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

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BACKGROUND

- Hemophilia is a hereditary condition in which the body's blood clotting mechanism is disrupted due to a deficiency of coagulation factors.
  - Hemophilia A is an X-linked bleeding disorder due to reduced blood levels of coagulation FVIII that affects approximately 1 of every 5,000 to 10,000 live-born males.[1]
  - Hemophilia B is also an X-linked disorder that occurs predominantly in males, with an incidence of approximately 1 in 25,000 births, and it is associated with abnormal bleeding due to reduced levels of or the defective or absence of FIX.[1]
- Hemophilia A and B are clinically indistinguishable from each other, and the bleeding tendencies associated with each disorder tend to correlate directly with plasma concentrations of FVIII and FIX, respectively.[1,2]
- Prophylactic administration of factor replacement therapy (FVIII for hemophilia A and FIX for hemophilia B) is the standard of care for hemophilia. They are administered intravenously for routine prophylaxis or as on-demand treatment.[3]
- However, patients with hemophilia treated with factor replacement therapy are at increased risk of developing inhibitory antibodies (inhibitors) directed against FVIII or FIX that neutralize the effects of factor replacement therapy.[1]
- 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 investigate the economic burden of hemophilia A and B, including costs (direct, indirect, and/or total), HCRU, and cost drivers.

METHODS

- Literature searches were conducted in Embase, MEDLINE, and MEDLINE In-Process for English-language articles describing the clinical, humanistic, and economic burden of hemophilia.
- The search was limited to articles published from November 2012 through November 2022. Bibliographic lists of included studies and recent systematic reviews were also searched.
- Eligible studies included patients aged ≥ 12 years with hemophilia A or B with or without inhibitors.
- Studies were selected after a 2-level screening process. Titles and abstracts (level 1) and full-text articles (level 2) were reviewed by one researcher with a 10% check by a second researcher.
- Data extractions were performed by one researcher and cross-checked by a second researcher.

CONCLUSION

- Hemophilia is associated with substantial economic burden due to hemophilia-related treatment.
- In several countries, higher costs were associated with severe disease and presence of inhibitors.
- Significant differences in costs were observed between countries, likely due to variations in sample sizes, disease management, and health system strategies.

ABBREVIATIONS

EHL = extended half-life; FIX = factor IX; FVIII = factor VIII; HA = hemophilia A; HB = hemophilia B; HCRU = healthcare resource use; NR = not reported; SHL = standard half-life; SLR = systematic literature review; US = United States.

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RESULTS

- After screening of 6,057 titles and abstracts, 683 articles were progressed to level 2 screening, of which 151 were selected. Of these, 32 studies reported economic burden outcomes. Heterogeneity across studies limited the comparison of results.
- This SLR found that both hemophilia A and B are associated with significant economic burden, and the major drivers of costs were hemophilia-related treatment, severe disease, and inhibitor presence.

Direct and Indirect Costs and HCRU

- Across several countries, including Belgium, Finland, France, Italy, and the US, hemophilia-related treatment (factor replacement therapy) was the key driver of direct costs in patients with hemophilia A or B, accounting for up to 99% of total direct costs (Table 1).[7-13]
- In a US retrospective cohort study, the annual total healthcare costs per patient and HCRU were significantly higher in patients with hemophilia B than in matched controls.[12]
  - The mean annual total healthcare costs per patient for patients with hemophilia B (US $201,635) were over 25-fold higher than for matched controls (mean, US $7,879) ($P < 0.001$ between groups).
  - Patients with hemophilia B also had significantly higher HCRU than matched controls (Table 2).
- Patients with severe hemophilia B were more likely to visit a physical therapist than those with mild or moderate disease (23%, 26%, and 50% for mild, moderate, and severe disease, respectively).[14] Disability benefits were also more common among those with severe (38%) or moderate hemophilia (56%) than among those with mild hemophilia (20%).[14]
- The key drivers of indirect costs in adults were work stoppage or early retirement due to hemophilia[9,10,15]; in children, the main driver was productivity loss of caregivers.[9]

Table 1. Direct, Indirect, and Total Costs

Population	Study design	Country; author (year)	Cost year	Mean annual costs/patient
HA				
HA on prophylactic FVIII (n = 861)	Cross-sectional study using French claims database	France; Laurendeau et al. (2022)[8]	2017	Total direct costs: €210,590 Cost of FVIII: €173,254
HA (n = 189)	Retrospective administrative claims analysis	US; Croteau et al. (2021)[11]	2017	Total direct costs: US $287,055 Cost of FVIII: US $264,777
HA (n = NR)	Observational study	US; Zhou et al. (2015)[13]	2011	Total direct costs: US $230,662 Total indirect costs: US $12,293 Cost of FVIII: US $208,070
HB				
Severe HB (n = 75)	Cross-sectional analysis: CHESS II	Europe; Burke et al. (2021)[15]	2021	Total direct costs: €235,723 Total indirect costs: €8,973 Treatment costs: €232,328
Severe HB receiving SHL treatment (n = 42)	Cross-sectional analysis: CHESS II	Europe; Burke et al. (2021)[15]	2021	Total direct costs: €190,247 Total indirect costs: €11,907 Treatment costs: €186,528
Severe HB receiving EHL treatment (n = 33)	Cross-sectional analysis: CHESS II	Europe; Burke et al. (2021)[15]	2021	Total direct costs: €293,601 Total indirect costs: €4,083 Treatment costs: €290,620
HB (n = 44)	CHESS-US	US; Burke et al. (2021)[10]	2019	Total direct costs: US $614,886 Cost of FIX: US $611,971
HB (n = 454)	Retrospective cohort study	US; Buckner et al. (2021)[12]	2019	Total direct costs: US $201,635 Treatment costs: US $152,951
Mixed population (HA/HB)				
				Mean lifetime costs
HA or HB (n = NR)	Probabilistic model	Belgium; Henrard et al. (2014)[7]	2011	*2011 birth-year Belgian cohort*[a]*:* Total costs: €97,336,761 Direct costs: €91,773,744 Indirect costs: €5,563,016 Treatment costs: €75,446,373 HA treatment cost: €69,021,625 HB treatment cost: €6,424,748
HA or HB (n = 89)	Web-based cross-sectional survey	Italy; Kodra et al. (2014)[9]	2012	Total costs: €117,731.72 Total direct costs: €114,991.78 Total indirect costs: €2,739.94 Total drug costs: €107,728.30

[a] No time discounting.

Table 2. Annual HCRU

HCRU	Patients with HB (N = 454)	Matched[a] controls (N = 454)	*P* value
Inpatient admissions			
No. of admissions	0.3 (0.6)	0.1 (0.3)	< 0.001
Days of hospitalization	1.2 (3.7)	0.3 (1.5)	< 0.001
No. of emergency department admissions	0.6 (1.2)	0.2 (0.6)	< 0.001
No. of outpatient visits	17.7 (22.9)	8.0 (11.0)	< 0.001

Note: Values are mean (standard deviation). [a] Demographically matched controls without HB.
Source: Buckner et al. (2021)[12]

Impact of Disease Severity on Costs and Productivity

- Healthcare costs were found to increase with increasing disease severity (Table 3).
  - In Europe, data from the CHESS II study found that the mean adjusted direct medical costs were 4.7 times higher for severe versus mild hemophilia A or B without inhibitors (€3,949 vs. €844), and mean societal cost was €11,115 higher for patients with severe versus mild disease (2020 cost year).[16]
  - In the US, data from a cohort study assessing the economic burden of hemophilia B reported that the annual total healthcare cost per patient was 7.8 times higher in patients with severe disease than in those with mild disease (US $632,088 vs. US $80,811).[12] Patients with severe hemophilia B had 84-fold higher total healthcare costs than controls without hemophilia (US $632,088 vs. US $7,546), whereas those with mild disease had 7-fold higher costs than controls (US $80,811 vs. US $11,372) (2019 cost year).
- Patients with severe hemophilia A or B also experienced more absenteeism than patients with mild disease.[20]
  - A US study showed that regardless of the birth cohort, the proportion of participants with severe hemophilia that missed ≥ 10 days of school or work in the preceding year due to lower or upper extremity joint problems was 2 or 3 times that of males of the same age with mild hemophilia (Figure 1).

Impact of Inhibitors on Cost and HCRU

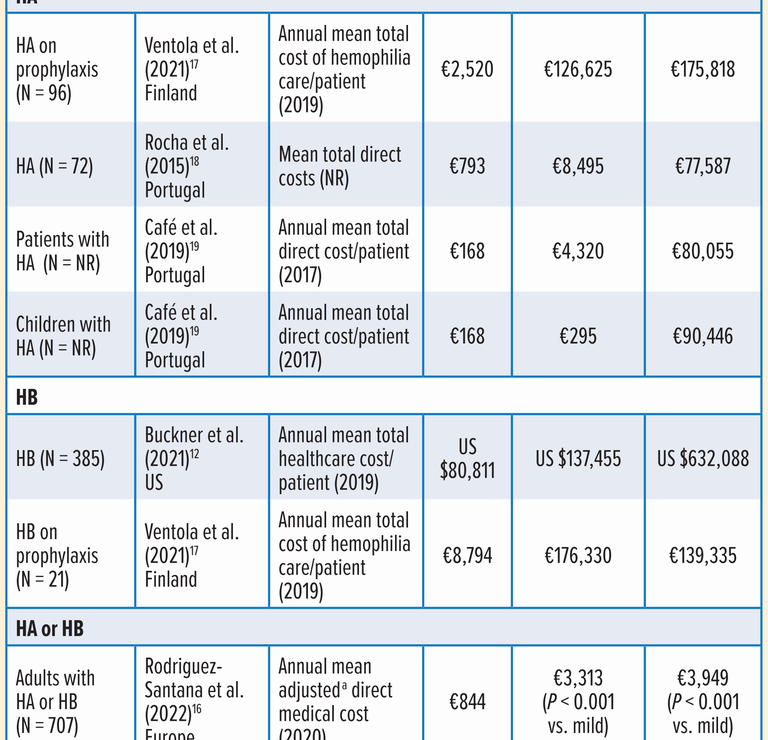
- Cost and resource use were impacted by inhibitor status. Data from Portugal showed that patients with hemophilia A or B with inhibitors had 3.3 times higher costs than patients with hemophilia A or B without inhibitors (€134,032 vs. €40,318 per year, respectively; $P = 0.030$).[18]
- Patients with hemophilia A without inhibitors treated with FVIII were less likely to be hospitalized than patients with inhibitors (annual hospitalization rate, 41.2% vs. 64.1%, respectively).[8]

Table 3. Costs by Hemophilia Severity

Population	Author (year), country/ region	Cost data description (cost year)	Costs by hemophilia severity		
			Mild	Moderate	Severe
HA					
HA on prophylaxis (N = 96)	Ventola et al. (2021)[17] Finland	Annual mean total cost of hemophilia care/patient (2019)	€2,520	€126,625	€175,818
HA (N = 72)	Rocha et al. (2015)[18] Portugal	Mean total direct costs (NR)	€793	€8,495	€77,587
Patients with HA (N = NR)	Café et al. (2019)[19] Portugal	Annual mean total direct cost/patient (2017)	€168	€4,320	€80,055
Children with HA (N = NR)	Café et al. (2019)[19] Portugal	Annual mean total direct cost/patient (2017)	€168	€295	€90,446
HB					
HB (N = 385)	Buckner et al. (2021)[12] US	Annual mean total healthcare cost/ patient (2019)	US $80,811	US $137,455	US $632,088
HB on prophylaxis (N = 21)	Ventola et al. (2021)[17] Finland	Annual mean total cost of hemophilia care/patient (2019)	€8,794	€176,330	€139,335
HA or HB					
Adults with HA or HB (N = 707)	Rodriguez-Santana et al. (2022)[16] Europe	Annual mean adjusted[a] direct medical cost (2020)	€844	€3,313 ($P < 0.001$ vs. mild)	€3,949 ($P < 0.001$ vs. mild)
Adults with HA or HB (N = 286)	Rodriguez-Santana et al. (2022)[16] Europe	Annual mean adjusted[a] societal cost (2020)	€3,101	€5,925 ($P < 0.01$ vs. mild)	€14,216 ($P < 0.001$ vs. mild)

[a] Cost models adjusted for hemophilia severity, age, body mass index, country, comorbidities, and weight-adjusted factor consumption.

Figure 1. Absenteeism by Hemophilia Disease Severity in 4 Birth Cohorts



Source: Mazepa et al. (2016).[20]

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