Treatment Burden and Its Relationship with Health-Related Quality of Life, Work Productivity and Activity Impairment in Adults with Severe Non-Inhibitor Hemophilia A in the United States: Data Analysis from the CHESS US+ Study

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Background

- Prophylactic Factor VIII treatment, recommended for severe hemophilia A (SHA) to control bleeding events, may be associated with significant treatment burden[1].

Aim

- This analysis aims at exploring potential areas of impact of treatment burden on patient-reported outcomes (PROs) as well as an initial investigation of the magnitude of this potential impact in adult non-inhibitor SHA patients in the United States.

Methods

- We conducted an exploratory analysis using cross-sectional data from the 'Cost of Haemophilia across the US+: a Socioeconomic Survey' (CHESS US+) patient study.
- Treatment burden was defined as "high" (HB) for patients treated with prophylaxis and "low" (LB) for patients treated on-demand.
- PROs; EQ-5D, EQ-VAS, work productivity and activity impairment [WPAI].
- We employed propensity score (PS) matching, which computes the probability, based on key observed characteristics, that a patient will have HB, using a logistic regression. HB patients were then matched with replacement to LB patients, and vice-versa, based on the propensity score, balancing the sample in terms of observed characteristics across cohorts. This provides two sets of outcomes for each patient (one observed and one imputed from their match from the "opposite" cohort), allowing for the creation of two comparable cohorts, from which the difference in outcomes between HB and LB can be calculated.
- A one-to-one PS Matching model with replacement was specified, where individuals with HB and LB are matched based on their calculated PS of having HB, to estimate Average Treatment Effects (ATE) and Average Treatment Effect on the Treated (ATET). ATE is the average outcome difference if all subjects had HB compared to all participants having LB; ATET is equivalent to ATE, except it only focuses on the HB group. The base model of variables selected for PS calculations included age, BMI, annualized bleeding rate (ABR), Problem Joint number (PJn), specific comorbidities and education (university/non university).

The variable selection process was guided by clinical and statistical (assessed via univariate analysis) relationships to the PROs.

Three sensitivity analyses were conducted around the base model:

- Chronic pain was added
- Employment status was added
- ABR was removed

- Rosenbaum bounds were also used to estimate the extent to which an unobserved variable could introduce bias into the estimation. This is reported as the odds ratio an unobserved covariate would at least have to reach for the significance of the ATET to be affected.

Results

Of the 250 eligible SHA patients included:

- The proportion of patients with LB and HB varied between 20-22% and 78-80% respectively, across different outcome cohorts (Table 1)
- Cohort characteristics are reported in Table 1. Sample characteristics pre- and post-match for the EQ-5D cohort (the outcome for which substantial and statistically significant differences were found) are presented in Table 2. PS matching resulted in a more balanced sample, particularly regarding age, BMI, ABR, and PJn.

Table 1. Sample characteristics across analysis cohorts

	Cohort			
	EQ-5D	EQ-VAS	Work impairment	Activity impairment
	N=239	N=240	N=161	N=198
Age, mean (SD)	34.2 (11.4)	34.2 (11.4)	34.0 (10.8)	35.2 (11.6)
BMI, mean (SD)	27.8 (6.9)	27.8 (6.9)	27.4 (6.6)	27.8 (6.8)
ABR, mean (SD)	5.5 (6.7)	5.5 (6.7)	6.0 (6.9)	5.7 (6.6)
PJn, mean (SD)	1.4 (2.0)	1.4 (2.0)	1.3 (1.9)	1.4 (2.0)
University degree, n (%)	107 (44.8%)	107 (44.8%)	88 (54.7%)	101 (51.0%)
Employed, n (%)	188 (78.7%)	188 (78.3%)	161 (100%)	188 (95.0%)
Treatment strategy, n (%)				
Prophylaxis (HB)	190 (79.5%)	191 (79.6%)	125 (77.6%)	155 (78.3%)
On-demand (LB)	49 (20.5%)	49 (20.5%)	36 (22.4%)	43 (21.7%)
Marital status N (%)				
Single	108 (45.2%)	108 (45.0%)	67 (41.6%)	82 (41.4%)
Married/partner	115 (48.1%)	116 (48.3%)	82 (50.9%)	102 (51.5%)
Separated/divorced/widowed	16 (6.7%)	16 (6.7%)	12 (7.4%)	14 (7.1%)
Outcome of interest (depending on cohort)[a]	**0.72 (0.3)**	**74.2 (18.7)**	**23.7 (24.8)**	**26.3 (26.6)**

Abbreviations: SD, standard deviation
Notes: [a]The outcome reported is the outcome of interest for the specific cohort

- Prior to matching, the mean difference in EQ-5D index score between HB and LB was -0.034 (Table 2). The ATE and ATET of HB on EQ-5D was -0.107 and –0.101, with both differences statistically significant ($p<0.05$) relative to the LB cohort, representing a clinically meaningful difference[2] (Table 3).
- ATE was -3.55 (p=0.208) for EQ-VAS, 2.42 (p=0.666) for activity impairment and -6.13 (p=0.416) for work impairment. ATET for each of the PROs followed a very similar pattern, to ATE, with no statistically significant differences.
- The directionality of the overall work impairment, in contrast with activity impairment results implies that those who have HB experience lower overall work impairment. However due to the lack of statistical significance and large confidence intervals within each of these estimations, we cannot draw any conclusion regarding them.
- Magnitude and statistical significance of results varied in sensitivity analyses (including chronic pain or employment or removing ABR as matching variables for PS generation). In sensitivity analysis, none of the differences in the PROs between the cohorts, while maintaining similar directionality, were statistically significant.
- Rosenbaum bounds were calculated for the EQ-5D base model and confirmed robustness of results, indicating that the significant negative effect would have to be questioned if an unobserved covariate caused the odds ratio of having HB to differ between HB and LB by a factor of more than 1.4.

Table 2. Pre- and post- matching sample characteristics (EQ5D cohort)

	Pre-matching		Post-matching	
	Low burden	High burden	Low Burden	High burden
	N=49	N=190	N=239	N=239
Age, *Mean (SD)*	38.88 (13.50)	32.98 (10.52)	33.15 (13.03)	33.77(10.95)
BMI, *Mean (SD)*	29.46 (8.72)	27.33 (6.32)	27.45 (6.95)	27.91 (6.50)
ABR, *Mean (SD)*	7.10 (7.58)	5.13 (6.42)	4.96 (5.79)	5.79 (7.00)
PJn, *Mean (SD)*	1.06 (1.61)	1.43 (2.08)	1.04 (1.50)	1.39 (2.09)
University degree, n (%)	20 (40.8%)	87 (45.8%)	118 (49.4%)	101 (42.3%)
Comorbidities, *n (%)*				
Anxiety	13 (26.5%)	35 (18.4%)	35 (14.6%)	47 (19.7%)
Depression	11 (22.4%)	33 (17.4%)	23 (9.6%)	44 (18.4%)
Osteoarthritis	8 (16.3%)	51 (26.8%)	38 (15.9%)	60 (25.1%)
Osteoporosis	2 (4.1%)	5 (2.6%)	5 (2.1%)	5 (2.1%)
Type 2 diabetes	4 (8.2)	5 (2.6)	13 (5.4)	13 (5.4)
HIV	5 (10.2)	20 (10.5)	25 (10.5)	25 (10.5)
EQ-5D-5L[a], *Mean (SD)*	0.75 (0.25)	0.71 (0.31)	-	-

Abbreviations: SD, standard deviation
Notes: [a]A relevant stratification could only be reported for the pre-matched sample. The difference post-match is presented in Table 3 as ATE and ATET.

Table 3. Effect of HB on PROs after PS matching

	Cohort			
	Coefficient (SE)	P	95% CI	N
ATE EQ-5D	**-0.11 (0.05)**	**0.02**	**-0.20, -0.02**	**239**
ATET EQ-5D	**-0.10 (0.05)**	**0.03**	**-0.19, -0.01**	**239**
ATE VAS	-3.55 (2.82)	0.21	-9.09, 1.98	240
ATET VAS	-3.58 (2.97)	0.23	-9.41, 2.25	240
ATE Activity impairment	2.42 (5.61)	0.67	-8.58, 13.43	198
ATET Activity impairment	1.94 (6.29)	0.76	-10.40, 14.27	198
ATE Work impairment	-6.13 (7.53)	0.42	-20.90, 8.63	161
ATET Work impairment	-9.49 (8.82)	0.28	-26.78, 7.79	161

Abbreviations: SD, standard deviation
Notes: Both ATE and ATET represent the difference in the outcome with LB as the control group and HB as the treatment group. A negative coefficient signifies a lower value of the PRO for the HB cohort compared with the LB cohort.

Limitations

This exploratory analysis used retrospectively collected, self-reported data has some limitations:

- Bias may be present if unobserved variables influence the probability of having HB and the descriptive nature of PSM does not allow to explore causality or individual variable effects.
- A degree of selection bias cannot be excluded due to the voluntary nature of the CHESS US+ study.
- Generic measures were used to measure health-related quality of life (HRQoL), which may not be sensitive enough to accurately capture differences in this specific population.

Conclusions

- The results of this analysis suggests that routine prophylactic infusions may be associated with reduced quality of life after controlling for key clinical parameters, though the impact on activity and work productivity is unclear.
- Though the study highlighted a likely impact of prophylaxis on HRQoL when compared to a less burdensome treatment approach, variability in the impact of treatment burden between PROs and the inherent limitations of the statistical technique employed
- Additional research is warranted to investigate causal relationships, particularly in light of the advent of novel therapies with less frequent administration.

References

1. O'Hara, S. *et al*. Haemophilia 2021;27, 113–119. **2.** Coretti, S., Ruggeri, M. & McNamee, P. Expert Rev. Pharmacoeconomics Outcomes Res. 2014;14, 221-233

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