



Real-world treatment, clinical outcomes and healthcare resource utilization among persons with hemophilia A by age

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Aim: Examine real-world characteristics, treatment patterns, and outcomes among treated persons with hemophilia A (PwHA) stratified by age. **Patients & methods:** This study utilized US claims data from 1 January 2007–31 July 2018 from the Humana Research Database. Unadjusted comparisons were conducted across PwHA (<18, 18–55, 56–89 years) enrolled in commercial or Medicare Advantage Prescription Drug plans. **Results:** A total of 294 PwHA were identified; 21.1% experienced ≥ 1 bleeding event, and 41.2 and 53.1% had evidence of arthropathy or related disorders, and pain, respectively. Along with all-cause and hemophilia-related healthcare resource utilization (HCRU), these were highest among PwHA aged 56–89 years. **Conclusion:** Insights into treatment, outcomes and HCRU may identify opportunities for enhanced disease management, particularly in older PwHA.

Tweetable abstract: New study from Caplan, *et al.* examines real-world treatment characteristics, treatment patterns and outcomes in treated persons with hemophilia A, including older persons aged 56–89 years.

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Congenital hemophilia A is an inherited bleeding disorder, mostly affecting males, resulting in insufficient endogenous production of clotting factor VIII (FVIII). In USA, approximately 20,000 individuals are thought to be living with hemophilia [1]. While no cure exists for hemophilia A, several treatments are available.

The mainstay hemophilia A treatment is intravenous concentrated FVIII, either as an on-demand regimen for acute bleeds or prophylaxis for bleeding prevention. Other nonfactor treatments may include desmopressin, emicizumab or bypassing agents. Persons with hemophilia A (PwHA), particularly those with exposure to FVIII replacement, are at risk of developing an antibody, called an inhibitor, which then renders FVIII treatment ineffective. Inhibitors are estimated to develop in approximately one in five patients [2].

Overall life expectancy for PwHA, particularly for those with mild or moderate disease without viral infections (e.g., HIV or hepatitis C), is now nearly equivalent to those without hemophilia A in high-income countries, due to improved management and treatment [3–5]. As with the general aging population, PwHA will also develop comorbidities, such as joint disease, cardiovascular disease, renal disease, pain, cancer and viral infections, with these conditions developing at earlier ages than the general population, which can complicate disease management [6,7].

Currently, there is a paucity of published literature describing aging PwHA. Evaluating characteristics and outcomes among PwHA in a cohort inclusive of patients enrolled in Medicare could help further understand this growing population. The objective of this study was to examine real-world patient characteristics, treatment patterns, and outcomes among treated PwHA, stratified by age.

Materials & methods

This retrospective study used data from 1 January 2007 to 31 July 2018. Data sources included member enrollment, medical, pharmacy, and laboratory data from Humana Inc., a US-based company that provides national Medicare Advantage and commercial plan offerings. Additionally, Humana's Clinical Guidance Exchange platform, a case tracking system and data mart for Humana's clinical operations and other non-claims clinical data, was used as a source.

Patient identification criteria

Patients had to meet one of the following criteria for inclusion from 1 January 2007–31 July 2017, modified from Lyons, *et al.* [8]: ≥ 1 medical or pharmacy claim for FVIII therapy, factor eight inhibitor bypassing agent, or recombinant factor VIIa therapy (Appendix A) AND ≥ 1 diagnosis of congenital hemophilia A (Appendix B); ≥ 1 medical or pharmacy claim for FVIII/von Willebrand complex therapy (Appendix A) AND no diagnoses of von Willebrand's disease (Appendix B) AND ≥ 1 diagnosis of congenital hemophilia A or ≥ 1 medical or pharmacy claim for desmopressin (Appendix A) AND ≥ 1 diagnosis of congenital hemophilia A (Appendix B). Patients >90 years of age, and those with ≥ 2 medical claims for another coagulation disorder (both claims had to be for the same disorder) were excluded (Appendix C). The index date was the date of first treatment observed after meeting the identification criteria. Patients were required to have continuous post-index enrollment for at least 12 months of follow-up.

Treatments

Pharmacy and medical claims over a 12-month period were used to classify each patient's FVIII regimen type as either prophylactic or on-demand. The expected lower limit (LL) for continuous prophylaxis dosing was defined by the 25th percentile of body weight by sex and age from the National Health and Nutrition Examination Survey [9], the estimated low end of continuous prophylaxis dose range (25 international units [IU]/kg), and the recommended dosing frequency (times three per week for 45 weeks per year [12 months] [10]) denoted by the following equation:

$$\text{Expected Monthly LL} = \frac{\text{kg} \times 25 \frac{\text{IU}}{\text{kg}} \times 3 \text{ times} \times 45 \text{ weeks}}{12 \text{ months}}$$

Patient-specific per-month FVIII dosing was determined by summing the total FVIII quantity dispensed (IU) from each claim observed during the 12-month period. The calculated monthly average dose was compared with the expected monthly LL to classify the treatment pattern as consistent with prophylactic (including standard and extended half-life FVIII products) or on-demand therapy. If the calculated monthly FVIII dosing was $< \text{LL}$, it was classified as 'on-demand'. If dosing was $\geq \text{LL}$, the patient was designated as utilizing 'prophylactic' therapy.

Patients with evidence of inhibitors were excluded from classification by prophylaxis or on-demand treatment type and were classified separately. Use of desmopressin was also measured.

Clinical outcomes

Hemophilia-related bleeding events were identified using ICD-9 and ICD-10 codes corresponding to bleeds in joints and muscles (hemarthrosis) and associated sequelae (hematoma), and other less common acute bleeds, including intracranial, neck/throat and gastrointestinal hemorrhages (Appendix B). Bleeding-related claims were grouped by body part and assumed to belong to the same event if they occurred within 7 days of each other. Bleeding events occurring in different body parts were considered separate events if the claims were observed on different days [11].

Joint health and related medical conditions (arthropathy, osteoarthritis, physical therapy, difficulty walking, osteoporosis and stiff joints) and joint procedures/surgery (synovectomy, arthrodesis, osteotomy, excision of joint, arthroscopy and arthroplasty) were examined (Appendices B and E). Patients with ≥ 1 fracture code on a medical claim were identified (Appendix F). Pain was assessed via diagnosis codes, including general pain or joint-related pain, or prescription claims for pain medications and anti-inflammatories (Appendix B).

Healthcare resource utilization

All-cause and hemophilia-related inpatient hospitalizations, emergency department (ED) visits, physician office visits, and outpatient visits were measured. Hemophilia-related encounters were defined as a diagnosis of

congenital hemophilia A (ICD-9: 286.0; ICD-10: D66) in any diagnosis position for ED visits, physician office visits, or outpatient visits. For inpatient hospitalizations, encounters were defined as a diagnosis of hemophilia A in the primary position or a diagnosis of a hemophilia-related bleeding event in the primary position and a diagnosis of hemophilia A in any other position.

Patients were identified as receiving care at a hemophilia treatment center (HTC) if: ≥ 1 medical claim was associated with a provider listed as an essential community provider [12] serving predominately low-income, medically underserved individuals under the HTC category; ≥ 1 medical claim was associated with an HTC address (based on either full address match or 5-digit zip code) listed in the CDC HTC Directory [13] or if there was evidence of care at an HTC based on supplementary data.

Additional characteristics

The age, sex, geographic location and population density of patients were described. Plan type was determined from enrollment data and included patients in Medicare Advantage Prescription Drug or commercial plans as of the index date.

Elixhauser comorbidity index score [14–16], RxRisk-V score [17], hepatitis C (Appendix B) and frailty/disability were measured [18]. Hemophilia severity was determined by documentation in supplementary data or from factor level documented in lab results (Appendix D). Patients were classified, based on the minimum FVIII lab value, as mild (5% to $<40\%$ normal clotting activity or 0.05–0.40 IU/ml), moderate (1–5% normal clotting activity or 0.01–0.05 IU/ml) or severe ($<1\%$ normal clotting activity or <0.01 IU/ml) [10].

Statistical analysis

Demographic, clinical characteristics and outcomes were analyzed descriptively. Categorical variables were summarized as counts and percentages. Continuous variables were summarized using mean, standard deviation, median, interquartile range, minimum and maximum. Unadjusted comparisons among age subgroups were assessed with chi-square for categorical variables and Analysis of Variance or Kruskal–Wallis tests for continuous variables. Note that cell sizes less than ten were suppressed in order to protect study subjects from potential re-identification and privacy considerations. Where no comparisons could be made due to ≥ 1 cell being suppressed, p-values were removed (nonapplicable; n/a). All analyses were conducted using SAS version 9.4 (SAS Institute, NC, USA). The study protocol was approved by Advarra, an independent institutional review board.

Results

Demographics & patient characteristics

A total of 294 patients were identified based on the inclusion and exclusion criteria (Figure 1). Demographic characteristics are summarized in Table 1. The mean age of the overall cohort was 33.8 years (standard deviation ± 20.7). The majority of the patients in the study ($n = 176$, 59.9%) were 18–55 years of age and 95.6% of the cohort was male.

Selected clinical characteristics are summarized in Table 2. The most common comorbidities overall were arthritis and hepatitis C, with prevalence increasing with age.

Severity could be assessed in 57 (19.4%) patients. Among those whose severity was available, 50.9% were mild, with 65.5% ≤ 55 and 34.5% 56–89 years old. The number of individuals classified in each age group as moderate or severe was small (specific cell counts are masked as required by privacy policies).

Treatments

Treatment data are reported in Table 3. There were <10 patients identified as having inhibitors based on treatments or laboratory results. Overall, 29.9% ($n = 88$) of patients were identified as utilizing prophylaxis and 61% ($n = 179$) were identified as utilizing on-demand FVIII treatment, not including those with evidence of inhibitors. Prophylaxis use was highest among patients aged <18 years (44.8%); however, approximately one-quarter of patients ≥ 18 also received prophylaxis. On-demand and desmopressin use were more common among the 18–55 and 56–89 years age groups.

Clinical outcomes

A total of 21.1% patients experienced ≥ 1 bleeding event. There were statistically significant differences in the proportion of patients with bleeding events (<18 years 28.4%, 18–55 years 14.8% and 56–89 years 33.3%;

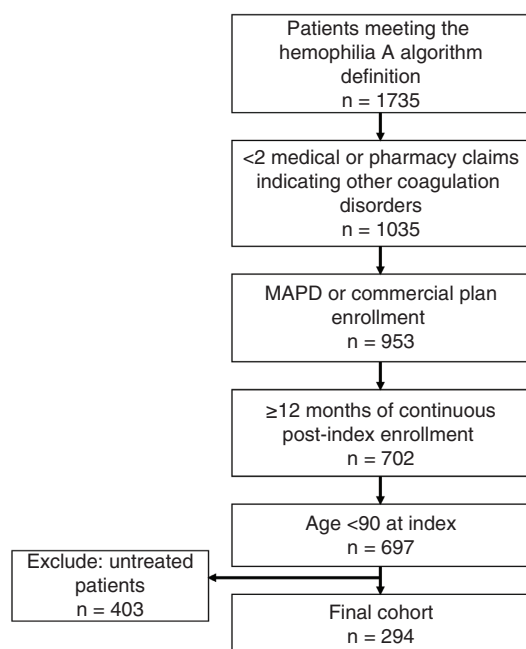


Figure 1. Patient identification.
MAPD: Medicare advantage prescription drug.

Table 1. Demographic characteristics overall and by age group.

Baseline demographics	Overall (N = 294)	<18 (n = 67)	18–55 (n = 176)	56–89 (n = 51)	p-value [†]
Age					
Mean (SD)	33.8 (20.7)	9.7 (4.8)	33.1 (10.9)	68.3 (8.8)	<0.001
Median (IQR)	29 (18–48)	10 (6–14)	31 (24–42)	68 (61–73)	<0.001
Minimum, maximum	0, 88	0, 17	18, 55	56, 88	
Sex, n (%)					
Male	281 (95.6)	66 (98.5)	167 (94.9)	48 (94.1)	0.403
US region, n (%)					
Northeast	<10	<10	<10	<10	0.456
Midwest	74 (25.2)	22 (32.8)	42 (23.9)	10 (19.6)	
South	195 (66.3)	39 (58.2)	121 (68.8)	35 (68.6)	
West	<30	<10	<20	<10	
Population density, n (%) [‡]					
Urban	218 (74.1)	47 (70.1)	136 (77.3)	35 (68.6)	0.272
Suburban	54 (18.4)	17 (25.4)	26 (14.8)	11 (21.6)	
Rural	<20	<10	<20	<10	
Missing	<10	<10	<10	<10	
Plan type, n (%)					
MAPD	76 (25.9)	0 (0.0)	34 (19.3)	42 (82.4)	<0.001
Commercial	218 (74.1)	67 (100.0)	151 (66.5) [§]		
Cell sizes less than ten were suppressed in order to protect study subjects from potential re-identification and privacy considerations. Where no comparisons could be made due to one or more cells being suppressed, p-values were removed (i.e., non applicable).					
[†] p-value is for comparison across age groups. Chi-square was used for categorical variables and ANOVA or Kruskal–Wallis for continuous variables.					
[‡] Analysis was restricted to patients with a known value (i.e., excluded ‘missing’).					
[§] Combined groups due to n <10 in at least one adjacent cell.					
ANOVA: Analysis of Variance; IQR: Interquartile range; MAPD: Medicare advantage prescription drug; NA: Non applicable; SD: Standard deviation.					

p = 0.004) (Figure 2). Arthropathy or related disorders and pain were evidenced in 41.2 and 53.1% of patients, and generally increased with age. Fractures occurred in 8.2% of patients, fewer than ten patients overall had osteoporosis, osteopenia, difficulty walking, or stiff joints, and only 12 patients had indication of any joint procedures or surgery.

Table 2. Clinical characteristics overall and by age group.

Clinical characteristics	Overall (N = 294)	<18 (n = 67)	18–55 (n = 176)	56–89 (n = 51)	p-value [†]
Elixhauser comorbidity index					
Mean (SD)	1.8 (2.0)	0.9 (0.5)	1.7 (1.7)	3.7 (2.7)	<0.001
Median (IQR)	1 (1–2)	1 (1–1)	1 (1–2)	3 (2–5)	<0.001
Minimum, maximum	0, 12	0, 2	0, 10	0, 12	
Elixhauser comorbidities, n (%)					
Cardiac arrhythmia	12 (4.1)	0 (0.0)		12 (5.3) [‡]	<0.001
Hypertension (uncomplicated)	54 (18.4)	0 (0.0)	20 (11.4)	34 (66.7)	<0.001
COPD	20 (6.8)	0 (0.0)		20 (8.8) [‡]	<0.001
Diabetes (uncomplicated)	18 (6.1)	0 (0.0)	<10	<10	NA
Liver failure	29 (9.9)	0 (0.0)		29 (12.8) [‡]	0.004
HIV/AIDS	27 (9.2)	<10	21 (11.9)	<10	NA
Coagulopathy	244 (83.0)	57 (85.1)	143 (81.3)	44 (86.3)	0.615
Depression	26 (8.8)	<10	17 (9.7)	<10	NA
RxRisk score					
Mean (SD)	2.2 (2.7)	0.5 (0.8)	2.3 (2.7)	4.3 (3.1)	<0.001
Median (IQR)	1 (0–4)	0 (0–1)	1 (0–4)	5 (2–7)	<0.001
Minimum, maximum	0, 15	0, 3	0, 15	0, 13	
Hepatitis C, n (%)	57 (19.4)	0 (0.0)	43 (24.4)	14 (27.5)	<0.001
Frailty					
Mean (SD)	1.0 (1.5)	0.5 (0.7)	0.8 (1.2)	2.1 (2.3)	<0.001
Median (IQR)	1 (0–1)	0 (0–1)	0 (0–1)	1 (1–3)	<0.001
Minimum, maximum	0, 10	0, 3	0, 8	0, 10	
Frailty comorbidities, n (%)					
Arthritis	116 (39.5)	18 (26.9)	69 (39.2)	29 (56.9)	0.004
Heart failure	10 (3.4)	0 (0.0)	<10	<10	NA
Sepsis	15 (5.1)	<10	<10	<10	NA
Psychiatric	34 (11.6)	<10	24 (13.6)	<10	NA
Difficulty walking	16 (5.4)	0 (0.0)	<10	<10	NA
Stroke	18 (6.1)	<10	<10	<10	NA
Weakness	14 (4.8)	<10	<10	<10	NA
Ambulance [§]	18 (6.1)	<10	12 (6.8)	<10	NA

Cell sizes less than 10 were suppressed in order to protect study subjects from potential re-identification and privacy considerations. Where no comparisons could be made due to one or more cells being suppressed, p-values were removed (i.e., NA).

[†]p-value is for comparison across age groups. Chi-square was used for categorical variables and ANOVA or Kruskal–Wallis for continuous variables.

[‡]Combined groups due to n <10 in at least one adjacent cell.

[§]Study subject utilized ambulance services.

ANOVA: Analysis of Variance; COPD: Chronic obstructive pulmonary disease; IQR: Interquartile range; NA: Non applicable; SD: Standard deviation.

HCRU

A total of 15.0 and 34.4% of patients had ≥ 1 all-cause inpatient admission and ED visit during follow-up, respectively (Table 4). Generally, as age increased, measures of healthcare resource utilization (HCRU) increased and were highest for the 56–89 years age group; however, all-cause and hemophilia-related ED visits, and hemophilia-related physician office visits were similar across groups. HTC use was greatest in the 18–55 years age group.

Discussion

This analysis identified 294 PwHA from 2007 to 2017, 17.3% of whom were 56–89 years of age. These older PwHA had higher comorbidity burden, including hepatitis C and hemophilia-related comorbidities than the other age groups. The majority of these patients utilized on-demand FVIII treatment, and this group had the highest proportion of patients with bleeding events, as well as incurring the highest HCRU across a majority of utilization categories.

Table 3. Hemophilia A treatments overall and by age group.

12-month postindex treatments	Overall (N = 294)	<18 (n = 67)	18–55 (n = 176)	56–89 (n = 51)	p-value [†]
Treatments, n (%)					
Prophylaxis	88 (29.9)	30 (44.8)	58 (25.6) [‡]		<0.001
On-demand	179 (60.9)	33 (49.3)	111 (63.1)	35 (68.6)	0.066
Evidence of inhibitors	<10	<10	<10	<10	NA
Desmopressin	34 (11.6)	21 (8.6) [‡]		13 (25.5)	0.002
Number of FVIII claims (separate service dates)					
Mean (SD)	7.1 (9.2)	10.1 (15.2)	7.2 (6.4)	2.8 (3.5)	<0.001
Median (IQR)	6 (2–11)	10 (2–13)	6 (2–11)	2 (1–4)	<0.001
Minimum, maximum	0, 124	0, 124	0, 57	0, 15	

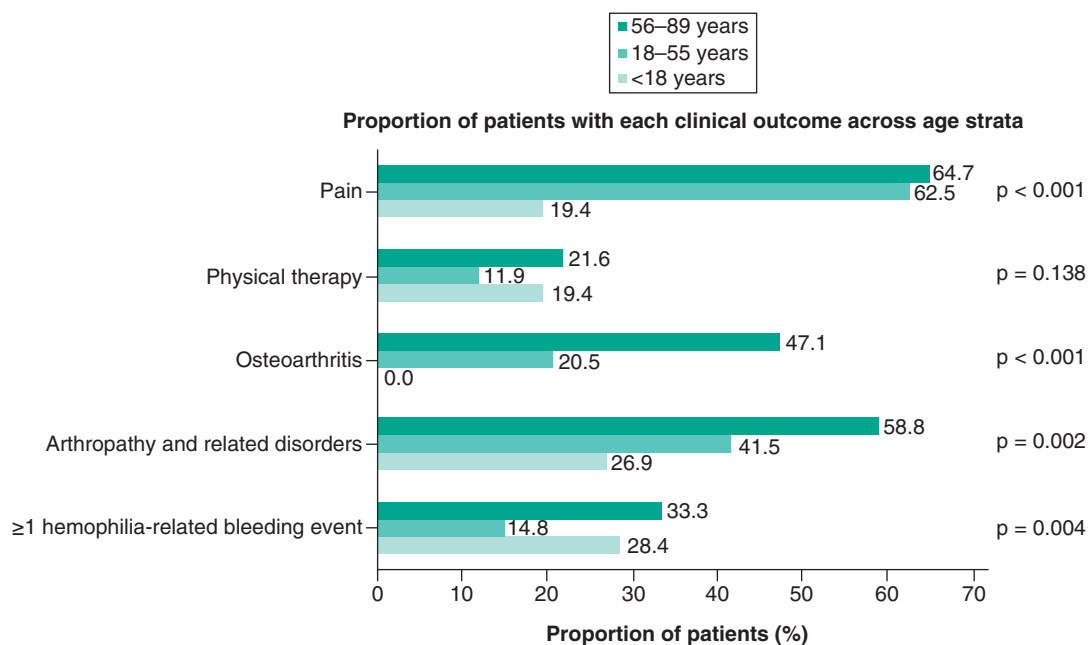
Cell sizes less than ten were suppressed in order to protect study subjects from potential re-identification and privacy considerations. Where no comparisons could be made due to one or more cells being suppressed, p-values were removed (i.e., NA). When <10 patients overall had the outcome of interest, it was not reported in the table but described in the results.

[†]p-value is for comparison across age groups. Chi-square was used for categorical variables and ANOVA or

[‡]Kruskal–Wallis for continuous variables.

Combined groups due to n <10 in at least one adjacent cell.

ANOVA: Analysis of Variance; FVIII: Factor VIII; IQR: Interquartile range; NA: Non applicable; SD: Standard deviation.

**Figure 2. Clinical outcomes* by age categories.**

*Fractures, joint procedures/surgery, osteoporosis, osteopenia, difficulty walking or stiff joints are not included in this figure due to sample sizes <10 overall or in one or more age strata.

p-value is from omnibus chi-square test for comparison across all age groups.

The cohort of patients included in this study represents an older age distribution of PwHA compared with those enrolled in the CDC Registry or included in the HTC Population Profile [19]. For example, 51% of patients in the CDC Registry were <20 years of age, versus only 22.8% <18 years of age in the current study [19]. While a small number of patients overall were ≥65 in the current study (~10%), even fewer were reported in the CDC HTC Population Profile or Registry (4 and 5%, respectively [19]).

The relatively small proportion of older PwHA in the general population may be due to several factors. Many died or had a shortened lifespan due to contracting HIV or hepatitis C in the 1970s/1980s from blood-based infusions (e.g., plasma, factor) [20], and patients with more severe disease may have died due to bleeds before prophylaxis was established as standard of care in the US in the mid-1990s [20]. Approximately 25% of patients in this study were

Table 4. Healthcare resource utilization overall and by age group.

12-month post-index HCRU	Overall (N = 294)	<18 (n = 67)	18–55 (n = 176)	56–89 (n = 51)	p-value [†]
HCRU					
All-cause inpatient hospitalizations (at least one), n (%)	44 (15.0)	25 (10.3) [‡]	19 (37.3)		<0.001
Hemophilia-related inpatient hospitalizations (at least one), n (%)	12 (4.1)	<10	<10	<10	NA
All-cause ED visits (at least one), n (%)	101 (34.4)	18 (26.9)	60 (34.1)	23 (45.1)	0.118
Hemophilia-related ED visits (at least one), n (%)	83 (28.2)	17 (25.4)	48 (27.3)	18 (35.3)	0.448
Number of all-cause physician office visits					
Mean (SD)	6.7 (8.0)	5.1 (4.4)	5.8 (7.1)	12.3 (11.4)	<0.001
Median (IQR)	4 (2–9)	4 (2–7)	3 (1–8)	8 (4–16)	<0.001
Minimum, maximum	0, 45	0, 18	0, 45	0, 45	
Number of hemophilia-related physician office visits					
Mean (SD)	1.5 (1.8)	1.7 (2.3)	1.3 (1.5)	1.8 (2.1)	0.058
Median (IQR)	1 (0–2)	1 (0–2)	1 (0–2)	1 (0–3)	0.355
Minimum, maximum	0, 13	0, 13	0, 9	0, 7	
Number of all-cause outpatient visits, overall					
Mean (SD)	8.9 (9.8)	6.9 (5.6)	7.8 (9.0)	15.6 (13.4)	<0.001
Median (IQR)	5.5 (2–12)	5 (3–9)	4 (2–10)	11 (8–21)	<0.001
Minimum, maximum	0, 67	1, 24	0, 49	1, 67	
Number of hemophilia-related outpatient visits					
Mean (SD)	2.5 (2.7)	2.9 (2.9)	2.1 (2.4)	3.5 (3.2)	0.003
Median (IQR)	2 (1–3)	2 (1–3)	1 (1–3)	3 (1–5)	0.002
Minimum, maximum	0, 16	0, 16	0, 12	0, 15	
Hematologist visits					
Mean (SD)	1.8 (2.6)	2.1 (3.6)	1.5 (2.1)	2.4 (2.5)	0.055
Median (IQR)	1 (0–2)	1 (0–2)	1 (0–2)	2 (0–4)	0.037
Minimum, maximum	0, 18	0, 18	0, 13	0, 12	
HTC utilization, yes, n (%)	173 (58.8)	33 (49.3)	116 (65.9)	24 (47.1)	0.011

Cell sizes less than ten were suppressed in order to protect study subjects from potential re-identification and privacy considerations. Where no comparisons could be made due to one or more cells being suppressed, p-values were removed (i.e., NA).

[†] p-value is for comparison across age groups. Chi-square was used for categorical variables and ANOVA or Kruskal–Wallis for continuous variables.

[‡] Combined groups due to n <10 in at least one adjacent cell.

ANOVA: Analysis of Variance; ED: Emergency department; HCRU: Healthcare resource utilization; HTC: Hemophilia treatment center; IQR: Interquartile range; NA: Non applicable; SD: Standard deviation.

enrolled in an Medicare Advantage Prescription Drug plan due to either age or disability, representing a group that may otherwise be excluded from studies conducted only in commercial health plan populations. As PwHA age, the management of multimorbidity and polypharmacy in this population will challenge providers, necessitating a collaborative team approach to delivery of effective care for these patients [5–7].

Identifying prophylaxis use via claims is challenging given assumptions that must be made regarding dosing. While not yet validated, this methodology provides an alternative approach to identification, which may benefit from further assessment. Approximately 30% of patients were classified as having evidence of receiving a prophylaxis regimen. This is lower than the rate of prophylaxis observed in a surveillance study of PwHA, which identified approximately 59% in 2010 [21]. The highest proportion of prophylaxis was seen among patients ≤19 years of age (75%) and the lowest (~20%) in patients 50–69 years of age [21]; a similar trend was seen in the current study where the highest proportion of prophylaxis use was among those <18 and lowest among those 56–89 years of age. Differences in the proportion of patients utilizing prophylaxis may reflect the demographic makeup of the study cohort. Patients in the surveillance study were on average 17.7 years of age with 64.2% ≤19 years versus an average age of 33.8 years with 77.2% ≥18 years in the current study. Shrestha *et al.* also reported that a lower proportion of patients aged 45–64 years had ever been on prophylaxis (27.0%) compared with younger age groups [11], possibly due to past fears of hepatitis C and HIV contamination with factor infusions in the 1980s [5]. The use of claims-based measures to classify treatment type may also impact these estimates, given the assumptions necessary for the calculations of prophylaxis versus nonprophylaxis therapy. Desmopressin utilization was highest

among those patients 56–89 years (25.5%) compared with the younger populations. This could be related to severity of disease, with a greater proportion of older patients potentially having nonsevere (i.e., mild or moderate) hemophilia A [19,22], where desmopressin use is most commonly indicated [10].

The 56–89 years age group had the highest proportion of patients with ≥ 1 hemophilia-related bleeding event. While the absolute number of patients was small ($n = 17$), and results need to be interpreted with caution, these older patients may be at risk for bleeding due to other conditions or medications regardless of their hemophilia severity. This age group also had the highest proportion of patients with arthropathy and related disorders as well as osteoarthritis, though it was not determined if these were hemophilia-related. In Shrestha *et al.*, the 45–64 years age group had the highest proportion of individuals who ever experienced hemophilia-related joint problems (64.86%), compared with younger adults 19–44 years (45.88%) or children 6–18 years (12.23%) [11]. While primary prophylaxis is recommended to prevent hemophilia-related joint disease [10], there has been evidence that secondary and tertiary prophylaxis may still be beneficial for reduction of bleeding events and improved joint health [23]. It is unclear if the higher proportion of patients with joint conditions in the older population is due to aging or other conditions, or if the lower prophylaxis use may be a contributing factor.

Severity was only identified in approximately 20% of patients, given the limitations of the data sources, with 50.9% identified as mild. It has been cited that up to 60% of PwHA may suffer from the severe form of the disease [24]. A claims-based analysis with supplemental electronic medical records data reported 41.9% of PwHA without inhibitors had the severe form of the disease, 12.3% moderate, and 45.8% mild; however, the median age of those patients was 6 years old [25]. The severe form of the disease is often recognized early in life and the mostly adult population in the current study may have included more patients with less severe forms of the disease, similar to what has been reported in registries ($\sim 60\%$) [19,22]. In addition, this study did not include patients covered by Medicaid, which may include younger individuals and those with more severe hemophilia A.

Across age groups, there was higher all-cause HCRU for older patients. These patients had a greater number of comorbidities, which may require additional management, and the high burden in this population warrants further study of how current treatments can improve their condition. The overall proportion of patients who were identified as receiving care from an HTC was 58.8% versus 70–80% as reported by the CDC registry [19,22]. Patients in the HTC registry were younger and may have greater severity of disease requiring more intensive and specialized care, which may explain the overall rate of HTC utilization in addition to the limitations of HTC utilization capture methods in claims data.

Limitations

As with most studies reporting administrative claims data, limitations include inaccurate claims coding and the absence of certain relevant information in the database, such as disease severity and body weight. While this study also used data available from clinical reviews and prior authorization requests, these data are not available for all patients and often exist for specific reasons (medication authorization, pre-operative reviews). Further, Medicaid patients were not included in the study due to limitations of the data; thus, our results may not be representative of this population. The algorithm used for hemophilia identification has not been validated, thus may have not included everyone with hemophilia and may have included patients who have other bleeding disorders, despite the exclusions applied. Additionally, this study did not impose a requirement for continuous pre-index enrollment without evidence of treatment, and this was a descriptive study that did not control for unmeasured confounding (e.g., patient disease severity).

Limitations to this study also include several assumptions that had to be made for the algorithm for prophylaxis treatment. Thus, the proportion of patients on prophylaxis may have been under- or over-estimated. Additionally, it was neither possible to identify when patients first initiated prophylaxis, nor to clearly identify if patients were receiving immune tolerance induction, although patients with inhibitors were identified to the extent possible. Not all encounters with an HTC may have been captured using the methods described, thus potentially underestimating the proportion receiving care in those centers. Hemophilia severity was identified either from claims or supplemental sources in only 57 (19.4%) patients. Without a validated claims-based proxy for severity, outcomes based on this important clinical factor were not able to be measured or controlled. Bleeding events may have been underestimated as minor bleeding occurrences (e.g., nose bleeds) may be managed at home.

Conclusion

PwHA represent a medically complex group of individuals who incur substantial HCRU. Treatment patterns, clinical outcomes, and utilization vary across different ages of this population. Insights on shifts in outcomes and HCRU as PwHA age may identify opportunities for enhanced management of older patients with this condition.

Summary points

- Understanding characteristics of persons with hemophilia A (PwHA) across age categories is critical to informing appropriate management strategies.
- Currently, there is a paucity of published literature describing the older population of PwHA.
- In this retrospective study, the US administrative claims data from 1 January 2007 to 31 July 2018 from the Humana Research Database were utilized and unadjusted comparisons on characteristics, clinical outcomes and healthcare resource utilization (HCRU) were conducted in PwHA across age groups (<18, 18–55, 56–89 years).
- Among the 294 PwHA identified, 22.8, 59.8 and 17.3% were <18, 18–55 and 56–89 years old, respectively.
- The most common comorbidities were arthritis and hepatitis C.
- Overall, 29.9% of PwHA had evidence of prophylactic treatment, of whom 44.8% were <18 years old.
- A total of 21.1% of patients overall experienced ≥ 1 bleeding event, and 41.2 and 53.1% had evidence of arthropathy or related disorders, and pain, respectively; along with all-cause and hemophilia-related HCRU, these were all highest among PwHA aged 56–89 years.
- This study is subject to limitations inherent to an administrative claims database study, including lack of clinical information such as disease severity and body weight.
- As PwHA live longer, insights into differences in treatment, outcomes, and HCRU may identify opportunities for enhanced disease management.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/suppl/10.2217/cer-2021-0109

Author contributions

All authors contributed to the study design and data interpretation. RW DeClue and TF Shaffer analyzed the data. EO Caplan and BT Suehs drafted the manuscript, with critical review and revisions from all authors. All authors approve the final version to be published and agree to be accountable for all aspects of the work.

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Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval from the independent review board Advarra. Informed consent was not required due to the nature of this study.

Data sharing statement

The code listings used can be found in the appendices.

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