Systematic Literature Review of the Humanistic Burden of Hemophilia A and B

Cynthia Khanji,[1] Weyinmi Nuabor,[2] Hae Kyung Kim,[1] Alexis Yubin Sohn,[1] Ruth Kim,[1] Annete Njue[2]

[1] Pfizer Inc., New York, NY, United States; [2] RTI Health Solutions, Manchester, United Kingdom

BACKGROUND

- Regular bleeding in the blood clotting disorder hemophilia may cause joint damage, poor mobility, and/or pain that can lower HRQOL for patients and caregivers.[1-3]
- Prophylactic administration to replace defective or missing blood clotting factors (FVIII for hemophilia A and FIX for hemophilia B) is the SOC; however, patients can develop inhibitory antibodies (inhibitors) that neutralize the effects of factor replacement therapy.[3]
- Nonfactor therapies also are available for routine prophylaxis; more recently, gene therapies have been approved for use in patients with hemophilia A and B.[4-6]

OBJECTIVES

- This SLR aimed to examine the humanistic burden of hemophilia A or B, with or without inhibitors, for patients aged ≥ 12 years and their caregivers.

METHODS

- Systematic searches were performed in Embase, MEDLINE, and MEDLINE In-Process for English-language articles, published from November 2012 through November 2022, describing the humanistic burden experienced by patients aged ≥ 12 years with hemophilia A or B with or without inhibitors and their caregivers.
- Studies were selected after a 2-level screening process. Abstracts (level 1) and full text articles (level 2) were screened by one researcher, with a 10% quality check by a second researcher.

RESULTS

- After screening of 6,057 titles and abstracts, 151 of 683 articles passed level 2 screening. Of these, 42 studies reported HRQOL outcomes.
  - Hemophilia-specific (e.g., HAL/PedHAL; Haem-A-QoL/Haemo-QoL-SF; A36 Hemofilia-QoL; WPAI+CIQ:HS; PROBE; and CHO-KLAT)
  - Nonspecific (e.g., EQ-5D index or VAS; SF Health Survey; BPI; PedsQL; IPAQ; and J-KIDSCREEN-52)

Humanistic Burden Measures

- The studies were heterogenous, using different HRQOL scales intended for use in adults and/or children.
- Caregiver burden was assessed using hemophilia-specific (HEMOCAB, HCI, WPAI) and nonspecific (CarerQol, GAD, PedsQL, PHQ) measures,[7-12] a new disease-specific questionnaire (name not provided),[8,12] or a series of questions.[13]

HRQOL in Patients With Hemophilia Treated With Prophylactic or On-demand Treatment

- A multi-national study showed that adult patients with severe hemophilia A experienced poor HRQOL despite prophylactic treatment (Table 1 and Figure 1).[14]
- A study in Portugal found that pain significantly lowered global HRQOL in patients with hemophilia (Table 1).[15]
- Patients with hemophilia A without inhibitors had lower HRQOL over time for episodic FVIII versus prophylactic FVIII replacement therapy (Figure 2).[16]
  - Patients on episodic FVIII—with reported higher impairment in HRQOL—missed more days of school (7.8 vs. 1.9 days) or work (8.4 vs. 1.2 days) than those on prophylactic FVIII.[16]
- In a global study (HERO), patients with hemophilia A or B with inhibitors had lower mean EQ-5D scores (reflecting a worse health state) than patients with hemophilia A without inhibitors (Table 1).[17]

Impact of Disease Severity on HRQOL

- HRQOL was worse in patients with severe or moderate disease compared with those with mild disease based on the EQ-5D questionnaire (Table 2).[7]
- A study in the US found that the median BPI pain severity score was higher for patients with moderate hemophilia than for patients with severe or mild hemophilia (Table 2).[7]
- In a cross-sectional study in several European countries, the mean predicted EQ-5D-5L score for patients with mild disease was 0.78 (95% CI, 0.73-0.82), which was 11% lower for those with moderate disease (−0.089) and 13% lower for patients with severe disease (−0.105).[18]

Functional Ability in Patients With Hemophilia Treated With SOC

- Two studies that used the HAL questionnaire in The Netherlands reported reduced and minimal negative effects on functionality (median HAL score) for patients with severe and moderate hemophilia, respectively (Table 1).[19,20]

Work Productivity in Patients With Hemophilia Treated With SOC

- A multi-national study found that, despite treatment with SOC, patients with hemophilia may be less productive at work at times.[14]
  - The median (range) WPAI+CIQ:HS Activity Impairment percentage score was 20.0% (0%-90.0%); score range was 0%-100%, with a higher score indicating less productivity.
  - The overall work impairment (presenteeism plus absenteeism) was 24% for all patients; there was no absenteeism.

Caregiver Burden

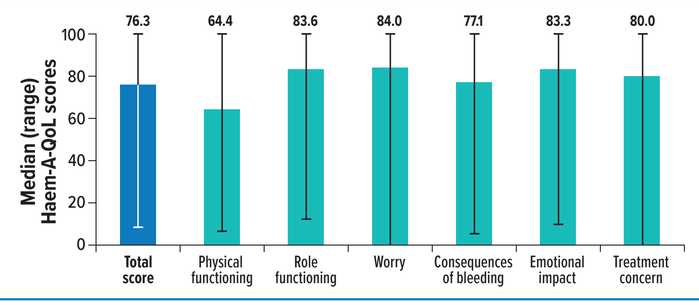
- Disease severity and inhibitor status influenced caregiver burden.[12,27]
  - In the US, over half of caregivers had depression (PHQ-9 scores ≥ 5); PHQ-9 scores were higher in caregivers of children with moderate hemophilia than those with mild or severe hemophilia.[27]
  - Caregivers of children with inhibitors had a significantly higher median total burden score (99.0 vs. 76.5; $P < 0.0001$) and median burden VAS score (5.5 vs. 3.0 [0-10; 10 = worst possible burden]; $P < 0.0001$) compared with those providing care to children without inhibitors.[12]
- A multi-national study across Europe found that caregivers lost an average of 8.35 (SD, 14.5) days over 12 months due to hemophilia.[11]

Table 1. HRQOL of Patients With Hemophilia Treated With Prophylactic or On-demand Treatment

Patient population (N); country; study name	Primary author (year)	Measure	Value[a]
Patients with HA (N = 293); 13 countries[b]	Kenet et al. (2021)[14]	HAL summary score, median (IQR)	80.5 (range, 20.5-100.0) (scale, 0-100)
Patients with HA (N = 498); global HERO population	Forsyth et al. (2015)[17]	EQ-5D, mean	0.7453 (scale, 0-1)
Patients with HA (N = 111); US HERO population			0.7598 (scale, 0-1)
Patients with HB (N = 86); global HERO population			0.7407 (scale, 0-1)
Patients with HB (N = 33); US HERO population			0.7645 (scale, 0-1)
Patients with HB (N = 299); US	Buckner et al. (2018)[7]	HAL overall score, mean (SD)	60 (scale, 0-100)
Patients with severe HB (N = 40); UK, Germany, France, Italy, and Spain	Burke et al. (2021)[21]	EQ-5D, mean (SD)	0.67 (0.21) (scale, 0-1)
Patients with HA or HB (N = 127); Portugal	Pinto et al. (2018)[22]; Pinto et al. (2018)[23]	A36 Hemofilia-QoL global score, mean (SD)	96.45 (27.33)
Patients with HA or HB (N = 84); Sweden	Brodin et al. (2015)[24]	HAL overall score, median (IQR)	20.5 (range, 0-89)
Patients with HA or HB (N = NR); US	Witkop et al. (2017)[25]	HAL overall score, mean	99 (scale, 0-100)
Patients with HA or HB without pain (N = 22); Portugal	Pinto et al. (2020)[15]	A36 Hemofilia-QoL, mean (SD)	83.87 (16.90) (n = 22)
Patients with HA or HB with pain (N = 82); Portugal[b]			49.40 (25.52) (n = 82)
Patients with moderate HA or HB (N = 75); The Netherlands	den Uijl et al. (2014)[20]	HAL sum score, median (IQR)	96 (83-100) (scale, 0-100)
Patients with severe HA or HB (N = 86); The Netherlands	Binnema et al. (2014)[19]	HAL overall score, median (IQR)	71.6 (59.0-91.7) (scale, 0-100)
Males with HA or HB (N = 102); global	Pinto et al. (2018)[22]	HAL: Functionality, median (IQR)	67.14 (5-100) (scale, 0-100)
Patients with HA without inhibitors (N = 498); global HERO population	Forsyth et al. (2015)[17]	EQ-5D, mean	0.7453 (scale, 0-1)
Patients with HA or HB with inhibitors (N = 91); global HERO population		EQ-5D, mean	0.7075 (scale, 0-1)

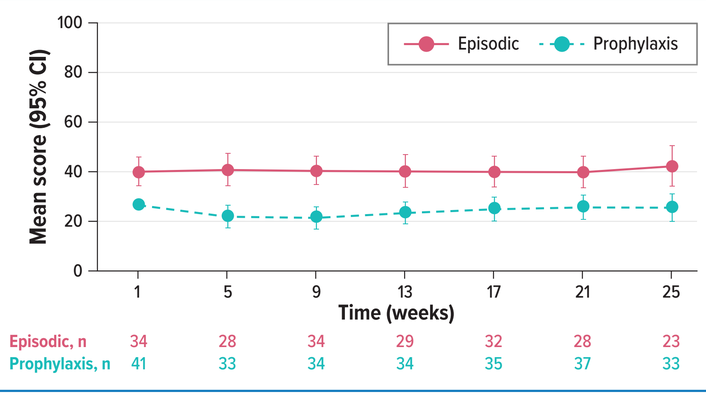
Notes: NR indicates study did not report N number. For EQ-5D and HAL scales, higher scores indicate better HRQOL. A higher BPI score indicates greater interference with daily activities.
[a] Single score indicates total population: HA and HB *or* HA or HB.
[b] Australia, Belgium, Brazil, France, Germany, Israel, Italy, South Africa, South Korea, Spain, Taiwan, the UK, and the US.
[b] Odds ratio = 0.928; 95% CI, 0.888-0.970, $P = 0.001$ versus patients with HA or BA without pain.

Figure 1. Total Haem-QoL-A and Domain Scores at Baseline for Global Population of Adults With Severe Hemophilia A



Note: Haem-A-QoL total and domain score scales range from 0 (no impairment) to 100 (high impairment).
Source: Kenet et al.[14]

Figure 2. Quality of Life Over Time in Adults With Hemophilia A Without Inhibitors



Note: Haem-A-QoL total scores over time; scale ranges from 0 to 100, with higher scores indicating better HRQOL.
Source: Oldenburg et al.[16]

Table 2. HRQOL and Functional Ability According to Hemophilia Disease Severity in Patients Treated With Prophylactic or On-demand Treatment

Patient population; country	Primary author (year)	Measure	HRQOL value based on disease severity[a]		
			Mild	Moderate	Severe
Patients with HA (N = NR); US	Witkop et al. (2021)[26]	HAL overall score, mean	84.5	76.5	
Patients with HB (N = NR); US		HAL overall score, mean	79	78	
Patients with HB (N = 295)	Buckner et al. (2018)[27]	BPI composite score, median (IQR)	3.25 (2.13-4.19)	6.38 (4.25-7.50)	4.75 (2.13-6.00)
Patients with HB (N = 295); US	Buckner et al. (2017)[28]	EQ-5D IUS, median (IQR)	0.73 (0.68-0.82)	0.63 (0.52-0.68)	0.74 (0.56-0.81)
Patients with HA or HB (N = 94); The Netherlands	den Uijl et al. (2013)[29]	EQ-5D, median (IQR)	NR	0.92 (0.72-1)	0.80 (0.72-1)
Patients with HA or HB (N = 263); US	Witkop et al. (2021)[26]	HAL overall score, mean	73.1	61.9	

Notes: NR indicates study did not report N number. For all scales, higher scores indicate better HRQOL.
[a] Single score indicates total population: hemophilia A (HA) and B (HB) or HA or HB.

CONCLUSIONS

- Despite treatment, there is a considerable burden of illness for patients with hemophilia and their caregivers across the different clinical profiles of hemophilia.
- Lower QOL is associated with higher bleeding rates observed in patients with severe disease and is also associated with inhibitor development.

ABBREVIATIONS

BPI = Brief Pain Inventory; CarerQol = Care-Related Quality of Life; CHO-KLAT = Canadian Hemophilia Outcomes–Kids' Life Assessment Tool; CI = confidence interval; FIX = factor IX; FVIII = factor VIII; GAD = generalized anxiety disorder; HA = hemophilia A; Haem-A-QoL = Hemophilia-Specific Quality of Life Questionnaire for Adults; Haemo-QoL-SF: Haemophilia-Specific Quality-of-Life Assessment for Children and Adolescents Short Form; HAL = Hemophilia Activities List; HB = hemophilia B; HCI = Hemophilia Caregiver Impact; HEMOCAB = Hemophilia-Associated Caregiver Burden Scale; HERO = Hemophilia Experiences, Results, and Opportunities; HRQOL = health-related quality of life; IPAQ = International Physical Activity Questionnaire; IQR = interquartile range; IUS = index utility score; NR = not reported; PedHAL = Pediatric Haemophilia Activities List; PedsQL = Pediatric Quality of Life Inventory; PHQ = Patient Health Questionnaire; PROBE = Patient Reported Outcomes, Burdens, and Experiences; QOL = quality of life; SD = standard deviation; SF-36 = 36-Item Short Form Health Survey; SLR = systematic literature review; SOC = standard of care; UK = United Kingdom; US = United States; VAS = visual analog scale; WPAI = Work Productivity and Activity Impairment; WPAI+CIQ:HS = WPAI plus Classroom Impairment Questions: Haemophilia Specific.

REFERENCES

1. Castaman G, et al. Haematologica. 2019;104(9):1702-9.
2. Shaikh A, et al. Haemophilia. 2022;28(5):796-805.
3. Thorat T, et al. J Manag Care Spec Pharm. 2018;24(7):632-42.
4. PR Newswire. https://www.prnewswire.com/news-releases/fda-approves-first-gene-therapy-to-treat-adults-with-hemophilia-b-301685648.html.
5. Pfizer Press Release. https://www.pfizer.com/news/press-release/press-release-detail/us-fda-approves-pfizers-beqveztm-fidanacogene-elaparvovec.
6. FDA. https://www.fda.gov/news-events/press-announcements/fda-approves-first-gene-therapy-adults-severe-hemophilia.
7. Buckner TW, et al. Eur J Haematol. 2018;100 Suppl 1:5-13.
8. DeKoven M, et al. Haemophilia. 2014;20(4):541-9.
9. Schwartz CE, et al. Qual Life Res. 2018;27(5):1335-45.
10. Schwartz CE, et al. Psychol Health. 2020;35(12):1516-30.
11. von Mackensen S, et al. Haemophilia. 2019;25(3):424-32.
12. DeKoven M, et al. Haemophilia. 2014;20(6):822-30.
13. Cutter S, et al. Eur J Haematol. 2017;98 Suppl 86:18-24.
14. Kenet G, et al. J Clin Med. 2021;10(24).
15. Pinto PR, et al. Pain Med. 2020;21(3):458-71.
16. Oldenburg J, et al. Haemophilia. 2021;27(3):398-407.
17. Forsyth AL, et al. Patient Prefer Adherence. 2015;9:1549-60.
18. Rodriguez-Santana I, et al. Orphanet J Rare Dis. 2022;17(1):148.
19. Binnema M, et al. Haemophilia. 2014;20(4):513-8.
20. den Uijl I, et al. Blood Transfus. 2014;12 (Suppl 1): s330-6.
21. Burke T, et al. Orphanet J Rare Dis. 2021;16(1):521.
22. Pinto PR, et al. Haemophilia. 2018;24(5):e344-53.
23. Pinto PR, et al. TH Open. 2018;2(1):e54-67.
24. Brodin E, et al. Eur J Haematol. 2015;95(4):336-41.
25. Witkop M, et al. Haemophilia. 2017;23(4):556-65.
26. Witkop M, et al. Haemophilia. 2021;27 (Suppl 1):8-16.
27. Buckner TW, et al. Eur J Haematol. 2018;100(6):592-602.
28. Buckner TW, et al. Eur J Haematol. 2017;98 (Suppl 86):5-17.
29. den Uijl I, et al. Blood Transfus. 2013;11(3):364-9.

CONTACT INFORMATION

Alexis Yubin Sohn, PharmD, MPH, MS
Director, HTA Value & Evidence Hemophilia

Pfizer Inc.
New York, NY 10001, United States
Phone: +1.929.720.1000
Email: alexis.sohn@pfizer.com

Presented at: ISPOR Europe 2024; 17-20 November 2024; Barcelona, Spain