	9 (11.68)/ 9 (11.68)	3 (12) / 1 (4)	
	13 (12.74)/ 13	13 (16.88)/ 13	0 / 0	
	(12.74)	(16.88)		
Total historic joint bleedings (median, IQR)	24.00 [2.00:47.00]	33.00 [15.25:50.00]	0.00 [0.00:6.00]	**<.001; 1.42**
ABJR (median, IQR)	0.00 [0.00:0.00]	0.0 [0.00:1.00]	0.0 [0.00:0.00]	
0 (n, %)	79 (77.45)	57 (74.03)	22 (88)	
1 (n, %)	16 (15.69)	13 (16.88)	3 (12)	-
2 (n, %)	6 (5.88)	6 (7.79)	0	
4 (n, %)	1 (0.98)	1 (1.30)	0	
Inhibitor development (n, %)	17 (16.66)	17 (22.07)	0	
Comorbidities (n, %)				
HCV (n, %)	43 (42.15)	37 (48.05)	6 (25)	
HIV (n, %)	28 (27.45)	28 (36.36)	0	
Modality of treatment (n, %):				
On demand	25	-	25	
Primary prophylaxis	22 (21.57)	22 (28.57)	-	-
Secondary prophylaxis	8 (7.84)	8 (10.39)	-	
Tertiary prophylaxis	47 (42.16)	47 (61.04)		
Haemostatic agents (n, %):				
Plasma factors	17 (16.66)	17 (22.07)	0	
SHL	20 (19.67)	18 (23.40)	2 (8)	-
EHL	36 (35.37)	35 (45.50)	1 (4)	
Emicizumab	6 (5.88)	6 (7.80)	0	
Bypass agent	1 (0.98)	0	1 (4)	
Desmopressin and AF	21 (20.58)	0	21 (84)	

Data are shown as mean (standard deviation) or median [interquartile range: 25-75 percentile]. P: p-value; d: Effect size, d-Cohen; SD: standard deviation; IQR: interquartile range; ABJR: annual bleeding join rate; HCV: hepatitis C virus; HIV: human immunodeficiency virus; SHL: standard half-life recombinant factors; EHL: extended half-life recombinant factors; AF: antifibrinolytics

Table 2. Physical status.

	TOTAL (102)	G1: Prophylaxis (77)	G2: On demand (25)	p; d
JOINT HEALTH				
Total HJHS (median, IQR)	12.00 [2.00:32.25]	23.00 [6.00:37.00]	3.00 [1.00:5.50]	**<.001; 0.96**
HJHS elbows (median, IQR)	1.00 [0.00:11.00]	5.00 [0.00:12.50]	0.00 [0.00:0.00]	**<.001; 0.97**
HJHS knees (median, IQR)	2.00 [0.75:9.00]	2.00 [0.00:10.50]	2.00 [1.00:3.00]	.19
HJHS ankles (median, IQR)	2.50 [0.00:12.00]	8.00 [1.00:13.00]	0.00 [0.00:2.00]	**<.001; 0.99**
ULTRASONOGRAPHIC PROTOCOL				
Total effusion	0.0 [0.00:0.00]	0.0 [0.00:1.00]	0.00 [0.00:0.00]	.211
0 (n, %)	78 (76.47)	57 (74.03)	21 (84)	
1 (n, %)	20 (19.61)	16 (20.78)	4 (16)	
2 (n, %)	3 (2.94)	3 (3.90)	0	
3 (n, %)	1 (0.98)	1 (1.30)	0	
Total synovitis	2.00 [0.00:4.00]	3.00 [1.00:4.50]	0.0 [0.00:1.00]	**<.001; 1.11**
0 (n, %)	32 (30.39)	14 (18.20)	18 (72)	
1 (n, %)	16 (15.69)	12 (15.58)	4 (16)	
2 (n, %)	13 (12.75)	11 (14.29)	2 (8)	
3 (n, %)	9 (8.82)	9 (11.69)	0	
4 (n, %)	12 (12.75)	12 (15.58)	0	
5 (n, %)	13 (12.75)	12 (15.58)	1 (4)	
6 (n, %)	7 (6.86)	7 (9.09)	0	
SELF-PERCEIVED FUNCTIONALITY				
Total HAL (median, IQR)	87.60 [69.50:98.70]	79.00 [66.90:96.65]	97.10 [91.45:99.75]	**.002; 0.66**
Lying/sitting/kneeling/standing	82.50 [56.25:100.00]	67.50 [51.25:100.00]	95.00 [83.75:100.00]	**.016; 0.48**
Functions of the legs	80.00 [56.67:100.00]	66.67 [50.00:100.00]	97.78 [85.55:100.00]	**.001; 0.65**
Functions of the arms	90.00 [75.00:100.00]	90.00 [70.00:100.00]	100.00 [95.00:100.00]	**.001; 0.64**
Use of transportation	100.00 [80.00:100.00]	93.33 [66.67:100.00]	100.00 [96.67:100.00]	**.019; 0.45**
Selfcare	100.00 [84.00:100.00]	100.00 [80.00:100.00]	100.00 [98.00:100.00]	**.016; 0.43**
Household tasks	100.00 [85.00:100.00]	96.67 [80.00:100.00]	100.00 [100.00:100.00]	**<.001; 0.66**
Leisure activities and sport	97.14 [72.38:100.00]	88.75 [70.00:100.00]	100.00 [95.72:100.00]	**.008; 0.53**
Upper extremity component	95.56 [82.22:100.00]	93.33 [77.78:100.00]	100.00 [95.56:100.00]	**.002; 0.64**
Basic lower extremity comp.	90.00 [66.67:100.00]	80.00 [60.00:100.00]	100.00 [85.00:100.00]	**.004; 0.58**
Complex lower extremity comp.	75.56 [42.22:98.89]	62.22 [35.55:97.78]	93.33 [83.33:100.00]	**.003; 0.62**
SELF-PERCEIVED PHYSICAL HEALTH (A36-Haemophilia QoL)				
Physical health (median, IQR)	26.00 [20.75:30.00]	25.00 [19.00:29.00]	29.00 [25.50:30.50]	**.003; 0.56**
Daily activities (median, IQR)	12.00 [8.00:16.00]	11.00 [6.50:16.00]	14.00 [12.00:16.00]	**.006; 0.45**
Joints (median, IQR)	9.00 [8.00:10.00]	9.00 [7.50:10.00]	10.00 [9.00:10.00]	.10
Pain (median, IQR)	6.00 [4.00:7.00]	5.00 [3.00:7.00]	6.00 [6.00:7.00]	**.037; 0.42**

Data are shown as median [interquartile range: 25-75 percentile]. P: p-value; d: Effect size, d-Cohen; IQR: interquartile; HJHS: haemophilia joint health score; HAL: haemophilia activity list.

Table 3. Quality of life

	TOTAL (102)	G1: Prophylaxis (77)	G2: On demand (25)	p; d
QUALITY OF LIFE				
A36-Haemophilia QoL	106.00 [81.00:118.00]	100.00 [78.00:116.00]	114.00 [107.50:119.00]	**.003; 0.63**
EMOTIONAL STATE				
'Emotional functioning' Total score	15.00 [11.00:17.00]	15.00 [10.00:17.00]	15.00 [11.50:16.50]	.42
Feeling of being overwhelmed	3.00 [2.00:4.00]	3.00 [2.00:4.00]	4.00 [2.50:4.00]	.07
To feel different	3.00 [2.00:4.00]	3.00 [2.00:4.00]	4.00 [2.00:4.00]	.22
To feel uncertain future	3.00 [2.00:4.00]	3.00 [2.00:4.00]	3.00 [2.00:4.00]	.89
Feeling annoyed by the lack of knowledge about the disease	4.00 [2.50:4.00]	4.00 [2.00:4.00]	4.00 [3.00:4.00]	.43
Feeling that everything is going well	2.00 [1.00:3.00]	2.00 [1.00:3.00]	2.00 [0.50:2.00]	**.028; 0.44**
MENTAL STATE				
'Mental health' Total score	9.00 [7.00:11.00]	9.00 [6.00:11.00]	9.00 [8.00:10.00]	.20
Feeling discouraged or sad	3.00 [2.00:4.00]	3.00 [2.00:4.00]	3.00 [2.00:4.00]	.42
Feeling fatigue, disability or weakness	3.00 [2.00:4.00]	3.00 [2.00:4.00]	3.00 [3.00:3.50]	.96
To feel limited in their personal growth	3.00 [2.00:4.00]	3.00 [2.00:4.00]	4.00 [3.00:4.00]	**.024; 0.44**
SOCIAL STATE				
'Relationships and social activity' Total score	18.00 [14.00:20.00]	18.00 [13.50:20.00]	20.00 [18.00:20.00]	**.004; 0.58**
Family	4.00 [3.00:4.00]	4.00 [3.00:4.00]	4.00 [4.00:4.00]	**.031; 0.38**
Friendships	4.00 [3.00:4.00]	4.00 [3.00:4.00]	4.00 [4.00:4.00]	**.014; 0.40**
Love life	4.00 [3.00:4.00]	4.00 [3.00:4.00]	4.00 [4.00:4.00]	**.005; 0.47**
Recreational activities	3.00 [2.00:4.00]	3.00 [2.00:4.00]	4.00 [3.00:4.00]	.07
Social activity	4.00 [3.00:4.00]	3.00 [2.00:4.00]	4.00 [4.00:4.00]	**.003; 0.57**

Data are shown as median [interquartile range: 25-75 percentile]. P: p-value; d: Effect size, d-Cohen.

Table 4. Correlation analyses

		Total HJHS	Total syn	QoL Ph	QoL Da	QoL Jd	QoL Pain	HAL
G1: Prophylaxis								
QoL Ef	Rho; p	-.19; .11	-.14; .23	**.48; <.001**	**.56;**	**.31; .006**	**.49;**	**.48;**
	95%	-.40 to .05	-.36 to .09	.28 to .64	.37 to .70	.09 to .51	.29 to .64	.28 to .64
QoL Mh	Rho; p	**-.34; .002**	**-.33; .003**	**.66; <.001**	**.70;**	**.44;**	**.55;**	**.68;**
	95%	-.53 to -	-.52 to -	.51 to .76	.57 to .80	.23 to .61	.37 to .69	.53 to .79
QoL Rs	Rho; p	**-.43;**	**-.36; .001**	**.58; <.001**	**.72;**	**.32; .004**	**.52;**	**.67;**
	95%	-.60 to -	-.54 to -	0.41 to	.59 to .81	.10 to .51	.33 to .67	.52 to .78
Prophylaxis EHL								
QoL Ef	Rho; p	-.24; .17	-.21; .23	**.47; .004**	**.55;**	.30; .08	**.44; .008**	**.54;**
	95%	-.54 to .11	-.52 to .14	.16 to .70	.25 to .75	-.05 to	.12 to .68	.24 to .75
QoL Mh	Rho; p	**-.43; .010**	**-.52; .002**	**.73; <.001**	**.73;**	**.48; .004**	**.61;**	**.73;**
	95%	-.67 to -	-.73 to -	.52 to .86	.51 to .86	.16 to .71	.34 to.78	.51 to .85
QoL Rs	Rho; p	**-.52; .002**	**-.51; .002**	**.60; <.001**	**.62;**	.25; .155	**.45; .007**	**.75;**
	95%	-.73 to -	-.73 to -	.32 to .78	.35 to .80	-.11 to	.12 to .68	.54 to .87
Prophylaxis SHL								
QoL Ef	Rho; p	-.08; .75	.13; .62	.23; .36	.28; .26	.12; .65	.38; .12	.19; .45
	95%	-.54 to .41	-.38 to .57	-.28 to	-.03 to	-.39 to	-.12 to	-.32 to
QoL Mh	Rho; p	-.42; .08	-.26; .30	**.55; .018**	**.58; .012**	**.48; .045**	.26; .31	**.70; .001**
	95%	-.75 to .08	-.66 to .25	.10 to .81	.14 to .83	-.01 to	-.25 to	.34 to .88
QoL Rs	Rho; p	-.16; .53	.26; .30	.23; .36	**.64; .005**	.40; .10	**.63; .005**	**.63; .005**
	95%	-.59 to .35	-.66 to .25	-.28 to	.22 to .85	-.09 to	.21 to .85	.21 to .85
G2: On-demand								
QoL Ef	Rho; p	-.09; .67	.01; .95	.10; .65	**.52; .007**	-.07; .75	-.25; .24	-.22; .29
	95%	-.48 to .33	-.39 to .42	-.32 to	.15 to .77	-.46 to	-.59 to	-.58 to
QoL Mh	Rho; p	.02; .92	-.10; .63	.13; .55	.13; .54	.06; .77	.25; .24	.12; .57
	95%	-.39 to .42	-.49 to .32	-.30 to	-.29 to	-.35 to	-.18 to	-.30 to
QoL Rs	Rho; p	-.10; .63	-.14; .50	.14; .51	.32; .12	**.54; .005**	.29; .16	.04; .87
	95%	-.49 to .32	-.52 to .28	-.28 to	-.10 to	.17 to .76	-.13 to	-.38 to

Significant correlations (p<0.05) are highlighted in bold. Rho: Spearman's correlation coefficient; p: p-value; 95% CI: Confidence Intervals of Spearman's rho; QoL: Quality of life; Ef: Emotional functioning; Mh: Mental health; RS: Relationships and social activity; HJHS: Haemophilia Joint Health Score; Syn: synovitis; Ph: Physical health; Da: Daily activities; Jd: Joints; HAL: Haemophilia activity list; SHL: standard half-life recombinant factors; EHL: extended half-life recombinant factors

Table 5. Results of the stepwise multiple linear regression analyses for the QoL and HJHS dependent variables.

Model		B	95% CI for B	β	Adjusted R^2	SEE
Total QoL	Constant	28.59 (6.43)	15.83 to 41.35			
	HAL	.89 (.08)	.74 to 1.04	.75		
	ABJR	-7.07 (3.34)	-13.69 to -.44	-.13	.61	13.88
QoL **EF**	Constant	5.91 (1.75)	2.44 to 9.39			
	HAL	.09 (.02)	.05 to .13	.41	.16	3.94
QoL **Mh**	Constant	-1.92 (1.55)	-4.99 to 1.16			
	HAL	.12 (.02)	.09 to .15	.78		
	HJHS	.04 (.02)	.01 to .07	.23	.41	2.20
QoL **Rs**	Constant	6.80 (1.26)	4.30 to 9.30			
	HAL	.12 (.02)	.09 to .15	.63	.39	2.83
HJHS	Constant	12.98 (5.63)	1.80 to 24.17			
	Synovitis	4.76 (.66)	3.44 to 6.08	.56		
	HAL	-.26 (.06)	-.38 to -.14	-.28		
	Mh	.80 (.32)	.15 to 1.44	.13		
	Age	.15 (.07)	.02 to .28	.11		
	Historic bleedings	.14 (.06)	.01 to .27	.17	.83	7.20

B: Regression coefficients and standard errors. CI: Confidence Intervals. β: Standardized regression coefficients. R^2: Coefficient of determination. SEE: Standard error of the estimate. Total HJHS, age, IMC, severity, treatment, total historic bleedings, ABJR, HAL, total effusion, total synovitis and start of treatment was included as the independent variables. For HJHS model, the same variables (except HJHS) were included as the independent variables. Only independent variables retained by the model are shown ($p<0.05$)

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐ The author is an Editorial Board Member/Editor-in-Chief/Associate Editor/Guest Editor for *[Journal name]* and was not involved in the editorial review or the decision to publish this article.

☐ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Highlights

Emotional, mental and social states are correlated to physical status in haemophilia.

Self-perceived functionality is the variable that most influenced quality of life.

Integral care must contribute to an improvement in joint health, functionality and quality of life.

Healthcare should be multidisciplinary, contributing to a comprehensive disease management.