Can German Health Insurance Claims Data Fill Information Gaps in Rare Chronic Diseases: Use Case of Haemophilia A

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Abstract

Claims data are increasingly discussed to evaluate health care for rare diseases (resource consumption, outcomes and costs). Using haemophilia A (HA) as a use case, this analysis aimed to generate evidence for the aforementioned information using German Statutory Health Insurance (SHI) claims data. Claims data (2017–2019) from the German SHI 'AOK Bayern - Die Gesundheitskasse' were used. Patients with ICD-10-GM codes D66 and HA medication were included in descriptive analyses. Severity levels were categorized according to HA medication consumption. In total, 257 patients were identified: mild HA, 104 patients (mean age: 40.0 years; SD: 22.9); moderate HA, 17 patients, (51.2 years; SD: 24.5); severe HA, 128 patients, (34.2 years; SD: 18.5). There were eight patients categorized with inhibitors (37.8 years; SD: 29.6). Psychotherapy was reported among 28.8% (mild) to 32.8% (severe) of patients. Joint disease was documented for 46.2% (mild) to 61.7% (severe) of patients. Mean direct costs per patient per year were 1.34× for mild, 11× for moderate, 81× higher for severe HA patients and 223× higher for inhibitor patients than the mean annual expenditure per AOK Bayern insurant (2019). German SHI data provide comprehensive information. The patient burden in HA is significant with respect to joint disease and psychological stress regardless of the HA severity level. The cost of HA care for patients is high. Large cost ranges suggest that the individual situation of a patient must be considered when interpreting costs. The main limitation of SHI data analysis for HA was the lack of granularity of ICD codes.

Keywords

- haemophilia A
- claims data
- health economics
- rare disease

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Zusammenfassung

Abrechnungsdaten werden zunehmend diskutiert, um die Gesundheitsversorgung bei seltenen Erkrankungen (Ressourcenverbrauch, Outcomes und Kosten) zu evaluieren. Ziel dieser Analyse war es, am Beispiel der Hämophilie A (HA) anhand von Abrechnungsdaten der gesetzlichen Krankenversicherung (GKV) Evidenz für die oben genannten Informationen zu generieren.

Verwendet wurden Abrechnungsdaten (2017 bis 2019) der AOK Bayern - Die Gesundheitskasse. In die deskriptiven Analysen wurden Patienten mit den ICD-10-GM-Codes D66 und/oder D68.31 und HA-Medikation eingeschlossen. Die Schweregrade wurden nach der Einnahme von HA-Medikation klassifiziert.

Insgesamt wurden 257 Patienten identifiziert: leichte HA, 104 Patienten (Durchschnittsalter 40,0 Jahre; SD 22,9); mittelschwere HA, 17 Patienten (51,2 Jahre; SD 24,5); schwere HA, 128 Patienten (34,2 Jahre; SD 18,5). Es gab 8 Patienten, die mit Inhibitoren kategorisiert wurden (37,8 Jahre; SD 29,6). Eine Psychotherapie wurde bei 28,8% (leicht) bis 32,8% (schwer) der Patienten dokumentiert. Eine Gelenkerkrankung wurde bei 46,2% (leicht) bis 61,7% (schwer) der Patienten dokumentiert. Die durchschnittlichen direkten Kosten/Patient/Jahr lagen bei Patienten mit leichter HA um das 1,34-fache, bei Patienten mit mittelschwerer HA um das 11-fache, bei Patienten mit schwerer HA um das 81-fache und bei Patienten mit Inhibitoren um das 223-fache über den durchschnittlichen jährlichen Ausgaben pro Versicherten der AOK Bayern (2019). Die deutschen GKV-Daten liefern umfassende Informationen. Die Belastung der Patienten durch HA ist unabhängig vom Schweregrad der HA im Hinblick auf Gelenkerkrankungen und psychische Belastung erheblich. Die Kosten der HA-Versorgung für die Patienten sind hoch. Große Kostenspannen legen nahe, dass bei der Interpretation der Kosten die individuelle Situation des Patienten berücksichtigt werden muss. Die größte Einschränkung bei der Analyse der GKV-Daten für Hämophilie A war die fehlende Granularität der ICD Codes.

Schlüsselwörter

- Hämophilie A
- Leistungsdaten
- Gesundheitsökonomie
- Seltene Krankheit

Introduction

Rare diseases affect approximately 263 to 446 million people worldwide.[1] Gene therapy and other new technologies have become available and offer great promise in treating rare diseases. To evaluate whether these new therapies are advantageous (in terms of treatment patterns, outcomes in relation to costs) compared to established standard therapies, information for the innovative treatment, and the current standard therapy is needed. Haemophilia A (HA) disease is a suitable use case for a rare chronic disease with high treatment costs. FVIII replacement therapy[2] has been the standard of care for many years. Since 2017, a series of innovative therapies, such as gene therapies, bispecific antibodies, and substances with prolonged half-lives, have been licenced or are nearly ready for market launch.[3]

Congenital HA is a rare hereditary X-linked blood clotting disorder. A mutation in the FVIII gene coding for coagulation factor VIII (FVIII) results in impaired haemostasis.[4] Depending on the residual activity of the clotting factor, which is determined by the respective mutation, different degrees of haemophilia are distinguished: severe (<1%), moderate (1% to ≤5%), and mild (>5 to 40%).[5] In Germany, approximately 6,000 to 7,000 patients are affected by haemophilia, of whom approximately 3,000 to 4,000 require permanent treatment.[6,7] The main clinical symptom is recurrent joint bleeding, particularly in the ankle, knee, and elbow joints, which can lead to long-term joint damage and even complete loss of function and disability.

Treatment of HA is 90% dependent on factor VIII replacement. As the therapy has to be adapted to the individual patient, the costs of therapy can vary greatly, ranging from €46,879 to nearly €281,274 (U.S. study, exchange rate 07.03.2023) annually, depending on disease severity.[8] Costs also depend on therapy regimens, as prophylaxis costs are approximately four times higher than those of on-demand therapy.[9] In Germany, the economic burden of direct costs for severe HA is estimated to be 79 times higher than the mean per capita health expenditure.[10] The increasing costs for innovative therapies such as bispecific monoclonal antibodies or gene therapies[11,12] raise questions about the value of innovative treatments compared to standard treatments for decisions on health care resource allocation. Basic updated information for treatment patterns, outcomes, costs of HA, and HA-specific comorbidities stratified by age and severity is a necessary basis for value assessment of innovative therapies. To describe these aspects fully, cross-sectoral information on the care-associated resource consumption,

outcomes, and costs of as many patients as possible is needed. For many other diseases, secondary data have already been increasingly used to meet the information needs mentioned earlier. A major advantage of secondary data is the chance to obtain access data from larger populations more quickly compared to prospective observational studies. Especially in the case of a rare disease such as HA, observational studies are time-consuming, and the logistical effort for these studies is huge. Secondary data sources such as registries cannot be used, as the national German register of haemophilia patients does not contain comorbidity variables such as joint and cardiovascular disease (CVD).[13] Clinical medical records include only inpatient health services, and the dataset of the Association of Statutory Health Insurance Physicians (Kassenärztliche Vereinigung, KV) solely covers outpatient services. Only the claims data from the health insurance funds contain cross-sectoral information on inpatient and outpatient care of a patient.

For Germany, there is currently no updated evidence on treatment pathways, resource use and costs, severity, age, or comorbidities for patients with HA inhibitors. The aim of the analysis is to generate this evidence using statutory health insurance claims data and to investigate whether this data source contains all necessary information for additional evidence on the use case of HA beyond clinical trials of rare diseases.

Methods

Study Design

A retrospective analysis of anonymised claims data from the statutory health insurance 'AOK Bayern - Die Gesundheitskasse'[14] was performed. The observation period was from 2017 to 2019. An application (including guarantee of confidentiality Art. 32 EU-DSGVO) in accordance with § 75 Transmission of Social Data for Research was submitted, and approval was obtained from the highest state authority (Bavarian State Ministry for Health and Care). The analysis of the German Statutory Health Insurance (SHI) claims data was in accordance with the guidelines of STandardized Reporting Of Secondary data Analyses (STROSA).[15]

Study Cohort

Inclusion criteria were male of any age, ≥350 days per year with AOK Bayern, and a confirmed ICD-10-GM diagnosis of D66 (hereditary factor VIII deficiency). The inclusion criterion was as follows: patients who received HA-specific medication, including at least one prescription of HA medication (FVIII concentrates, bypassing agents, emicizumab, desmopressin or tranexamic acid) between 2017 and 2019.

Severity Level and Inhibitory Antibodies

As there is no ICD coding for different degrees of haemophilia severity, the severity of haemophilia was estimated using the highest annual consumption of HA-specific medication during the study period. The following thresholds were based on data from the German Haemophilia Registry and expert knowledge:

- Severe: ≥90,000 IU/year of FVIII concentrates or at least one prescription of emicizumab between March and December 2019.
- Moderate: ≥40,000 to <90,000 IU/year of FVIII concentrates.
- Mild: <40,000 IU/year of FVIII concentrates or at least one prescription of desmopressin/tranexamic acid without FVIII use.

Categorisation of severe HA and additionally having one of the following criteria was defined to indicate the presence of inhibitory antibodies:

- Administration/prescription of bypassing agents.
- At least one prescription of emicizumab between February 2018 and February 2019.
- Additional ICD-10-GM D68.31 (haemorrhagic disorder due to factor VIII antibodies).

Treatment Patterns

Treatment patterns were determined by inpatient visits, hospital length of stay (LOS), hospital emergency admissions, outpatient physician visits, diagnostic procedures (laboratory tests and ultrasound), joint surgeries (arthroscopic and arthroplastic surgery), pain therapy, psychotherapy, outpatient physiotherapy, and the quantity of administered/prescribed medication for HA and comorbidities (human immunodeficiency virus [HIV]/hepatitis B virus [HBV]/hepatitis C virus [HCV]) medication, analgesics, antidepressants).

Resource Consumption and Costs

Resource consumption and direct costs in the inpatient and outpatient medical sectors were determined based on the number of medical services if HA or HA-related ICD-GM-10 codes, such as bleedings, HIV, HBV, HCV, depression, joint diseases, or CVDs, were used. Medical services with no link to the diagnoses were excluded.

- *Resource consumption*: Resource consumption considered the following categories—inpatient visits, hospital LOS, hospital emergency admissions, outpatient physician visits, diagnostic procedures (laboratory tests and ultrasound), joint surgeries (arthroscopic and arthroplastic surgery), pain therapy, psychotherapy, outpatient physiotherapy, and the quantity of administered/prescribed medication for HA and comorbidities. Inpatient and outpatient medical services were merged in the analysis.
- *Direct costs*: Direct costs could be identified for the following categories—costs for inpatient medical care and costs for outpatient medical care (medication, total outpatient physician visits per treatment case, diagnostics, joint surgeries, psychotherapy, pain therapy, and physiotherapy). Inpatient costs per inpatient visit, including all services provided except additional fees, could be calculated using G-DRG data by multiplying the basic DRG value by the relative weight. The costs of physician medical services per treatment case were included based on

the accounting data from AOK Bayern. For subgroups, costs such as diagnostic procedures, joint surgeries, pain therapy, and psychotherapy were calculated on the basis of reimbursement rates of the EBM catalogue for the relevant calendar quarter. The costs of outpatient medication prescriptions were determined using the mean price per defined daily doses for SHIs in Germany. Outpatient physiotherapy costs were calculated on the basis of the mean cost per treatment unit of the 'AOK-Bundesverband' in the calendar year the service was provided.

Statistical Analysis

Descriptive data analysis was used. The mean, standard deviation (SD), median, minimum, and maximum were calculated for subgroups stratified by severity and age groups.

Statistical analyses were performed using R version 4.1.3 statistical software.

Results

Detailed tables on resource consumption, costs, and inhibitors stratified by age and severity can be found in the **Appendix**.

Patient Characteristics

Between 2017 and 2019, for 752 male patients, a diagnosis of D66 or D68.31 was documented. One patient was excluded due to missing year of birth. Because of missing HA medication, 494 patients were excluded. The final patient cohort consisted of 257 patients.

►Table 1 shows the baseline characteristics of the study population. Of the study cohort, 57 (22.2%) patients were children aged ≤18 years, 105 (40.9%) were adults aged ≥19 to ≤44 years, and 95 (37.0%) were ≥45 years old. Severity categorized by FVIII consumption showed 104 (40.5%) patients with mild HA, 17 (6.6%) with moderate HA, and 128 (49.8%) with severe HA. There were eight inhibitor patients (3%). Bleeding was documented in 18 patients (7.0%) during the study period. The most common documented comorbidities were joint disease ($n = 142$, 55.3%) and depression ($n = 56$, 21.8%). CVDs were documented for 10 (3.9%) patients.

Resource Consumption

A total of 113 (44.0%) patients had an inpatient visit during the analysed period. The mean length of hospital stays ranged from 4.0 days in severe patients to 9.7 days in inhibitor patients (see ►Table 2). Outpatient visits were

Table 1 Baseline characteristics of the study population

	Mild ($N = 104$)	Moderate ($N = 17$)	Severe ($N = 128$)	Inhibitor ($N = 8$)	Total ($N = 257$)
Mean-age, years (SD)	40.0 (22.9)	51.2 (24.5)	34.2 (18.5)	37.8 (29.6)	37.8 (21.5)
Age groups, *n* (%)					
Children ≥ 0 to ≤ 18 y	25 (24.0)	<5	27 (21.1)	<5	57 (22.2)
Adults ≥ 19 to ≤ 44 y	35 (33.7)	<5	65 (50.8)	<5	105 (40.9)
Adults ≥ 45 y	44 (42.3)	12 (70.6)	36 (28.1)	<5	95 (37.0)
Bleedings					
n (%)	<5	<5	12 (9.4)	0 (0.0)	18 (7.0)
Mean (SD)	NA	NA	1.1 (1.6)	NA	0.87 (1.3)
Median [min; max]	NA	NA	0.33 [0.33, 5.7]	NA	0.33 [0.33; 5.7]
HIV, *n* (%)	<5	<5	17 (13.3)	<5	20 (7.8)
HBV, *n* (%)	10 (9.6)	<5	34 (26.6)	<5	50 (19.5)
HCV, *n* (%)	<5	<5	12 (9.4)	<5	15 (5.8)
Depression, *n* (%)	28 (26.9)	3 (17.6)	23 (18.0)	<5	56 (21.8)
Joint disease, *n* (%)	48 (46.2)	9 (52.9)	79 (61.7)	6 (75.0)	142 (55.3)
Haemophilic arthropathy	7 (6.7)	<5	35 (27.3)	<5	47 (18.3)
Osteoarthritis	31 (29.8)	6 (35.3)	51 (39.8)	<5	92 (35.8)
Joint arthroplasty	10 (9.6)	2 (11.8)	14 (10.9)	<5	28 (10.9)
Other joint disease	28 (26.9)	5 (29.4)	49 (38.3)	<5	85 (33.1)
Cardiovascular disease, *n* (%)	5 (4.8)	<5	<5	<5	10 (3.9)
Care level, *n* (%)	13 (12.5)	<5	10 (7.8)	<5	28 (10.9)

Abbreviations: HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; min, minimum; max, maximum; *n*, number; SD, standard deviation.
Note: Results are not given for $n < 5$ due to data protection reasons.

Table 2 Total mean resource consumption and medical services per year stratified by severity level

	Mild ($N = 104$)	Moderate ($N = 17$)	Severe ($N = 128$)	Inhibitor ($N = 8$)
Factor replacement therapy (IU)				
n (%)	69 (66.3)	17 (100.0)	128 (100.0)	8 (100.0)
Mean (SD)	3,572 (4,740)	32,113 (14,671)	220,481 (115,589)	1,325,729 (1,337,429)
Median [min; max]	1.667 [167; 26,667]	26,667 [13,333; 56,000]	199,833 [35,000; 531,667]	878,377 [350,595; 4,353,355]
Emicizumab (DDD)				
n (%)	0 (0.0)	0 (0.0)	<5	7 (87.5)
Mean (SD)	NA	NA	NA	120 (106)
Median [min, max]	NA	NA	NA	80 [28; 332]
Antidepressants (DDD)				
n (%)	15 (14.4)	<5	12 (9.4)	0 (0.0)
Mean (SD)	133 (205)	NA	195 (191)	NA
Median [min, max]	27 [2.7; 610]	NA	123 [2.2; 502]	NA
Analgesics (DDD)				
n (%)	77 (74.0)	12 (70.6)	90 (70.3)	8 (100.0)
Mean (SD)	58 (142)	206 (347)	92 (201)	183 (310)
Median [min; max]	16 [0.56; 1,007]	28 [7.2; 1,159]	23 [1.1; 1,687]	54 [6.2; 934]
Hospital LOS days				
n (%)	41 (39.4)	11 (64.7)	48 (37.5)	5 (62.5)
Mean (SD)	8.7 (14)	8.4 (7.9)	4.0 (5.3)	9.7 (11)
Median [min; max]	2.3 [0.33; 73]	5.0 [0.33; 24]	1.7 [0.33; 23]	4.7 [0.67; 26]
Hospital emergency admissions				
n (%)	28 (26.9)	8 (47.1)	26 (20.3)	<5
Mean (SD)	0.52 (0.31)	1.1 (0.85)	0.60 (0.38)	NA
Median [min; max]	0.33 [0.33; 1.3]	0.67 [0.33; 2.7]	0.50 [0.33; 1.7]	NA
Outpatient physician visits				
n (%)	101 (97.1)	17 (100.0)	125 (97.7)	8 (100.0)
Mean (SD)	10 (13)	18 (23)	13 (12)	19 (9.3)
Median [min; max]	5.3 [0.33; 78]	13 [0.33; 98]	8.7 [0.33; 62]	20 [7.7; 35]
Joint surgeries				
n (%)	6 (5.8)	<5	9 (7.0)	0 (0.0)
Mean (SD)	0.39 (0.14)	NA	0.37 (0.11)	NA
Median [min; max]	0.33 [0.33; 0.67]	NA	0.33 [0.33; 0.67]	NA
Psychotherapy				
n (%)	30 (28.8)	6 (35.3)	42 (32.8)	<5
Mean (SD)	5.2 (15)	3.1 (3.2)	2.7 (4.0)	NA
Median [min; max]	0.67 [0.33; 79]	1.8 [0.33; 7.5]	0.67 [0.33; 18]	NA
Physiotherapy				
n (%)	20 (19.2)	<5	48 (37.5)	6 (75.0)
Mean (SD)	7.6 (15)	NA	30 (64)	38 (33)
Median [min; max]	2.3 [0.33; 58]	NA	7.8 [0.67: 377]	24 [2.0; 81]

Abbreviations: n = total number during study period of 3 years; mean and median = per year; results are not given for $n < 5$ for data protection reasons; min, minimum; max, maximum; SD, standard deviation; DDD, defined daily dose; IU, international unit; LOS, length of stay.

documented for 251 (97.7%) patients with a mean of 10 visits/year for mild HA, 18 visits/year for moderate HA, 13 visits/year for severe HA, and 19 visits/year for inhibitory HA. Ultrasound diagnostics were billed for 46 (17.9%) patients, and laboratory diagnostics were performed on 129 (50.2%) patients. Overall, 77 (30.0%) received outpatient physiotherapy. Psychotherapy was prescribed in 81 (31.5%) patients. Of these 30 had mild haemophilia, 6 had moderate haemophilia, 42 had severe haemophilia, and less than 5 had inhibitory haemophilia. The age structure regardless of the severity level shows that 13 (21.0%) patients who received psychotherapy were 18 years or younger, 31 (38.3%) were between 19 and 44 years, and 37 (45.7%) were 45 years and older (see **Appendix**).

Direct Costs

The total mean annual costs per severe HA-categorised patient were 264,666 € (SD: 141,302; median: 238,311; see ►**Fig. 1** and ►**Table 3**). In children with severe HA, the mean annual cost per patient was 210,267 € (SD: 88,801), the mean annual cost per adult patient (19 to ≤ 44 years) with severe HA was 292,925 € (SD: 152,276), and in adults (≥ 45 years) with severe HA, it was 254,440 € (SD: 142,537). In patients with moderate HA, the mean annual total costs were 36,122 € (SD: 24,891), with the most expensive age group being adults (19 to ≤ 44 years) with 50,724€ (SD 29,386). Mild HA patients' mean annual total costs were 4.371€ (SD: 7.514), whereas adults (≥ 45 years) were the most expensive with 5,123€ (SD: 8,906). HA medication costs accounted for 99.7% in severe HA patients, 90.5% in moderate HA patients, and 46.1% in mild HA patients. Inpatient mean annual costs were 4,715€ (SD: 8,939) in mild HA patients, 4,292€ (SD: 3,970) in moderate HA patients, and 2,317€ (SD: 2,521) in severe HA patients.

Inhibitor Patients

Bypassing FVIII medication mean ($n \leq 5$) consumption was 574,417 IU/year (SD: 715,548), and bypassing FVIIa mean ($n = 8$) consumption was 901,333 IU/year (SD: 1,346,377). The mean total costs were 725,441 €/patient/year (SD: 697,275; see ►**Fig. 1**). HA medication covered 99.3% (720,274 € [SD: 697,962]) of mean annual total costs. The mean inpatient costs were 3,642 €/patient/year (SD 3,600), and the mean outpatient medical services were 639 €/-patient/year (SD 408). HA medication covered 99.3% of the mean annual direct costs per patient.

Discussion

In this study, basic evidence was generated on treatment patterns in routine care and the cost of HA patients from the SHI perspective by using data from Bavarian statutory health

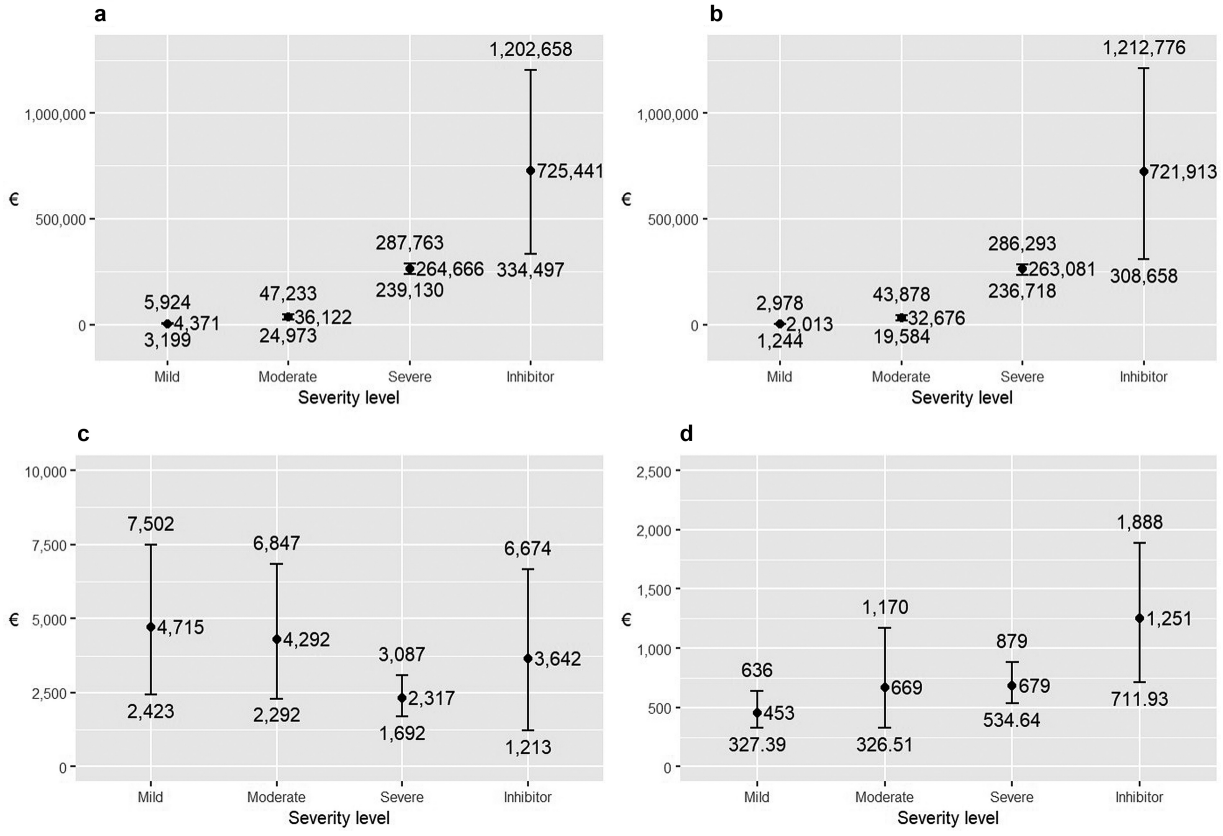

Fig. 1 Mean direct (**a**) total costs, (**b**) medication costs, (**c**) inpatient costs, and (**d**) outpatient costs (mean, 95% confidence interval) in €/patient/year for 2017 to 2019 stratified by severity level based on haemophilia A–specific medication. *N* (mild) = 104; *N* (moderate) = 17; *N* (severe) = 128; *N* (inhibitor) = 8.

Table 3 Mean direct costs (€) per year of inpatient and outpatient medical care stratified by severity levels

	Mild ($N = 104$)	Moderate ($N = 17$)	Severe ($N = 128$)	Inhibitor ($N = 8$)
Total costs				
n (%)	104 (100.0)	17 (100.0)	128 (100.0)	8 (100.0)
Mean (SD)	4,371 (7,514)	36,122 (24,891)	264,666 (141,302)	725,441 (697,275)
Median [min; max]	1,534 [23; 54,651]	34,884 [6,083; 76,493]	238,311 [2,258; 657,647]	578,301 [49,021; 2,107,897]
Inpatient costs[a]				
n (%)	42 (40.4)	11 (64.7)	50 (39.1)	5 (62.5)
Mean (SD)	4,715 (8,939)	4,292 (3,970)	2,317 (2,521)	3,642 (3,600)
Median [min; max]	1,958 [244; 52,916]	2,830 [654;13,447]	1,244 [363; 11,827]	3,710 [475; 9,386]
Outpatient costs: medication for HA				
n (%)	84 (80.8)	16 (94.1)	127 (99.2)	8 (100.0)
Mean (SD)	2,284 (4,948)	32,029 (24,187)	263,874 (139,733)	720,274 (697,962)
Median [min; max]	127 [1.6; 30,029]	31,849 [31; 71,338]	239,657 [22,286; 651,803]	574,802 [46,036; 2,107,134]
Medication for HIV, HBV, HCV, antidepressants, analgesics				
n (%)	78 (75.0)	14 (82.4)	96 (75.0)	8 (100.0)
Mean (SD)	225 (1,180)	3,073 (5,584)	1,692 (4,068)	1,639 (3,785)
Median [min; max]	17 [0.95; 10,149]	38 [4.8; 14,962]	31 [0.93; 20,173]	58 [9.0; 10,910]
Patient physician visits				
n (%)	102 (98.1)	17 (100.0)	126 (98.4)	8 (100.0)
Mean (SD)	430 (798)	657 (981)	433 (446)	639 (408)
Median [min; max]	266 [11; 7,486]	377 [9.3; 4,143]	262 [10; 2,731]	548 [197; 1,468]

Abbreviations: *n* = total number during study period of 3 years; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; mean and median = per year; min, minimum; max, maximum; SD, standard deviation.
[a]Additional fees (Zusatzentgelte) are not included. Aggregated information on additional costs for the analysed patients is as follows: 12 times > €50,000EUR and 13 times > € 100,000EUR have been charged.

insurance. To date, there is only limited current information on HA inpatient and outpatient treatment patterns, resource consumption, costs, and outcomes. HA medication covered 46.1 to 99.7% of the mean annual direct costs per patient. Depression was documented for 21.8% of patients, and over 30% of HA patients received psychotherapy. Joint disease was documented for 55.3% of patients, and 10 (3.9%) had documented CVD.

The number of HA patients with joint diseases in this cohort was higher than in the German adult male population, with a lifetime prevalence for osteoarthritis of 18.1%.[16] Of the 10 patients with CVD, 8 were 45 years and older. Therefore, the dataset contained 8.4% of older HA patients with documented CVD, which is less than the German adult male population of similar age (12.3%).[17]

According to this analysis, the mean HA-related direct costs per patient were 1.34 times higher for mild HA, 11 times higher for moderate HA, 81 times higher for severe HA, and even 223 times higher for inhibitor patients than the mean annual expenditure per insurant for health care (3,256.45€) by the AOK Bayern in 2019.[14] The total HA-specific cost per year was the highest for inhibitory patients with 725,441€ (SD: 697,275), followed by patients with severe HA, with a mean annual total cost of 246,666€ (SD: 141,302). Total costs for patients with moderate HA were 36,122€ (SD: 24,891) and 4,371€ (SD: 7,514) in mild HA patients per year. For mild and moderate HA, LOSs were longer than those for severe and inhibitor patients. One reason for this might be the age distribution in the severity groups. Mild and moderate patients had the highest proportion of patients over 45 years and the highest mean age. The mean annual inpatient costs per patient based on OPS codes for patients with mild HA were €4,715 (SD: 8,939), which was comparable to the costs for patients with moderate HA at €4,292 (SD: 3,970). For patients with severe HA, the mean annual per patient–inpatient cost based on the OPS codes was 2,317€ (SD: 2,521). It should be noted that these inpatient costs do not include additional fees ('Zusatzentgelte') for HA medication, as they were not included in the dataset. Based on the AOK side communicated aggregated information, additional fees of about € 1.9 Mio were charged for the underling cohort: 12 times > €50,000 and 13 times > €100,000. It is assumed that most of these additional fees were charged in the context for major procedures in patients with severe haemophilia. Haemophilia-associated outpatient visits and, therefore, costs did not differ

substantially between severity levels. Yet especially the higher inpatient costs for mild and moderate HA patients as well as the high number of outpatient visits suggest that probably also for services without HA association corresponding ICD codes were coded and thus appear in the results presented here.

Data on the cost of haemophilia in Germany are scarce. One study analysed haemophilia A and B across all severities and showed mean costs of €194,000,[18] whereas another study analysed patients with severe haemophilia A and B and showed mean costs of €319,000 per year per patient.[10] U.S. studies show a wide range of costs: from a median cost per year of €306,530 (exchange rate 06.03.2023) for patients with inhibitors and €92,523 for HA patients without inhibitors[19] to €383,658 to €519,048 per patient mean total annual health care costs for HA on FVIII prophylaxis.[20] In Portugal, the yearly cost per patient without inhibitors is €39,654, and it is €302,189 per patient with inhibitors.[21] This overview of the international range of costs shows that costs vary greatly with haemophilia subtype, severity level, inhibitors, and the costs for factor concentrates. The data analysis presented here shows updated evidence on treatment pathways, resource use and costs, severity, age, comorbidities, and patients with HA inhibitors, for which there were scarce data for Germany. The HA costs shown here fit well into the overall international cost range. Differences in health care systems and medication costs, especially in FVIII unit costs and dosing regimens, must be taken into account in international comparisons. The following aspects must be taken into consideration for the interpretation of haemophilia-specific outpatient and medication costs based on the German SHI claims database. The presented drug treatment costs might be slightly overestimated, as SHIs negotiate pharmacy and manufacturer discounts that are not included in the dataset.

With a market share of approximately 40% for AOK-Bayern, this group does represent a large part of the Bavarian population.[22] However, it is unclear whether the results can be extrapolated to the whole population with statutory health insurance due to the given socio-structural characteristics of AOK-Bayern insurances.[23] As the dataset was primarily generated for the purpose of billing, some information is not appropriately documented for epidemiological analyses. The first reading of the SHI data, just using ICD D66 as the filter, resulted in a far too large number of patients and a male/female distribution of almost 50/50, which does not correspond to the biology of HA. In addition, approximately 500 patients were excluded because they did not receive any HA-specific medication during the observation period of 3 years. It cannot be ruled out that the exclusion criteria may have excluded a number of mild patients who have not needed medication in 3 years. However, referring to the mean factor consumption of the Paul-Ehrlich-Institute, there should not be many patients with HA who have not received any medication in 3 years. These patient identification problems might be caused by coding deficits. However, these problems can be managed with appropriate expert knowledge of the clinical picture of the target disease and its typical treatment pathways. Therefore, in this study, only patients with a confirmed D.66 and at least one HA medication prescription were included in the analysis. Medical services were included in the analysis only if they were associated with a diagnosis of HA or an HA-associated comorbidity (indicated by corresponding ICD codes) to approximate HA costs as closely as possible. The main issue while analysing SHI data for HA was the lack of severity level classification, as there is currently no differentiated ICD coding of HA severity levels. As the phenotype and disease burden of haemophilia are strongly related to severity, this is a major limitation. One way to establish an approximate classification is to assess severity levels according to annual FVIII consumption, as done in this analysis.

This SHI data analysis showed signals such as the increased psychological stress of haemophilia patients. Depression was diagnosed in 21.8% ($n = 56$) of patients, which is considerably higher than the 12-year prevalence in the general male population of 6.1%.[24] Previous studies assessing anxiety and depression using questionnaires reported 38 to 54% of haemophilia patients with these diseases.[25] It is also interesting to note that on average, even patients with mild and moderate haemophilia (categorised by factor VIII consumption) suffer more frequently from depression than the average non-haemophilic population in Germany. This data analysis suggests that mild and moderate haemophilia patients do not consume large amounts of FVIII but require other resources and medications to a similar extent as severe haemophilia patients. Further studies have already confirmed that even patients with mild and moderate HA have more limitations in quality of life and physical and psychosocial impacts than the general population.[26,27] To generate more comprehensive evidence, additional studies should be carried out on the aforementioned points. German statutory health insurance claims data are a source of information for generating signals and answering a variety of health care–related questions. However, it is also important to carefully consider the specifics associated with claims data as described in sections 'Method' and 'Discussion'. The completion of claims data by more granular clinical data would be crucial to increase the strength of evidence based on claims data and their interpretation. It is also important to note that SHIs vary in the number of their insured patient population and the demographics of their insured individuals, including social status. Therefore, analyses based on data from multiple SHI funds would be the best approach for comprehensive evidence generation, especially when large data sets are needed to analyse even rarer diseases than HA. However, due to access hurdles to administrative and regulatory time consuming processes, the analysis of data from multiple SHIs is challenging. The need to combine information from different sources is addressed by decision-makers and health policymakers through the Gesundheitsdatennutzungsgesetz (GDNG), which was signed in December 2023. The main objective of the law is to facilitate the use of health data. Based on this law, the Health Research Data Centre 'Forschungsdatenzentrum Gesundheit (FDZ)' at the Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinprodukte, BfArM) is being further

developed. It is intended that the FDZ will be able to link pseudonymised health data from different data sources. Nonetheless, understanding the data structures and context of data from different sources remains a prerequisite for generating and interpreting reliable evidence.

Conclusion

Data analyses of SHI as shown here on the use case HA provide information on resource consumption and costs. This information can be used as baseline information for subsequent value assessments. Further signals, such as patient burden and psychological stress in mild/moderate and severe HA patients and the significant number of joint diseases in mild haemophilia patients, are underestimated. These signals should be investigated in subsequent studies. The limitations in severity coding in ICD-10-GM are fundamental in HA research based on real-world data. The introduction of individual codes for severity levels would improve the analyses considerably. As outcomes (e.g., bleedings) are rarely recorded or the association with haemophilia is not clear, more precise statements, data linkage (e.g., FDZ), or further studies (e.g., surveys) are needed.

What is known about this topic?

- Haemophilia is a rare bleeding disorder and its treatment is cost intensive. High innovative treatments have been recently (or just before) launched.
- Comprehensive information for decision-making is key.
- Real-world data from claims databases are increasingly discussed in the context of rare diseases as sources for evidence generation to describe resource consumption, costs, and outcomes. Information on how German claims data analyses can provide evidence to answer aforementioned questions for rare disease is limited.

What does this paper add?

- This paper shows that claims data are an important source to improve evidence as a basis for rational decision-making from different perspectives. Identified limitations should be taken into consideration for subsequent discussion on improvement data quality improvement and data linkage needs.
- German SHI data provide comprehensive information to determine treatment patterns, resource consumption, and outcomes. The analysis also suggests an underestimation of patient burden (documented depression, psychotherapy, treatments) in all severity groups and documented joint disease in mild haemophilia patients. Contemporary costs of real-world care for HA patients are also presented and wide ranges demonstrated the need for individualized treatment.
- Previously potentially underestimated consequences of haemophilia, such as a high burden in mild patients, could be demonstrated.

Ethical Approval and Consent to Participate

Cooperation agreement to comply with the provisions of Regulation (EU) 2016/679 (General Data Protection Regulation—'DSGVO') and that data are used only to the extent permitted by data protection law (78 SGB X).

Consent for Publication

Not applicable.

Availability of Data and Materials

Data are not publicly available but were made available to the authors via §75 SGB X proposal.

Competing Interests

U.M., K.B., V.K., V.R., A.S., and J.B. have no relevant financial or nonfinancial interests to disclose. C.B. received honoraria research grants or advisory boards: Bayer, Biotest, CSL Behring, NovoNordisk, Pfizer, Roche/Chugai, Sanofi, SOBI, Takeda. C.B. is co-principal investigator of the German Pediatric Hemophilia Research Database which is or was supported with research grants by most companies in the field of haemophilia. R.K. received honoraria, research grants, or advisory boards: Bayer, BioMarin, Biotest, CSL Behring, Grifols, NovoNordisk, Octapharma, Pfizer, Roche/Chugai, Sanofi, SOBI, and Takeda.

Authors' Contributions

All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by V.K., V.R. The first draft of the manuscript was written by V.K., and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Conflict of Interest

RK: Grants or contracts from any entity: Bayer, BioMarin, Biotest, CSL Behring, Grifols, NovoNordisk, Octapharma, Pfizer, Roche/Chugai, Sanofi, SOBI, Takeda; Participation on a Data Safety Monitoring Board or Advisory Board: Bayer, BioMarin, Biotest, CSL Behring, Grifols, NovoNordisk, Octapharma, Pfizer, Roche/Chugai, Sanofi, SOBI, Takeda.
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Appendix 1: Total mean resource consumption, medical services per year, mean direct costs (€) per year of inpatient and outpatient medical care stratified by severity levels and age

	Mild				Moderate				Severe				Inhibitor[a]
	Children ≥ 0 to ≤ 18 years	Adults ≥ 19 to ≤ 44 years	Adults ≥ 45 years	Total	Children ≥ 0 to ≤ 18 years	Adults ≥ 19 to ≤ 44 years	Adults ≥ 45 years	Total	Children ≥ 0 to ≤ 18 years	Adults ≥ 19 to ≤ 44 years	Adults ≥ 45 years	Total	Total
	(*N* = 25)	(*N* = 35)	(*N* = 44)	(*N* = 104)	(*N* = 3)	(*N* = 2)	(*N* = 12)	(*N* = 17)	(*N* = 27)	(*N* = 65)	(*N* = 36)	(*N* = 128)	(*N* = 8)
Factor replacement therapy (IU)													
n (%)	12 (48.0)	22 (62.9)	<5	69 (66.3)	<5	<5	12 (100.0)	17 (100.0)	27 (100.0)	65 (100.0)	36 (100.0)	128 (100.0)	8 (100.0)
Mean (SD)	6,153 (8,228)	3,742 (4,273)	NA	3,572 (4,740)	NA	NA	31,292 (15,095)	32,113 (14,671)	174,526 (75,061)	247,679 (127,235)	205,840 (107,097)	220,481 (115,589)	1,325,729 (1,337,429)
Median [Min, Max]	3,583 [167, 26,667]	2,417 [167, 19,000]	NA	1,667 [167, 26,667]	NA	NA	26,083 [13,333, 56,000]	26,667 [13,333, 56,000]	166,000 [45,167, 371,667]	238,000 [55,000, 516,667]	196,042 [35,000, 531,667]	199,833 [35,000, 531,667]	878,377 [350,595, 4,353,355]
Emicizumab (DDD)													
n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	<5	0 (0.0)	<5	<5	7 (87.5)
Mean (SD)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	120 (106)
Median [Min, Max]	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	80 [28, 332]
Desmopressin (DDD)													
n (%)	<5	NA	<5	10 (9.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	<5	<5	0 (0.0)
Mean (SD)	NA	NA	NA	4.7 (2.3)	NA	NA	NA	NA	NA	NA	NA	NA	NA
Median [Min, Max]	NA	<5	NA	4.2 [1.7, 8.3]	NA	NA	NA	NA	NA	NA	NA	NA	NA
Tranexamic acid (DDD)													
n (%)	17 (68.0)	18 (51.4)	15 (34.1)	50 (48.1)	0 (0.0)	0 (0.0)	5 (41.7)	5 (29.4)	9 (33.3)	17 (26.2)	8 (22.2)	34 (26.6)	<5
Mean (SD)	4.7 (3.8)	5.3 (3.1)	5.1 (6.0)	5.1 (4.3)	NA	NA	7.0 (5.9)	7.0 (5.9)	4.8 (3.5)	5.9 (6.3)	7.2 (5.8)	5.9 (5.5)	NA
Median [Min, Max]	4.2 [0.83, 12]	4.6 [0.83, 13]	4.2 [0.42, 25]	4.2 [0.42, 25]	NA	NA	4.2 [1.7, 17]	4.2 [1.7, 17]	4.2 [0.83, 13]	4.2 [0.42, 27]	5.0 [1.7, 17]	4.2 [0.42, 27]	NA
HIV/HBV/HVC medication (DDD)													
n (%)	0 (0.0)	0 (0.0)	<5	<5	0 (0.0)	0 (0.0)	<5	<5	0 (0.0)	<5	13 (36.1)	16 (12.5)	<5
Mean (SD)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	320 (195)	329 (175)	NA
Median [Min, Max]	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	370 [28, 660]	370 [28, 660]	NA
Antidepressants (DDD)													
n (%)	0 (0.0)	6 (17.1)	9 (20.5)	15 (14.4)	0 (0.0)	<5	<5	<5	0 (0.0)	8 (12.3)	<5	12 (9.4)	0 (0.0)
Mean (SD)	NA	50 (84)	188 (246)	133 (205)	NA	NA	NA	NA	NA	136 (162)	NA	195 (191)	NA
Median [Min, Max]	NA	19 [6.0, 222]	74 [2.7, 610]	27 [2.7, 610]	NA	NA	NA	NA	NA	75 [2.2, 467]	NA	123 [2.2, 502]	NA
Analgesics (DDD)													
n (%)	16 (64.0)	25 (71.4)	36 (81.8)	77 (74.0)	<5	0 (0.0)	11 (91.7)	12 (70.6)	22 (81.5)	39 (60.0)	29 (80.6)	90 (70.3)	8 (100.0)
Mean (SD)	9.0 (7.4)	21 (29)	105 (197)	58 (142)	NA	NA	223 (359)	206 (347)	9.9 (8.0)	112 (276)	128 (134)	92 (201)	183 (310)
Median [Min, Max]	4.8 [1.7, 24]	11 [0.56, 130]	33 [1.7, 1,007]	16 [0.56, 1,007]	22 [22, 22]	NA	29 [7.2, 1,159]	28 [7.2, 1,159]	5.8 [2.2, 27]	19 [1.1, 1,687]	75 [2.2, 404]	23 [1.1, 1,687]	54 [6.2, 934]

(*Continued*)

Appendix 1: (*Continued*)

	Mild				Moderate				Severe				Inhibitor[a]
	Children ≥ 0 to ≤ 18 years	Adults ≥ 19 to ≤ 44 years	Adults ≥ 45 years	Total	Children ≥ 0 to ≤ 18 years	Adults ≥ 19 to ≤ 44 years	Adults ≥ 45 years	Total	Children ≥ 0 to ≤ 18 years	Adults ≥ 19 to ≤ 44 years	Adults ≥ 45 years	Total	Total
	(*N* = 25)	(*N* = 35)	(*N* = 44)	(*N* = 104)	(*N* = 3)	(*N* = 2)	(*N* = 12)	(*N* = 17)	(*N* = 27)	(*N* = 65)	(*N* = 36)	(*N* = 128)	(*N* = 8)
Inpatient visits													
n (%)	6 (24.0)	11 (31.4)	26 (59.1)	43 (41.3)	<5	<5	8 (66.7)	11 (64.7)	13 (48.1)	23 (35.4)	18 (50.0)	54 (42.2)	5 (62.5)
Mean (SD)	0.39 (0.14)	0.52 (0.35)	0.87 (0.58)	0.71 (0.52)	NA	NA	1.6 (1.2)	1.3 (1.1)	0.79 (0.50)	0.70 (0.44)	0.72 (0.74)	0.73 (0.56)	1.3 (1.6)
Median [Min, Max]	0.33 [0.33, 0.67]	0.33 [0.33, 1.3]	0.67 [0.33, 2.3]	0.67 [0.33, 2.3]	NA	NA	1.2 [0.33, 3.7]	0.67 [0.33, 3.7]	0.67 [0.33, 1.7]	0.67 [0.33, 2.0]	0.33 [0.33, 3.3]	0.67 [0.33, 3.3]	0.67 [0.33, 4.0]
Hospital length of stay													
n (%)	6 (24.0)	10 (28.6)	25 (56.8)	41 (39.4)	<5	<5	8 (66.7)	11 (64.7)	13 (48.1)	20 (30.8)	15 (41.7)	48 (37.5)	5 (62.5)
Mean (SD)	1.1 (0.62)	9.7 (23)	10 (11)	8.7 (14)	NA	NA	10 (8.4)	8.4 (7.9)	4.6 (6.4)	2.5 (2.1)	5.3 (7.1)	4.0 (5.3)	9.7 (11)
Median [Min, Max]	1.0 [0.33, 2.0]	1.7 [0.33, 73]	6.3 [0.67, 43]	2.3 [0.33, 73]	NA	NA	7.2 [3.3, 24]	5.0 [0.33, 24]	1.3 [0.67, 21]	1.8 [0.67, 9.3]	1.7 [0.33, 23]	1.7 [0.33, 23]	4.7 [0.67, 26]
Hospital emergency admissions													
n (%)	<5	<5	20 (45.5)	28 (26.9)	<5	0 (0.0)	6 (50.0)	8 (47.1)	9 (33.3)	9 (13.8)	8 (22.2)	26 (20.3)	<5
Mean (SD)	NA	NA	0.58 (0.34)	0.52 (0.31)	NA	NA	1.3 (0.90)	1.1 (0.85)	0.70 (0.42)	0.56 (0.24)	0.54 (0.47)	0.60 (0.38)	NA
Median [Min, Max]	NA	NA	0.33 [0.33, 1.3]	0.33 [0.33, 1.3]	NA	NA	1.0 [0.33, 2.7]	0.67 [0.33, 2.7]	0.67 [0.33, 1.7]	0.67 [0.33, 1.0]	0.33 [0.33, 1.7]	0.50 [0.33, 1.7]	NA
Outpatient physician visit													
n (%)	24 (96.0)	34 (97.1)	43 (97.7)	101 (97.1)	<5	<5	12 (100.0)	17 (100.0)	27 (100.0)	63 (96.9)	35 (97.2)	125 (97.7)	8 (100.0)
Mean (SD)	6.1 (8.1)	8.0 (14)	14 (12)	10 (13)	NA	NA	24 (26)	18 (23)	11 (8.3)	11 (11)	18 (15)	13 (12)	19 (9.3)
Median [Min, Max]	4.7 [0.67, 41]	3.3 [0.33, 78]	9.7 [0.33, 62]	5.3 [0.33, 78]	NA	NA	16 [0.33, 98]	13 [0.33, 98]	8.0 [1.3, 33]	8.3 [0.33, 48]	16 [1.0, 62]	8.7 [0.33, 62]	20 [7.7, 35]
Ultrasound diagnostics													
n (%)	<5	<5	12 (27.3)	17 (16.3)	<5	0 (0.0)	5 (41.7)	6 (35.3)	<5	13 (20.0)	<5	20 (15.6)	<5
Mean (SD)	NA	NA	0.89 (1.0)	0.78 (0.87)	NA	NA	0.80 (0.65)	0.72 (0.61)	NA	0.46 (0.22)	NA	0.52 (0.40)	NA
Median [Min, Max]	NA	NA	0.67 [0.33, 4.0]	0.67 [0.33, 4.0]	NA	NA	0.33 [0.33, 1.7]	0.33 [0.33, 1.7]	NA	0.33 [0.33, 1.0]	NA	0.33 [0.33, 2.0]	NA
Laboratory analyses													
n (%)	14 (56.0)	15 (42.9)	31 (70.5)	60 (57.7)	<5	<5	6 (50.0)	8 (47.1)	14 (51.9)	28 (43.1)	16 (44.4)	58 (45.3)	<5
Mean (SD)	3.6 (2.7)	3.6 (5.3)	4.3 (5.4)	4.0 (4.8)	NA	NA	6.6 (8.4)	6.4 (7.2)	5.5 (7.8)	4.1 (4.0)	9.6 (8.6)	5.9 (6.8)	NA
Median [Min, Max]	3.3 [0.67, 9.7]	2.0 [0.33, 21]	1.7 [0.33, 23]	2.2 [0.33, 23]	NA	NA	3.3 [0.33, 23]	3.8 [0.33, 23]	1.7 [0.33, 26]	3.0 [0.33, 12]	7.8 [0.33, 33]	4.2 [0.33, 33]	NA
Joint surgeries													
n (%)	0 (0.0)	<5	5 (11.4)	6 (5.8)	0 (0.0)	0 (0.0)	<5	<5	0 (0.0)	5 (7.7)	<5	9 (7.0)	0 (0.0)
Mean (SD)	NA	NA	0.40 (0.15)	0.39 (0.14)	NA	NA	NA	NA	NA	0.40 (0.15)	NA	0.37 (0.11)	NA
Median [Min, Max]	NA	NA	0.33 [0.33, 0.67]	0.33 [0.33, 0.67]	NA	NA	NA	NA	NA	0.33 [0.33, 0.67]	NA	0.33 [0.33, 0.67]	NA

Appendix 1: (*Continued*)

	Mild				Moderate				Severe				Inhibitor[a]
	Children ≥ 0 to ≤ 18 years	Adults ≥ 19 to ≤ 44 years	Adults ≥ 45 years	Total	Children ≥ 0 to ≤ 18 years	Adults ≥ 19 to ≤ 44 years	Adults ≥ 45 years	Total	Children ≥ 0 to ≤ 18 years	Adults ≥ 19 to ≤ 44 years	Adults ≥ 45 years	Total	Total
	(*N* = 25)	(*N* = 35)	(*N* = 44)	(*N* = 104)	(*N* = 3)	(*N* = 2)	(*N* = 12)	(*N* = 17)	(*N* = 27)	(*N* = 65)	(*N* = 36)	(*N* = 128)	(*N* = 8)
Psychotherapy													
n (%)	7 (28.0)	6 (17.1)	17 (38.6)	30 (28.8)	0 (0.0)	<5	5 (41.7)	6 (35.3)	5 (18.5)	23 (35.4)	14 (38.9)	42 (32.8)	<5
Mean (SD)	0.48 (0.18)	17 (31)	2.9 (4.6)	5.2 (15)	NA	NA	3.6 (3.3)	3.1 (3.2)	1.3 (1.9)	2.3 (3.1)	3.8 (5.6)	2.7 (4.0)	NA
Median [Min, Max]	0.33 [0.33, 0.67]	1.3 [0.33, 79]	1.0 [0.33, 19]	0.67 [0.33, 79]	NA	NA	2.7 [0.33, 7.5]	1.8 [0.33, 7.5]	0.67 [0.33, 4.7]	0.67 [0.33, 11]	1.0 [0.33, 18]	0.67 [0.33, 18]	NA
Pain therapy													
n (%)	0 (0.0)	<5	6 (13.6)	7 (6.7)	0 (0.0)	0 (0.0)	<5	<5	0 (0.0)	<5	<5	6 (4.7)	0 (0.0)
Mean (SD)	NA	NA	1.1 (0.78)	2.1 (2.7)	NA	NA	NA	NA	NA	NA	NA	3.7 (5.3)	NA
Median [Min, Max]	NA	NA	1.0 [0.33, 2.3]	1.0 [0.33, 8.0]	NA	NA	NA	NA	NA	NA	NA	1.0 [0.33, 14]	NA
Outpatient physiotherapy													
n (%)	<5	5 (14.3)	14 (31.8)	20 (19.2)	0 (0.0)	<5	<5	<5	5 (18.5)	23 (35.4)	20 (55.6)	48 (37.5)	6 (75.0)
Mean (SD)	NA	3.1 (2.7)	9.7 (18)	7.6 (15)	NA	NA	NA	NA	12 (9.8)	16 (27)	51 (93)	30 (64)	38 (33)
Median [Min, Max]	NA	2.7 [0.67, 7.0]	2.3 [0.67, 58]	2.3 [0.33, 58]	NA	NA	NA	NA	10 [4.0, 29]	4.0 [0.67, 87]	19 [2.0, 377]	7.8 [0.67, 377]	24 [2.0, 81]
Total costs													
n (%)	25 (100.0)	35 (100.0)	44 (100.0)	104 (100.0)	<5	<5	12 (100.0)	17 (100.0)	27 (100.0)	65 (100.0)	36 (100.0)	128 (100.0)	8 (100.0)
Mean (SD)	3,567 (7,409)	3,999 (5,535)	5,123 (8,906)	4,371 (7,514)	NA	NA	35,039 (27,428)	36,122 (24,891)	210,267 (88,801)	292,925 (152,276)	254,440 (142,537)	264,666 (141,302)	725,441 (697,275)
Median [Min, Max]	282 [39, 31,165]	1,203 [27, 20,790]	2,803 [23, 54,651]	1,534 [23, 54,651]	NA	NA	28,781 [6,083, 76,493]	34,884 [6,083, 76,493]	198,717 [91,337, 432,145]	286,629 [61,515, 652,110]	238,623 [2,258, 657,647]	238,311 [2,258, 657,647]	578,301 [49,021, 2,107,897]
Inpatient medical care													
n (%)	6 (24.0)	10 (28.6)	26 (59.1)	42 (40.4)	<5	<5	8 (66.7)	11 (64.7)	13 (48.1)	21 (32.3)	16 (44.4)	50 (39.1)	5 (62.5)
Mean (SD)	978 (485)	3,207 (5,543)	6,157 (10,654)	4,715 (8,939)	NA	NA	5,473 (4,069)	4,292 (3,970)	2,617 (3,473)	1,891 (1,462)	2,633 (2,796)	2,317 (2,521)	3,642 (3,600)
Median [Min, Max]	1,007 [383, 1,542]	865 [269, 18,104]	2,495 [244, 52,916]	1,958 [244, 52,916]	NA	NA	4,252 [1,570, 13,447]	2,830 [654, 13,447]	1,187 [530, 11,827]	1,274 [629, 6,704]	1,499 [363, 10,046]	1,244 [363, 11,827]	3,710 [475, 9,386]
HA medication													
n (%)	25 (100.0)	31 (88.6)	28 (63.6)	84 (80.8)	<5	<5	11 (91.7)	16 (94.1)	27 (100.0)	65 (100.0)	35 (97.2)	127 (99.2)	8 (100.0)
Mean (SD)	3,079 (7,227)	2,899 (4,707)	891 (1,091)	2,284 (4,948)	NA	NA	29,382 (26,162)	32,029 (24,187)	208,621 (87,493)	291,318 (151,748)	255,529 (138,645)	263,874 (139,733)	720,274 (697,962)
Median [Min, Max]	32 [6.3, 30,029]	692 [6.3, 20,111]	680 [1.6, 4,069]	127 [1.6, 30,029]	NA	NA	14,323 [31, 61,873]	31,849 [31, 71,338]	197,511 [90,329, 423,189]	286,246 [61,482, 651,803]	242,452 [22,286, 651,791]	239,657 [22,286, 651,803]	574,802 [46,036, 2,107,134]

(*Continued*)

Appendix 1: (*Continued*)

	Mild				Moderate				Severe				Inhibitor[a]
	Children ≥ 0 to ≤ 18 years	Adults ≥ 19 to ≤ 44 years	Adults ≥ 45 years	Total	Children ≥ 0 to ≤ 18 years	Adults ≥ 19 to ≤ 44 years	Adults ≥ 45 years	Total	Children ≥ 0 to ≤ 18 years	Adults ≥ 19 to ≤ 44 years	Adults ≥ 45 years	Total	Total
	(*N* = 25)	(*N* = 35)	(*N* = 44)	(*N* = 104)	(*N* = 3)	(*N* = 2)	(*N* = 12)	(*N* = 17)	(*N* = 27)	(*N* = 65)	(*N* = 36)	(*N* = 128)	(*N* = 8)
Medication for HIV, HBV, HCV, antidepressants, analgesics													
n (%)	16 (64.0)	25 (71.4)	37 (84.1)	78 (75.0)	<5	<5	12 (100.0)	14 (82.4)	22 (81.5)	41 (63.1)	33 (91.7)	96 (75.0)	8 (100.0)
Mean (SD)	7.9 (6.5)	27 (55)	454 (1,696)	225 (1,180)	NA	NA	3,584 (5,904)	3,073 (5,584)	8.9 (6.9)	772 (2,408)	3,958 (5,793)	1,692 (4,068)	1,639 (3,785)
Median [Min, Max]	4.9 [0.98, 19]	12 [1.4, 282]	46 [0.95, 10,149]	17 [0.95, 10,149]	NA	NA	69 [4.8, 14,962]	38 [4.8, 14,962]	8.5 [1.5, 26]	34 [0.93, 10,829]	237 [2.0, 20,173]	31 [0.93, 20,173]	58 [9.0, 10,910]
Outpatient physician visits, total													
n (%)	25 (100.0)	34 (97.1)	43 (97.7)	102 (98.1)	<5	<5	12 (100.0)	17 (100.0)	27 (100.0)	64 (98.5)	35 (97.2)	126 (98.4)	8 (100.0)
Mean (SD)	248 (380)	500 (1,272)	480 (387)	430 (798)	NA	NA	857 (1,111)	657 (981)	329 (244)	373 (406)	624 (572)	433 (446)	639 (408)
Median [Min, Max]	142 [11, 1,909]	199 [13, 7,486]	417 [17, 1,794]	266 [11, 7,486]	NA	NA	507 [9.3, 4,143]	377 [9.3, 4,143]	254 [31, 1,193]	238 [10, 1,985]	473 [32, 2,731]	262 [10, 2,731]	548 [197, 1,468]
Outpatient diagnostic procedures (ultrasound, laboratory analyses)													
n (%)	14 (56.0)	19 (54.3)	32 (72.7)	65 (62.5)	<5	<5	9 (75.0)	11 (64.7)	16 (59.3)	34 (52.3)	17 (47.2)	67 (52.3)	5 (62.5)
Mean (SD)	122 (208)	102 (175)	70 (157)	91 (173)	NA	NA	144 (255)	134 (231)	107 (165)	133 (210)	275 (241)	163 (216)	80 (167)
Median [Min, Max]	77 [0.40, 824]	45 [1.8, 583]	9.1 [0.20, 680]	25 [0.20, 824]	NA	NA	14 [2.8, 714]	29 [2.8, 714]	31 [2.8, 573]	39 [0.20, 721]	213 [0.40, 756]	51 [0.20, 756]	2.8 [0.20, 378]
Outpatient joint surgeries													
n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	<5	<5	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Mean (SD)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Median [Min, Max]	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Outpatient pain therapy													
n (%)	0 (0.0)	<5	5 (11.4)	6 (5.8)	0 (0.0)	0 (0.0)	<5	<5	0 (0.0)	<5	<5	<5	0 (0.0)
Mean (SD)	NA	NA	24 (22)	50 (67)	NA	NA	NA	NA	NA	NA	NA	NA	NA
Median [Min, Max]	NA	NA	19 [3.9, 61]	21 [3.9, 181]	NA	NA	NA	NA	NA	NA	NA	NA	NA
Outpatient psychotherapy													
n (%)	7 (28.0)	6 (17.1)	17 (38.6)	30 (28.8)	0 (0.0)	<5	5 (41.7)	6 (35.3)	5 (18.5)	23 (35.4)	14 (38.9)	42 (32.8)	<5
Mean (SD)	3.9 (2.2)	1,371 (2,849)	86 (232)	324 (1,309)	NA	NA	36 (44)	31 (41)	17 (30)	63 (161)	122 (295)	78 (207)	NA
Median [Min, Max]	5.4 [0.99, 6.3]	38 [5.4, 7,130]	16 [5.3, 981]	11 [0.99, 7,130]	NA	NA	12 [5.3, 109]	11 [5.3, 109]	5.5 [1.0, 71]	11 [5.3, 779]	16 [5.3, 1,102]	11 [1.0, 1,102]	NA
Outpatient physiotherapy													
n (%)	<5	5 (14.3)	14 (31.8)	20 (19.2)	0 (0.0)	<5	<5	<5	5 (18.5)	23 (35.4)	20 (55.6)	48 (37.5)	6 (75.0)
Mean (SD)	NA	69 (65)	209 (379)	164 (323)	NA	NA	NA	NA	268 (200)	350 (569)	1,088 (1,986)	649 (1,375)	816 (694)
Median [Min, Max]	NA	57 [13, 169]	53 [13, 1,223]	53 [6.4, 1,223]	NA	NA	NA	NA	233 [96, 606]	82 [13, 1,872]	404 [43, 8,115]	174 [13, 8,115]	529 [43, 1,718]

[a]Inhibitor patients are indicated only in total, since the group sizes are <5 and therefore may not be indicated for data protection reasons.