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Real-world clinical and patient-centric outcomes in people with haemophilia A in Italy: Findings from the CHESS II study

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Background

- Haemophilia A (HA; factor VIII [FVIII] deficiency), characterised by prolonged trauma-related and/or spontaneous intra-articular bleeding events, is associated with adverse impacts on physical functioning and health-related quality of life (HRQoL).[1]
- Little research currently exists on the clinical complications associated with HA in Italy and studies are limited to people with either moderate or severe HA.[2,3] Moreover, very few studies have assessed the HRQoL of people with HA (PWHA) in Italy.[4,5]
- This analysis describes variation in clinical and patient-centric outcomes for a cohort of mild (>5-40% normal FVIII activity), moderate (1-5%) and severe (<1%) PWHA in Italy, using real-world data.

Methods

- Data for PWHA living in Italy with no active inhibitor at the time of study capture were extracted from "Cost of Haemophilia in Europe: A Socioeconomic Survey – II" (CHESS II), a burden of illness study of adults with HA and haemophilia B in Europe. An interim dataset with study capture period Nov 2018 – Jul 2019 was used for this analysis.
- Patient demographics and clinical and patient-centric outcomes were assessed in total and stratified by baseline endogenous FVIII (mild, moderate, severe).
- Clinical outcomes of interest were as follows:
  - *FVIII replacement:* Strategies categorized as follows:
    - Patients on **Primary** treatment regimens (prophylaxis or on demand) were defined as managing their HA with the same regimen from diagnosis, with no switch (of prophylaxis to on demand or vice-versa).
    - Patients on **Secondary** regimens at some stage switched to an alternative regimen (prophylaxis to on demand or vice versa).
  - *Annual bleed rate (ABR):* Physician-report, based on the 12 months prior to study capture.
  - *Target joints:* Joints in which three or more spontaneous bleeds had occurred within a consecutive 6-month period prior to study capture.[6]
  - *'Problem joints':* Joints exhibiting symptoms of HA-related damage: chronic synovitis; arthropathy; reduced range of motion; recurrent bleeding.[7]
  - *Hospital admissions:* For joint procedures and/or bleeding events in the 12 months prior to study capture.
  - *Chronic pain:* Physician-report of the patient's level of chronic pain relating to their HA ('None', 'Mild', 'Moderate', 'Severe'), based on functional deficit and use of analgesics.
- HRQoL was captured in a subset of patients via the EQ-5D-5L. Respondents select from five levels of impairment (ranging from "no problems" in performing a particular activity to "extreme problems/being completely unable") across five dimensions of health (mobility, self-care, usual activities, pain/discomfort, anxiety/depression).[8]
- EQ-5D-5L responses were converted to a single 0–1 index score using the Italian-specific EuroQoL value set, with 0 representing a state "equivalent to death" and 1 representing "perfect health".[9]
- Outcomes by condition severity were compared using descriptive statistics (mean ± standard deviation [SD] or freq. [n; %]).
- Study methodology and interpretation of results were informed by a representative [AL] from the Italian Federation of Haemophilia Associations (FedEmo) patients' organisation.

Results

- Two hundred and thirty-two patients were included in the analysis (mild n=34, moderate n=76, severe n=122), with mean age 39.2 years (range mild [36.6] – moderate [41.4]). Body mass index (BMI) was similar across subgroups (mean 24.4) (**Table 1**).
- Similar levels of full-time employment were reported in patients with mild [47%] and moderate [43%] condition; this decreased to 26% for patients with severe condition (**Table 1**).
- FVIII replacement was used by less than one-third of patients with mild and moderate HA; a mixture of prophylaxis and on-demand regimens were used by subjects with severe HA (**Table 1**).
- A small number of individuals had a current diagnosis of HIV and HCV, the majority of those being in patients with severe HA (2% and 6% of patients, respectively) (**Table 1**).
- Frequency of HA-related complications increased with condition severity: ABR (mild [mean 1.06] – severe [3.94]), reporting of moderate or severe chronic pain (mild [3%] – severe [44%]) and prevalence of target joints (mild [0.12] – severe [0.75]) and problem joints (mild [0.15] – severe [1.02]) (**Table 2 / Figs 1, 2 & 3**).
- Twelve-month admissions for bleeding events were similar for moderate [1.05] and severe [0.94] subgroups (**Table 2 / Fig 4**).

Table 1. Cohort demographics and characteristics by HA severity

	Severity subgroup			Total (n=232)
	Mild (n=34)	Moderate (n=76)	Severe (n=122)	
Age (mean ± SD)	36.6 ± 12.0	41.4 ± 14.0	38.5 ± 13.5	39.2 ± 13.5
BMI score (mean ± SD)	24.7 ± 2.4	24.5 ± 2.8	24.3 ± 2.5	24.4 ± 2.6
BMI >25 (n [% of patients])	16 [47%]	29 [38%]	48 [39%]	93 [40%]
Employment status (n [% of patients])				
Employed full time	16 [47%]	40 [53%]	32 [26%]	88 [16%]
Employed part-time	2 [6%]	9 [12%]	19 [16%]	30 [22%]
Self-employed	9 [26%]	8 [11%]	26 [21%]	43 [30%]
Unemployed	1 [3%]	4 [5%]	11 [9%]	16 [4%]
Student	4 [12%]	10 [13%]	21 [17%]	35 [10%]
Other	2 [6%]	5 [7%]	13 [11%]	20 [9%]
Treatment strategy (n [% of patients])				
Receiving FVIII replacement	10 [29%]	21 [28%]	122 [100%]	153 [66%]
Primary on-demand	9 [90%]	16 [76%]	47 [39%]	72 [47%]
Primary prophylaxis	0 [-]	0 [-]	22 [18%]	22 [14%]
Secondary on-demand	1 [10%]	5 [24%]	5 [4%]	11 [7%]
Secondary prophylaxis	0 [-]	0 [-]	48 [39%]	48 [31%]
Coinfection (n [% of patients])				
HIV	0 [-]	1 [1%]	3 [2%]	4 [2%]
HCV	0 [-]	2 [3%]	7 [6%]	9 [4%]

Abbreviations: BMI, body mass index; HIV, human immunodeficiency virus; HCV, hepatitis C virus; SD, standard deviation.

- Joint procedure-related hospital admissions were reported with double the frequency in the moderate [0.55] vs severe [0.24] subgroup (**Table 2 / Fig 4**).
- EQ-5D-5L index scores deteriorated with condition severity (mild [0.94] – severe [0.78]) (**Table 2**).

Table 2. Clinical and patient-centric outcomes by HA severity

	Severity subgroup			Total (n=232)
	Mild (n=34)	Moderate (n=76)	Severe (n=122)	
ABR (mean ± SD)	1.06 ± 0.89	2.91 ± 2.80	3.94 ± 3.17	3.18 ± 2.99
Target joints (mean ± SD)	0.12 ± 0.33	0.30 ± 0.65	0.75 ± 0.85	0.51 ± 0.77
Problem joints (mean ± SD)	0.15 ± 0.44	0.70 ± 0.82	1.02 ± 1.04	0.79 ± 0.95
Hospital admissions (mean ± SD)				
Bleeding event related	0.06 ± 0.24	1.05 ± 1.06	0.94 ± 1.09	0.85 ± 1.05
Joint procedure	0.00 ± 0.00	0.55 ± 2.47	0.24 ± 0.76	0.31 ± 1.52
Chronic pain (n [% of patients])				
No pain	22 [65%]	21 [28%]	13 [11%]	56 [24%]
Mild pain	11 [32%]	39 [51%]	55 [45%]	105 [45%]
Moderate pain	1 [3%]	16 [21%]	40 [33%]	57 [25%]
Severe pain	0 [-]	0 [-]	14 [11%]	14 [6%]
EQ-5D-5L (sample (n); mean ± SD)	19; 0.94 ± 0.07	24; 0.81 ± 0.12	63; 0.78 ± 0.20	106; 0.82 ± 0.17

Abbreviations: ABR, annual bleed rate; SD, standard deviation.

Fig 1. ABR by HA severity

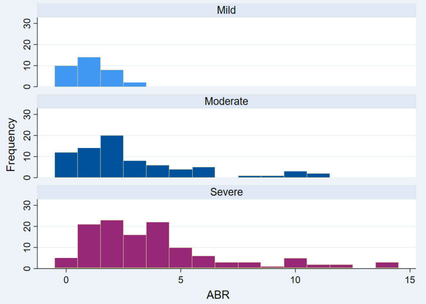


Fig 2. Target joints by HA severity

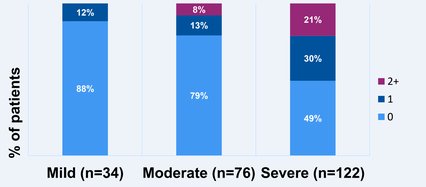


Fig 3. Problem joints by HA severity

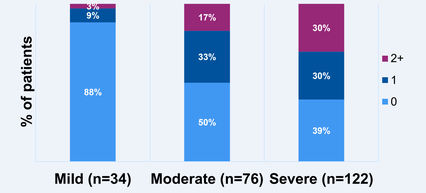
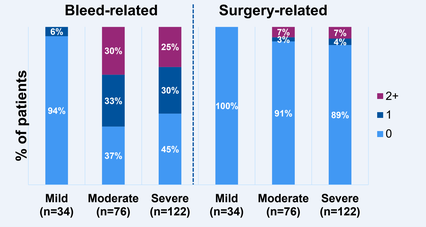


Fig 4. Hospital admissions by HA severity



Highlights from the community perspective

Italian Federation of Haemophilia Associations (FedEmo)

- *The findings of this analysis, and in particular the findings for patients with moderate haemophilia A, highlight the importance of recent changes to the scientific community perspective ensuring proactive clinical management of patients with moderate haemophilia A.*
- *There is now greater recognition of joint disease in patients in their 30s with moderate haemophilia A, and so management is starting at a younger age.*
- *Further useful research using this data could explore in greater depth the clinical management and outcomes, as well as life experiences, of patients with mild, moderate, and severe haemophilia A in Italy.*

Conclusions

- Clinical and patient-centric outcomes considered in this study progressively worsened with increasing condition severity, with the exception of hospital admission outcomes.
- The CHESS II study enrolled a large cohort of people with haemophilia A in Italy and provides an important resource for exploring differences in clinical outcomes and QoL across condition severity.
- Further study of the comparative clinical management, outcomes, and life experiences of subjects with mild, moderate, and severe haemophilia A in Italy should help validate and provide further insight into the trends observed in this study.
- Future research should focus on the incidence of joint disease and associated burden in patients with moderate condition, as well as outcomes associated with the newer therapies for haemophilia A available in Italy subsequent to this analysis.

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