Impact of hemophilia B on quality of life in affected men, women, and caregivers—Assessment of patient-reported outcomes in the B-HERO-S study

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Abstract

Introduction: Health-related quality of life (HRQoL) is impaired in patients with hemophilia; however, the impact in mild/moderate hemophilia B and affected women is not well characterized.

Objective: To evaluate factors that affect HRQoL in adults with hemophilia B and caregivers of affected children.

Methods: US adult patients and caregivers of affected children completed distinct ~1-hour online surveys including patient-reported outcome instruments.

Results: In total, 299 adult patients and 150 caregivers participated. Adults with moderate hemophilia reported poorer health status (median EQ-5D-5L index score, 0.63) than those with mild (0.73) or severe (0.74) hemophilia. Women reported greater pain severity than men on the Brief Pain Inventory v2 Short Form (median, 7.00 vs 5.00). Based on the Patient Health Questionnaire, mild or worse depression was observed in >50% of adult respondents, and depression was reported more often in those with moderate and severe hemophilia vs those with mild hemophilia. Most caregivers reported at least mild depression.

Conclusion: Pain, functional impairment, and depression/anxiety are present at higher-than-expected levels in individuals with hemophilia B. The large proportion of individuals with mild/moderate hemophilia and women with reduced health status suggests significant unmet needs in this population.

KEYWORDS
anxiety, caregivers, depression, functional impairment, hemophilia B, pain, patient-reported outcomes, quality of life

1 | INTRODUCTION

Hemophilia is a rare, congenital bleeding disorder resulting from the deficiency of coagulation factor VIII (hemophilia A) or factor IX (hemophilia B). Recurrent bleeding into joints (hemarthrosis) is common in individuals with hemophilia, and may cause pain and arthropathy. Evaluating the impact of pain on people with hemophilia is of growing interest, and some studies have addressed the prevalence of pain and its effects on health-related quality of life (HRQoL). The Hemophilia Experiences, Results, and Opportunities (HERO)
study provided a large-scale assessment of psychosocial issues in 675 adults with moderate-severe hemophilia A and B, and found that most participants experienced pain that interfered with their daily life in the past 4 weeks. Results from the Pain, Functional Impairment, and Quality of Life (P-FIQ) study, which assessed the impact of pain in 381 individuals with hemophilia and a history of joint pain or bleeding, indicated that participants reporting pain were more likely to experience anxiety and depression, worse health status, and functional impairment.

Furthermore, post hoc analyses suggest that independent of joint status (measured using the Hemophilia Joint Health Score v2.1), greater pain severity and interference as measured by the Brief Pain Inventory v2 Short Form (BPI) were associated with unemployment, use of opioids, use of anxiolytics, and self-reported anxiety/depression. Additionally, functional impairment as measured by the Hemophilia Activities List (HAL) was associated with similar factors (e.g., age, unemployment, inhibitor status, and use of anxiolytics) and greater pain severity.

Despite these recent advancements in our understanding of HRQoL and related outcomes in individuals with hemophilia, data specific to the subpopulation of individuals with hemophilia B are limited. Hemophilia B is less common than hemophilia A, as individuals with hemophilia B account for approximately 15%-20% of the overall hemophilia population (~5000 of ~21 000 US patients seen in treatment centers according to recent population profiles). Therefore, participation in previous studies consisted of large majorities of individuals with hemophilia A. For example, in the HERO study, which was one of the largest studies of HRQoL in people with hemophilia, individuals with hemophilia B accounted for only 13% of adults and 16% of children (described by their caregivers). In addition, women and girls with hemophilia have been underrepresented in hemophilia clinical trials, as they generally exhibit milder symptoms, and being a carrier has historically not been considered to be associated with bleeding.

The Bridging Hemophilia B Experiences, Results, and Opportunities Into Solutions (B-HERO-S) study was designed to build upon the HERO study by evaluating psychosocial issues and HRQoL in the hemophilia B population specifically, including women with hemophilia B and caregivers of children with hemophilia B. In addition, the study was open to individuals with any hemophilia severity and thus included those with mild and moderate hemophilia B. Previous reports from B-HERO-S have described the psychosocial impact of hemophilia B on affected individuals, including the impact on employment, education, and participation in recreational activities. Of note, while very rapid recruitment through 3 patient advocacy organizations may be expected to have biased the study population toward those most affected, B-HERO-S captured a substantial proportion of US hemophilia B patients (~4% of adults with mild and ~10% of adults with moderate hemophilia B). Most of the 299 adult participants indicated that hemophilia B had a negative impact on their work life, education, and ability to participate in recreational activities, suggesting that overall HRQoL may be impaired in individuals with hemophilia B. Furthermore, most of the 150 caregivers of children with hemophilia B (boys or girls, aged <18 years) reported that hemophilia affected their children's education, relationships, and physical activity, as well as their other children and the caregiver's/partner's employment. Here, we report the results of 6 patient-reported outcome (PRO) instruments administered in the B-HERO-S study to adult patients and/or caregivers. We used both generic and disease-specific PRO instruments to broadly characterize psychological issues, pain, functional ability, and quality of life.

2 METHODS

2.1 Study design

The B-HERO-S study methods were previously described in detail. In brief, participants were recruited in the United States via email and social media outlets through 3 patient advocacy organizations: Coalition for Hemophilia B, Hemophilia Federation of America, and National Hemophilia Foundation. Participants were either adults (aged ≥ 18 years) with hemophilia B or caregivers of a child (aged < 18 years) with hemophilia B. Participants completed an online survey consisting of approximately 100 questions between September 24, 2015, and November 2, 2015, which was approved by the Central Institutional Review Board (Quorum Review IRB, Seattle, WA, USA). Two distinct surveys were administered, one for adults with hemophilia B and one for caregivers of children with hemophilia B. The study was open to individuals with hemophilia B of any severity, with or without inhibitors, including women with hemophilia B and caregivers of girls with hemophilia B. Exclusion criteria were an inability to understand written English, lack of Internet access, and previous participation in the B-HERO-S study. General demographic information was collected from participants including hemophilia B severity, treatment methods, employment status, and self-reported illnesses. In addition, the following PRO instruments were administered: EQ-5D-5L with visual analog scale (VAS), BPI, International Physical Activity Questionnaire (IPAQ), HAL, Patient Health Questionnaire (PHQ-9; completed by both adults with hemophilia B and caregivers of children with hemophilia B), and Generalized Anxiety Disorder 7-Item (GAD-7) scale (completed by caregivers only).

2.2 PRO instruments

EQ-5D-5L measures overall health status "today" and is composed of 2 segments, a descriptive portion and aVAS. The descriptive section assesses 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). Index scores are calculated based on responses to each section and population-specific normative data using the EuroQol index value calculator. The VAS portion consists of an electronic version of the 20-cm printed scale. Participants are instructed to indicate their health state "today" using a 100-point scale with end points labeled as "worst health you can imagine" at 0 and "best health you can imagine" at 100.

Brief Pain Inventory v2 Short Form evaluates pain severity and interference in the past 7 days. Scores range from 0 ("no pain" or "does not interfere") to 10 ("pain as bad as you can imagine" or "complete interference"). BPI severity scores reported here were calculated as
averages of 4 severity domains (worst pain, least pain, average pain, and current pain) and BPI interference scores as averages of 7 interference domains (general activity, mood, walking ability, normal work, relations with other people, sleep, and enjoyment of life).

International Physical Activity Questionnaire assesses the extent of physical activity in the past 7 days using weighted activity-dependent metabolic equivalents of task (METs) to derive total physical activity scores for the week. METs for 3 general types of activities are as follows: walking, 3.3 METs/min; moderate activities, 4.0 METs/min; vigorous activities, 8.0 METs/min. Participants indicated how much time was spent doing each of the three types of activities for a minimum of 10 minutes during the past week, and total MET-minutes were calculated along with a qualitative activity category based on a standard scoring algorithm.17

Hemophilia Activities List is composed of 42 items across 7 domains (lying/sitting/kneeling/standing, function of the legs, function of the arms, use of transportation, self-care, household tasks, and leisure activities/sports), which are scored by participants based on level of difficulty to perform within the past month. Scores range from 0 to 100, with higher scores indicating better functional status. HAL also includes 3 component scores (upper extremity activities, basic lower extremity activities, and complex basic lower extremity activities) and an overall score that is derived from the domain scores.

Patient Health Questionnaire evaluates depression and consists of 9 items based on the Diagnostic and Statistical Manual of Mental Disorders: DSM-IV elements of depression (little interest or pleasure in doing things; feeling down or depressed; trouble falling or staying asleep, or sleeping too much; feeling tired or having little energy; poor appetite or overeating; feeling bad about yourself; trouble concentrating on things; moving or speaking slowly, or being fidgety or restless; thoughts that you would be better off dead or hurting yourself), each of which are scored from 0 (not at all) to 3 (every day). The sum of the item scores yields the total PHQ-9 score, which ranges from 0 to 27 and correlates to various diagnostic categories of depression as follows: 0-4, no depression; 5-9, mild depression; 10-14, moderate depression; 15-19, moderately severe depression; 20-27, severe depression.18 PHQ-9 score has previously been linked to treatment recommendations.19

Generalized Anxiety Disorder 7-Item uses a 7-item anxiety scale derived from the DSM-IV elements of generalized anxiety disorder (feeling nervous or anxious; not being able to stop worrying; worrying too much about things; trouble relaxing; being restless; becoming easily annoyed or irritable; feeling afraid as if something awful will happen). Each of the 7 items is scored from 0 (not at all) to 3 (nearly every day). Total GAD-7 score is calculated as the sum of the item scores and ranges from 0 to 21. The resulting scores are diagnostically categorized as follows: 5-9, mild anxiety; 10-14, moderate anxiety; ≥15, severe anxiety.20

2.3 | Statistical analysis

Results from each distinct survey (one for patients and one for caregivers) were analyzed separately. Data management was administered by Huron Consulting Services under the guidance of Novo Nordisk Inc. Statistical analyses were completed using Toluna Analytics version 5.0 (Dallas, TX, USA) on de-identified data from patient and caregiver analysis sets. Scores for PRO instruments were analyzed according to standardized protocols, as described above.15,17,18,20,21 Data from the PRO instruments were summarized for both patient and caregiver analysis sets. Descriptive statistics (frequency distributions, numbers of respondents, minimums, maximums, means, medians, and quartiles [Q1, Q3]) were calculated for all variables.

3 | RESULTS

3.1 | Participant demographics

In total, 299 adults with hemophilia B and 150 caregivers of children with hemophilia B participated in the B-HERO-S study (Table 1). Median age of adult participants with hemophilia was 29 years, and 29% were women. Most (63%) had moderate hemophilia B; fewer had mild hemophilia B (25%) or severe hemophilia B (11%). Most adults (80%) were receiving some form of routine factor infusions at various frequencies to prevent bleeding, and 20% were treated for bleeding on-demand or mostly on-demand. The majority of adults and caregivers reported modifying treatment around activity.11 Most participating adults with hemophilia were employed (81%). Self-reported comorbidities described by participants as related to their hemophilia included arthritis (48%), acute/intermittent pain (29%), anxiety (23%), depression (22%), and chronic/persistent pain (13%). All caregiver participants were parents of children with hemophilia B, a majority of whom were mothers (77%). The median age of caregivers was 35 years, and the median age of the children pertaining to the study was 10 years. Most caregivers were employed (86%).

3.2 | EQ-5D-5L in adults with hemophilia

On EQ-5D-5L, adults with hemophilia B commonly reported having moderate or severe problems with pain/discomfort (47%), anxiety/depression (41%), and usual activities (41%) (Figure 1A). Smaller percentages reported moderate or severe problems with mobility (19%) and self-care (20%). Most respondents with moderate hemophilia reported problems across the 5 domains, and more women than men reported problems with anxiety/depression (Table S1).

Overall, median (Q1, Q3) EQ-5D VAS score was 50 (42, 66), on a scale of 0-100, with higher scores indicating better quality of life (Figure 1B). Respondents with moderate hemophilia B had a lower median (Q1, Q3) VAS score (46 [42, 54]), indicating worse health status, than respondents with mild (61 [50, 78]) or severe hemophilia (65 [43, 85]). Similarly, on the index score, respondents with moderate hemophilia had a lower median (Q1, Q3) score (0.63 [0.52, 0.68]), indicating worse health status, compared with those with mild hemophilia (0.73 [0.68, 0.82]) and those with severe hemophilia (0.74 [0.56, 0.81]) (Figure 1C). Respondents who were receiving some form of routine infusions had a lower median (Q1, Q3) index score (0.66 [0.56, 0.68]) than those with on-demand regimens (0.83 [0.77, 0.86]).
3.3 | BPI in adults with hemophilia

Overall, most adult respondents with hemophilia reported some degree of pain (scores other than 0). Slightly more than half (57%) rated their current pain severity between 1 and 6 (higher scores indicate greater pain severity), and median BPI pain severity composite score was 5 (Figure 2A). Women had a higher median (Q1, Q3) BPI pain severity score than men (7.00 [3.25, 7.50] vs 5.00 [3.25, 6.75]). Additionally, respondents with moderate hemophilia had a higher median (Q1, Q3) BPI pain severity score (6.38 [4.25, 7.50]) than those with mild (3.25 [2.13, 4.19]) and severe hemophilia (4.75 [2.13, 6.00]). For BPI pain interference items, most adult respondents with hemophilia reported a score of ≥4.0 (a score of 10.0 indicates complete interference) for all 7 domains (Figure 2B). Median pain interference score was 6 for all domains except for general activities (median score 5.0). The overall mean composite score of BPI pain interference was 5.

3.4 | IPAQ in adults with hemophilia

On IPAQ, 94% of adults with hemophilia reported some activity during the past week. Nearly all (92%) reported time (>10 minutes) spent...
walking in the prior week, while 66% reported moderate activity (like bicycling at a regular pace or carrying light loads), and 40% reported vigorous activity (like heavy lifting, digging, aerobics). Median (Q1, Q3) MET scores for walking, moderate activity, and vigorous activity were 90 (75, 120) minutes per week, 60 (40, 90) minutes per week, and 80 (60, 100) minutes per week, respectively. Overall, 8% of respondents were categorized as "high" activity, 53.8% "moderate," 32.1% "low," and 5.7% did not report activity. The activity level categorization varied by age, gender, and hemophilia severity.

3.5 | HAL in adults with hemophilia

Hemophilia Activities List scores were similar across all 10 domains and the overall sum score. Median overall HAL score was 60 (on a scale of 0-100, with higher scores indicating better functional status) for each of the composite indexes of upper extremity activities, basic lower extremity activities, complex lower extremity activities, and overall score (Figure 3). Although ranges for HAL overall and composite index scores were individually widely distributed, aggregate (means/medians) scores were relatively consistent across age, gender, and hemophilia severity (Table S2).

3.6 | PHQ-9 in adults with hemophilia

For adults with hemophilia, median (Q1, Q3) score for PHQ-9 was 8 (0, 12) (higher scores indicate more severe depression), and most (62%) had a PHQ-9 score of at least 5 (indicating at least mild depression) (Table 2). Women had a higher median (Q1, Q3) score than men (11 [8, 13] vs 6 [0, 12]). Most adults with severe hemophilia had a PHQ-9 score of ≥5 (80%), compared with 66% of those with moderate hemophilia and 40% of those with mild hemophilia.

3.7 | PHQ-9 and GAD-7 in caregivers

Overall, approximately half (53%) of caregivers had a PHQ-9 score of 5 or greater (Table 3). Mothers had a higher PHQ-9 median (Q1, Q3) score than fathers (8 [2, 12] vs 2 [0, 5]), and more than twice as many mothers compared with fathers had a PHQ-9 score of ≥5 (mothers, 60%; fathers, 27%). Caregivers of children with moderate hemophilia had a higher median (Q1, Q3) score (11 [3, 12]) than those of children with mild hemophilia (2 [0, 5]) or severe hemophilia (3 [0, 5]). Sixty-three percent of caregivers of children receiving routine infusions had PHQ-9 scores of ≥5 compared with 31% of caregivers of children who treat on-demand.

On GAD-7, median (Q1, Q3) score for caregivers was 4 (1, 9) and 47% had a score of at least 5, indicative of at least mild anxiety. Sixty-eight percent of caregivers of children with moderate hemophilia had GAD-7 scores of ≥5, compared with 18% whose children had mild hemophilia and 21% whose children had severe hemophilia. Overall, mothers had a higher median (Q1, Q3) score (6 [2, 10]) than fathers (2 [0, 4]).

4 | DISCUSSION

The B-HERO-S study was developed to obtain a better understanding of the experiences of adults with hemophilia B and children...
with hemophilia B and their caregivers and families, including the impact of hemophilia B on pain, functional impairment, depression/anxiety, and other aspects of HRQoL. Given that hemophilia B is less common than hemophilia A, this population has historically been underrepresented in key studies of HRQoL and psychosocial issues.3,22,23 The B-HERO-S study is one of the largest studies of psychosocial issues in the hemophilia B population, with data suggesting that pain, mental health problems, and reduced health status.
are highly prevalent in women and men with hemophilia B and that anxiety and depression are common among caregivers of children with hemophilia B. Depression has been reported in 37%-43% of patients in other studies of hemophilia, including in 19% of patients with severe hemophilia in the P-FiQ study and in 30% of patients with both acute and chronic pain. Median PHQ-9 score for adults with hemophilia B in the B-HERO-S population was 8, a score consistent with mild depression. Thus, these data reinforce the need for formal depression screening in individuals with hemophilia who experience bleeding or report psychosocial issues.

Several studies have reported a high prevalence of pain in individuals with hemophilia. BPI has been validated and used for decades for the assessment of cancer-related and non-cancer-related pain, and was assessed for reliability and validity in 381 adults in P-FiQ, including test-retest reliability in 164 patients. Overall BPI pain severity scores for B-HERO-S adult respondents indicated substantial levels of pain (median pain severity composite score, 5.00) and notable differences in pain severity scores among hemophilia severities. For example, median BPI pain severity score was higher for individuals with moderate hemophilia (6.38) compared with those with mild (3.25) or severe (4.75) hemophilia. When considered in light of recent data from multiple countries (Netherlands, Italy, and United States [Centers for Disease Control and Prevention]) showing that patients with mild or moderate hemophilia often have joint disease and even require surgical interventions, our data confirm that there are individuals who would benefit from more comprehensive assessment and more proactive management of joint disease and pain. For example, respondents with mild or moderate hemophilia may experience delays in treatment due to a lack of bleed recognition or inability to rapidly self-manage bleeding episodes (only 18% of adults in B-HERO-S were able to self-infuse), leading to an increased incidence of hemophilia-related arthritic complications that cause pain. Potential differences in people with mild or moderate vs severe hemophilia in the trend for proactive vs reactive approaches to routine management of hemophilia, frequency of routine health care visits, and extent of proactive pain management may also contribute to high levels of self-reported pain among those with mild or moderate disease. Of note, respondents who were treated on-demand had a lower median BPI pain severity score than those on routine infusions (2.75 vs 6.00), which perhaps reflects more mild disease in respondents who treated on-demand.

Considering the high levels of pain and depression reported by individuals with moderate hemophilia B, it is not surprising that this group reported worse overall health status compared with those with mild and severe hemophilia B. Both the health index scores and VAS ratings of health status were lower in patients with moderate hemophilia B. These data highlight the comparatively poor outcomes for respondents with moderate hemophilia and suggest that this population may be more affected by pain and mental health issues than previously recognized. Interestingly, respondents with on-demand treatment regimens had a higher median EQ-5D-5L index score (0.83 vs 0.66 for those on routine infusions) and VAS score (70.0 vs 48.0 for those on routine infusions). Lower quality of life in respondents who were on some form of routine infusions may be due to a greater prevalence of bleeding issues in this group as a potential reason for changing to a prophylaxis regimen.
A unique attribute of the B-HERO-S study was the inclusion of women with hemophilia B, which provided the opportunity to identify unmet needs in this population. Notably, median BPI pain severity score was higher for women with hemophilia B than for men (7.0 vs 5.0, respectively), despite having much more similar self-reported functional abilities (HAL overall score 57.9 vs 60.0). Women respondents also reported higher levels of depression (median PHQ-9 score, 11 vs 6 for men). Although these data are consistent with evidence within the general population indicating that women have a higher prevalence of major depression than men, they also raise the interesting possibility that comorbid anxiety/depression may influence individuals’ perception of pain, resulting in greater self-reported pain severity. Of note, this potential effect is supported by results of a recent modeling analysis, which indicated that self-reported anxiety and anxiolytic use were each significantly associated with greater BPI pain severity scores, even after controlling for joint status (Hemophilia Joint Health Score), hemophilia severity, and treatment method. Although no conclusions can be drawn from the current analysis regarding the role of anxiety/depression in perception of pain among women with hemophilia, these data support a need for improved access to medical and mental health services for women with hemophilia B.

In caregivers of children with hemophilia B, levels of anxiety and depression as measured by PHQ-9 and GAD-7 were found to be greatest in caregivers of children with moderate hemophilia. In addition, mothers reported greater levels of depression and anxiety than fathers, which may be attributed to the higher incidence of major depression in women than men in the general population or may reflect gender-specific differences in management roles or approaches toward coping with their child’s disease. These findings highlight the need to increase routine education for caregivers of children with mild-moderate hemophilia and suggest that screening for depression and anxiety in caregivers should be performed on a routine basis.

| TABLE 2 | PHQ-9 scores in adults with hemophilia |
|---------|--------------------------------------|
|         | n   | Median | No depression (PHQ-9, 0-4) | Mild depression (PHQ-9, 5-9) | Moderate depression (PHQ-9, 10-14) | Moderately severe depression (PHQ-9, 15-19) | Severe depression (PHQ-9, 20-27) |
| Severity |      |        |                           |                            |                                   |                                       |                                  |
| Total    | 243  | 8      | 38%                       | 17%                        | 39%                                | 5%                                     | 1%                               |
| Mild     | 51   | 3      | 61%                       | 14%                        | 22%                                | 4%                                     | 0%                               |
| Moderate | 169  | 9      | 34%                       | 18%                        | 44%                                | 4%                                     | 0%                               |
| Severe   | 20   | 11     | 20%                       | 20%                        | 35%                                | 15%                                    | 10%                              |
| Age, years |      |        |                           |                            |                                   |                                       |                                  |
| <30      | 144  | 5      | 50%                       | 15%                        | 31%                                | 4%                                     | 1%                               |
| 30-45    | 89   | 10     | 21%                       | 18%                        | 55%                                | 6%                                     | 0%                               |
| >45      | 10   | 7      | 10%                       | 10%                        | 20%                                | 20%                                    | 0%                               |
| Gender   |      |        |                           |                            |                                   |                                       |                                  |
| Male     | 163  | 6      | 48%                       | 16%                        | 29%                                | 6%                                     | 1%                               |
| Female   | 80   | 11     | 18%                       | 20%                        | 60%                                | 3%                                     | 0%                               |
| Employed |      |        |                           |                            |                                   |                                       |                                  |
| Yes      | 202  | 9      | 33%                       | 19%                        | 44%                                | 5%                                     | 1%                               |
| No       | 41   | 0      | 63%                       | 10%                        | 17%                                | 7%                                     | 2%                               |
| Married/LTR |     |        |                           |                            |                                   |                                       |                                  |
| Yes      | 141  | 11     | 11%                       | 21%                        | 62%                                | 6%                                     | 0%                               |
| No       | 102  | 0      | 76%                       | 12%                        | 8%                                 | 3%                                     | 2%                               |
| Treatment |      |        |                           |                            |                                   |                                       |                                  |
| On-demanda | 13   | 6      | 23%                       | 62%                        | 15%                                | 0%                                     | 0%                               |
| Routine infusionsb | 216 | 9      | 40%                       | 13%                        | 42%                                | 5%                                     | 1%                               |
| Self-reported illnesses |      |        |                           |                            |                                   |                                       |                                  |
| Pain     | 99   | 0      | 75%                       | 7%                         | 6%                                 | 10%                                    | 2%                               |
| Anxiety/ depression | 105 | 11     | 14%                       | 16%                        | 63%                                | 5%                                     | 2%                               |

LTR, long-term relationship; PHQ-9, Patient Health Questionnaire.
aOn-demand treatment of bleeds.
bTreatment at least once per week to prevent bleeding.
**TABLE 3** PHQ-9 (depression) and GAD-7 (anxiety) in caregivers of children with hemophilia B

| Depression (PHQ-9) | Anxiety (GAD-7) |
|-------------------|-----------------|
| n | Median | None (0-4) | Mild (5-9) | Moderate (10-14) | Severe (15-19) | Median | None (0-4) | Mild (5-9) | Moderate (10-14) | Severe (15-19) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Total | 150 | 5 | 47% | 13% | 37% | 3% | 0% | 4 | 53% | 24% | 23% | 0% |
| Severity<sup>a</sup> | | | | | | | | | | | | |
| Mild | 27 | 2 | 70% | 11% | 19% | 0% | 0% | 2 | 82% | 7% | 11% | 0% |
| Moderate | 84 | 11 | 30% | 10% | 56% | 5% | 0% | 8 | 32% | 31% | 37% | 0% |
| Severe | 33 | 3 | 70% | 21% | 9% | 0% | 0% | 2 | 79% | 21% | 0% | 0% |
| Age, years | | | | | | | | | | | | |
| <30 | 8 | 5 | 50% | 13% | 38% | 0% | 0% | 6 | 38% | 50% | 13% | 0% |
| 30-45 | 130 | 5 | 47% | 12% | 38% | 4% | 0% | 4 | 52% | 22% | 26% | 0% |
| >45 | 12 | 4 | 50% | 25% | 25% | 0% | 0% | 3 | 75% | 25% | 0% | 0% |
| Gender | | | | | | | | | | | | |
| Male | 34 | 2 | 74% | 9% | 15% | 3% | 0% | 2 | 79% | 9% | 12% | 0% |
| Female | 116 | 8 | 40% | 14% | 43% | 3% | 0% | 6 | 45% | 28% | 27% | 0% |
| Employed | | | | | | | | | | | | |
| Yes | 129 | 5 | 45% | 12% | 40% | 3% | 0% | 5 | 50% | 24% | 26% | 0% |
| No | 21 | 3 | 62% | 19% | 14% | 5% | 0% | 3 | 71% | 24% | 5% | 0% |
| Treatment<sup>b</sup> | | | | | | | | | | | | |
| On-demand<sup>d</sup> | 26 | 3 | 69% | 19% | 8% | 4% | 0% | 2 | 73% | 27% | 0% | 0% |
| Routine infusions<sup>c</sup> | 97 | 11 | 37% | 8% | 51% | 4% | 0% | 8 | 39% | 26% | 35% | 0% |

GAD-7, Generalized Anxiety Disorder 7-Item [scale]; PHQ-9, Patient Health Questionnaire.

<sup>a</sup>Refers to severity or treatment regimen of caregiver’s child with hemophilia.

<sup>b</sup>On-demand treatment of bleeds.

<sup>c</sup>Treatment at least once per week to prevent bleeding.
Our study’s results indicate that there are unmet needs in people with hemophilia B as well as caregivers, consistent with the reported negative impact of hemophilia in this population in the areas of education, work, and participation in recreational activities in previous publications from B-HERO-S.\(^{11,12}\) Lower self-ratings of health status in B-HERO-S respondents, especially those with moderate hemophilia, may be reflective of higher levels of engagement of individuals with more severe disease in hemophilia management. Those with moderate hemophilia may be less likely to have routine visits to the hemophilia treatment center (HTC) or clinic, and may have less access to care than those with severe hemophilia, suggesting opportunities to improve patient management.

An important limitation of this study is a potential recruitment bias toward individuals associated with hemophilia B advocacy organizations and those receptive toward social media and email outreach. However, comparison with data from the Community Counts HTC Population Profile, consisting of data from individuals with bleeding disorders from 136 HTCs contained within the US HTC Network, suggests that B-HERO-S captured ~9% of eligible adults and children (449 total respondents/5099 patients with hemophilia B in the United States).\(^9\)

## 5 | CONCLUSIONS

The B-HERO-S study provided an opportunity to assess HRQoL among adults with hemophilia B and caregivers of children with hemophilia B. Importantly, the results demonstrate differences in depression and pain among individuals of different hemophilia severities, and differences between women and men with hemophilia. The outcomes discussed here suggest that complications from pain and depression may mediate the psychosocial impact of hemophilia B as described in previous reports.\(^{11,12}\) Taken together, the results from B-HERO-S emphasize the importance of addressing issues related to pain and depression in individuals with hemophilia B, regardless of severity or gender, in order to reduce the psychosocial impact of hemophilia and improve overall HRQoL.

## ACKNOWLEDGEMENTS

The authors acknowledge the medical writing assistance of Jessica Monteith, PhD, of ETHOS Health Communications in Yardley, Pennsylvania, which was supported financially by Novo Nordisk Inc., Plainsboro, New Jersey, in compliance with international Good Publication Practice guidelines.

## CONFLICTS OF INTEREST

T. Buckner has served on advisory boards for Novo Nordisk, Genentech, Shire, CSL Behring, and Pfizer, and as a consultant for Uniqure. M. Witkop is currently Head of Research at the National Hemophilia Foundation. At the time of this research, MW had received grant funding from Pfizer; served on advisory boards with Aptevo, Baxter Bioscience, Biogen Idec, Novo Nordisk, Octapharma, and Pfizer; and was on the Novo Nordisk Speakers Bureau. C. Guelcher has served on advisory boards for Bayer, Bioverativ, Genentech, Hema Biologics, Octapharma, Pfizer, and Novo Nordisk, and has served as secretary of the ATHN Board of Directors, as a Nurse Liaison to the Board (ad hoc) for THSNA, has served on the National Hemophilia Steering Committees, and is a World Federation of Hemophilia US Nurse Representative. R. Sidonio has participated in advisory boards for Aptevo, Novo Nordisk, Genentech, Bayer, Roche, Shire, CSL Behring, and Bioverativ and has contracted research with Grifols, Bioverativ, and Shire. C. Kessler has served on advisory boards for Baxalta, Bayer, Biogen, Genentech, Grifols, Novo Nordisk, Octapharma, and Pfizer and has received grant/research support from Bayer, Baxter, Novo Nordisk, and Octapharma. D. Clark has nothing to disclose. W. Owens has nothing to disclose. N. Frick has nothing to disclose. N. Iyer is an employee of Novo Nordisk Inc. D. Cooper is an employee of Novo Nordisk Inc.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

How to cite this article: Buckner TW, Witkop M, Guelcher C, et al. Impact of hemophilia B on quality of life in affected men, women, and caregivers—Assessment of patient-reported outcomes in the B-HERO-S study. Eur J Haematol. 2018;100:592-602. https://doi.org/10.1111/ejh.13055