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ORIGINAL ARTICLE

Burden of congenital hemophilia A requiring treatment in Japan: The HIKOBOSHI study

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Abstract

Background: Treatment of congenital hemophilia A (HA) in Japan has greatly improved with the widespread adoption of prophylactic factor (F)VIII concentrates. However, it is unknown if this has translated into a real-world reduction in disease and treatment burden.

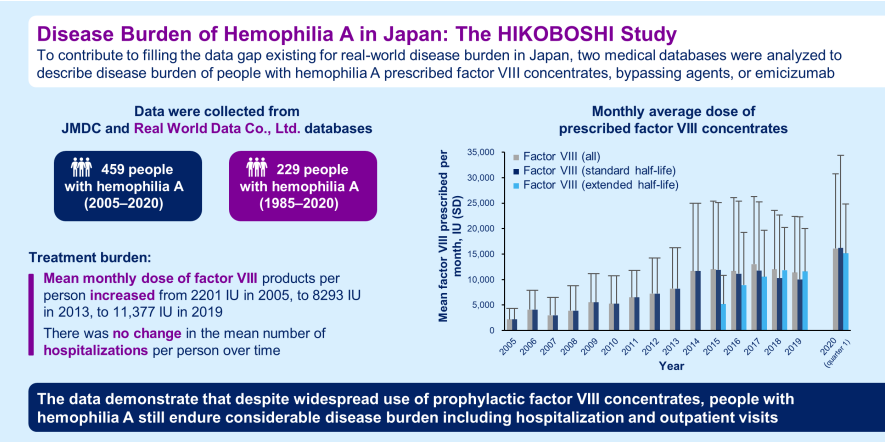
Objectives: To describe HA disease burden in Japan based on information from two medical information databases, JMDC and Real World Data Co., Ltd. (RWD).

Methods: Eligible individuals were diagnosed with congenital HA and prescribed FVIII concentrates, bypassing agents, or emicizumab. Treatment patterns and disease burden data were derived from health insurance claims and electronic medical records.

Results: Data on 459 people with HA were retrospectively collected from 2005 to 2020 in the JMDC database (median [min, max] of 37 [2, 186] months of available records), and 229 people with HA from 1985 to 2020 in the RWD database (median [min, max] of 154 [0, 409] months of available records). Mean (standard deviation) ages at the time of the first record were 25.0 (16.8) years (JMDC) and 19.2 (20.3) years (RWD). In the JMDC database, mean monthly FVIII dose increased from 2201 IU in 2005 to 8239 IU in 2013 to 11,377 IU in 2019; HA-related drug costs increased accordingly. Mean (95% confidence interval) annual outpatient and out-of-hours visits decreased slightly between 2013 and 2019 (outpatient visits: from 22.9 [16.8–29.0] to 14.3 [12.6–16.1] per person; out-of-hours visits: from 1.3 [0.2–2.5] to 0.6 [0–1.4]). There was no change in mean number of hospitalizations.

Conclusions: Challenges remain in HA, including treatment burden, outpatient visits, and hospitalizations.

KEYWORDS
cost of illness, factor VIII, hemophilia A, Japan, medical records



Essentials

- Evidence on real-world disease burden of congenital hemophilia A (HA) in Japan is lacking.
- Medical and claims databases were analyzed to describe disease burden of people with HA.
- Mean number of clinical visits decreased over time but mean hospitalizations were unchanged.
- Mean factor (F)VIII dose increased; FVIII administration is itself a burden for people with HA.

1 | INTRODUCTION

Congenital hemophilia A (HA) is a blood disorder caused by coagulation factor (F)VIII deficiency or dysfunction, with a disease burden that significantly impacts quality of life (QoL).[1] Widespread prophylaxis and comprehensive care have elongated lifespan among people with HA.[2] However, this does not necessarily translate to good health, and interest in the complications of aging has grown as these issues become apparent.[2] Of particular concern are events such as ischemic heart disease (IHD), which require a multidisciplinary approach to treatment to balance the risk of thrombosis with the risk of bleeding.[3] Moreover, because people with HA receive blood coagulation factor products, there is an interest in how this may affect those at high risk of thromboembolism.[3–5]

As treatment progresses, it is important to evaluate its effects on disease burden, which encompasses the burden of symptoms and the burden of treatment itself. Clinical studies have tracked the improvement of symptom burden: prophylaxis has reduced bleeding and helped prevent progressive joint damage.[6] However, it is not clear whether this has led to a reduction in the treatment burden related to daily QoL, including hospital visits and medical expenses.[7,8] A reduction in symptom burden and treatment burden together is expected to lead to enhanced QoL.[9]

The Nationwide Survey of Blood Coagulation Disorders, a project commissioned by the Japanese Ministry of Health, Labour, and Welfare, is the only public epidemiological investigation of bleeding disorders in Japan.[10] This survey provides data on the demographics and clinical characteristics of people with HA and the therapies they receive. Nevertheless, the actual situation of people with HA and their real-life burden is difficult to quantify. To fill this knowledge gap, several countries have used international disease registries and medical information databases. However, there are no disease registries for hemophilia in Japan, and no reports that have quantitatively investigated the state of medical care and disease burden for people with HA using a medical information database.

In Japan, health care is administered under a social insurance system that enables equality of access.[11] Health insurance is provided according to employment status, location, and age.[11] Health insurance providers cover the majority of treatment expenses, and the individual pays a fixed portion, so out-of-pocket expenses for patients at the point of care are minimal.[11] There are no dedicated hemophilia treatment centers; people with HA are treated at hospitals across the country and treatment is covered by their health insurance. Health insurance claims and other medical records are commonly collated in databases,[11,12] which afford a valuable opportunity to investigate real-world health care data in Japan. The objective of the HIKOBOSHI study is to describe HA treatment patterns and disease burden in Japan using health insurance claims and medical records databases.

2 | METHODS

2.1 | Selection of data sources and data retrieval method

The medical claims database supplied by JMDC Inc. (JMDC) and the electronic medical care records database supplied by Real World Data Co., Ltd. (RWD) were used in the HIKOBOSHI study. The JMDC database has collected health insurance claims data,

including inpatient, outpatient, and dispensing claims, and medical examination data from health insurance subscribers since 2005 (Table S1).[12] As of 2018, it included 7.4 million individuals whose data can be tracked across multiple medical facilities and hospitals, although it has little access to data on people aged ≥75 years.[12] The RWD hospital-based database is maintained by the Health, Clinic, and Education Information Evaluation Institute (Kyoto, Japan) with support from the Real World Data Co., Ltd. (Kyoto, Japan) (Table S2). It includes electronic medical record data dating back to 1985 on approximately 20 million individuals provided by more than 200 large institutions, and does include individuals aged ≥75 years.[13] Each person has a unique identifier, which enables tracking of his or her data within that institution, but is not transferrable across other institutions. Data from small institutions that do not provide data to the RWD database are not included. Subject demographics, diagnosis procedure combination information, laboratory test results, and partial claims data on prescriptions and procedures are accessible from the RWD database.

Two databases were used for this study because of the diversity of the facilities they offer and the bias in the age distribution. The RWD database was selected because of its inclusion of laboratory test results, as the symptoms and treatment burden of people with HA vary greatly depending on disease severity and the presence of FVIII inhibitors. The data periods comprised all periods for which data could be extracted from each data source. Approval for this study was obtained from the ethics review committee (the specified nonprofit organization, MINS; an institutional review board).

2.2 | Eligibility criteria

Eligible people with HA were narrowed down from those with a diagnosis (including suspected cases) of hereditary FVIII deficiency (International Classification of Diseases, Tenth Revision [ICD-10] subclass code of D66) to those who had a confirmed diagnosis (ICD-10 D66; excluding suspected cases) and had been prescribed FVIII concentrates, bypassing agents, or emicizumab during the data collection period.

People with HA were excluded from the JMDC database if the start and end months of the period for which records were available were the same. People with HA were excluded from the RWD database if the start and end months of the period for which records were available were the same or if they were hospitalized on the start date of the first record and died within 1 week.

The period for which records were available was defined as the first day of the insurance coverage month (JMDC database) or the date of the first medical record (RWD database) until the last day of the last month of the insurance coverage (JMDC database) or last record date (RWD database), death, or the record end date (March 31, 2020), whichever was the earliest.

2.3 | Outcome measures

For the purposes of this study, the overall disease burden was categorized into symptom burden (evidence of the disease experienced by the individual) and treatment burden (the impact of health care used to treat the disease on an individual's life) (Table 1). Outcome measures included patient background (demographic data, presence/absence of FVIII inhibitors, and activity levels); symptom burden, such as clinical outcomes (intracranial hemorrhage [ICH] and IHD with hospitalization) and comorbidities; and treatment burden, such as hospitalizations, outpatient and out-of-hours visits, and drug prescriptions (hemophilia-related medicines, analgesics, and anticoagulants for thrombotic disorders). Detailed definitions of outcome measures can be found in Appendix S1.

The minimum FVIII activity was defined for those people with HA who had a FVIII activity test result, according to three categories: <1%; ≥1%–≤5%; and >5%–≤40%. People with HA were defined as having a history of FVIII inhibitors if a test result of ≥0.6 Bethesda Units was recorded, with the first date of meeting the criteria defined as the inhibitor onset date. If an individual had one positive test for FVIII inhibitors, they were defined as having FVIII inhibitors from then onward and were included in the number of individuals each year.

To calculate the mean monthly prescribed amount of hemophilia medications, the sum of the total dosage for each prescription was calculated and then divided by the number of months in the prescription period. The mean number of days per month for which people with HA received a prescription of analgesics was

TABLE 1 Classification of disease burden for the purposes of this study

Classification of burden	Disease burden	
	Symptom burden	**Treatment burden**
Outcomes	• Clinical outcomes 1. Intracranial hemorrhage with hospitalization 2. Ischemic heart disease with hospitalization • Comorbidities	• Prescriptions • Clinical visits 1. Hospitalizations 2. Out-of-hours visits 3. Outpatient visits • Cost
Database	• JMDC database • RWD database	• JMDC database

Abbreviation: RWD, Real World Data Co., Ltd.

calculated by the total number of days with prescribed analgesics divided by the number of months for which records were available for that individual.

Medical expenses for surgical and laboratory costs were calculated from the mean Japanese remuneration points for each medical procedure, by converting one medical point to 10 Japanese yen (JPY) and then to United States Dollars (USD) using the exchange rate at the end of the study period (March 2020). Drug costs were calculated using the drug price at the time of prescription. In both cases, the month of the consultation was defined as the month in which the expense was incurred. People with HA with at least 1 month of expense in the year were included in the analysis set for that year. Consultation fees and prescription fees were not included in this analysis. No costs were discounted.

From 2005 to 2012, the total number of times for each medical consultation corresponding to an "out-of-hours visit" was obtained for each person in monthly units, and the maximum obtained was defined as the number of occurrences of an out-of-hours visit in a particular month. From 2013 onward, the total number of consultation dates was defined as the number of occurrences of an applicable medical consultation for each person.

2.4 | Data analysis

Missing data were not imputed for either the JMDC or the RWD database, except if the codes that defined out-of-hours visits or outpatient visits existed, but the number of visits was missing in the databases, in which case a value of one was imputed.

The period for which records were available was divided into units of 1 year, and the following analyses were performed in units of 1 year: proportion of people with HA with comorbidities; clinical outcomes; proportion of people with HA treated with each hemophilia-related medication; FVIII concentration dose; medical expenses; and clinical visits. For these annual analyses, people with HA who had the relevant health insurance claim at least once during the year were included in the number of individuals for that year. For example, if there was a year in which no FVIII concentration treatment was given, the individual was not included in the number of people with HA analyzed for average FVIII concentration dose in that year. For all analyses, a single person may be included in more than 1 year.

Descriptive statistics were calculated for demographic data. The proportions and 95% confidence intervals (CIs) of people with HA who had related claims were calculated for ICH and IHD hospitalizations, out-of-hours visits and outpatient visits, and a subgroup analysis according to age was performed.

3 | RESULTS

Data were collected from the JMDC database over the span of 2005–2020, with a median (min, max) of 37 (2, 186) months of records available. The data collection period for the RWD database ranged from 1985 to 2020, with a median (min, max) of 154 (0, 409) months of records available. Because data were only available for the first 3 months of 2020, they are included for reference purposes only.

3.1 | Patient background

3.1.1 | Demographics and baseline characteristics

The JMDC database and the RWD database contained 753 and 566 people with HA, respectively, of whom 461 and 236, respectively, were receiving prescriptions for FVIII, bypassing agents, or emicizumab. After nine exclusions because of matching record period start and end months, 459 people with HA from the JMDC database and 229 people with HA from the RWD database were included for analysis (Figure 1). People with HA from the RWD database were also excluded if they were hospitalized at the start date of the first record and died within 1 week; however, none of the people with HA in this study fell into this category. The mean (standard deviation [SD]) age at the start of the first record in the JMDC database was 25.0 (16.8) years, with more than half (61.0%) of individuals aged 0–29 years (Table 2). People with HA in the RWD database were slightly younger, with a mean (SD) age of 19.2 (20.3) years, and approximately half were in the 0–9 years age group. Both databases had a small proportion of people with HA aged ≥60 years (JMDC, 2.6%; RWD, 5.7%). Over time, the proportion of older people with HA (≥50 years of age) in the databases grew (Figure S1). The majority of people with HA across both databases were male (JMDC, 97.2%; RWD, 95.2%).

3.1.2 | FVIII activity and FVIII inhibitor status

FVIII activity-level data were available for 197/229 people with HA in the RWD database. The lowest value recorded was taken as the definitive value. Approximately half of these individuals (50.3%) had minimum FVIII activity levels corresponding to severe disease (<1%), whereas 23.4% and 26.4% had minimum FVIII activity levels corresponding to moderate (≥1%–≤5%) and mild (>5%–≤40%) disease, respectively (Table S3).

A total of 30/229 people with HA (13.1%) in the RWD database had confirmed FVIII inhibitors according to laboratory test data over the duration of the data collection period; the remaining 199 people with HA includes those who have never been tested for FVIII inhibitors.

3.2 | Symptom burden

3.2.1 | Comorbidities

The most common comorbidities observed were hepatitis C virus and neurological diseases, affecting 32.0% and 28.1% of people with HA

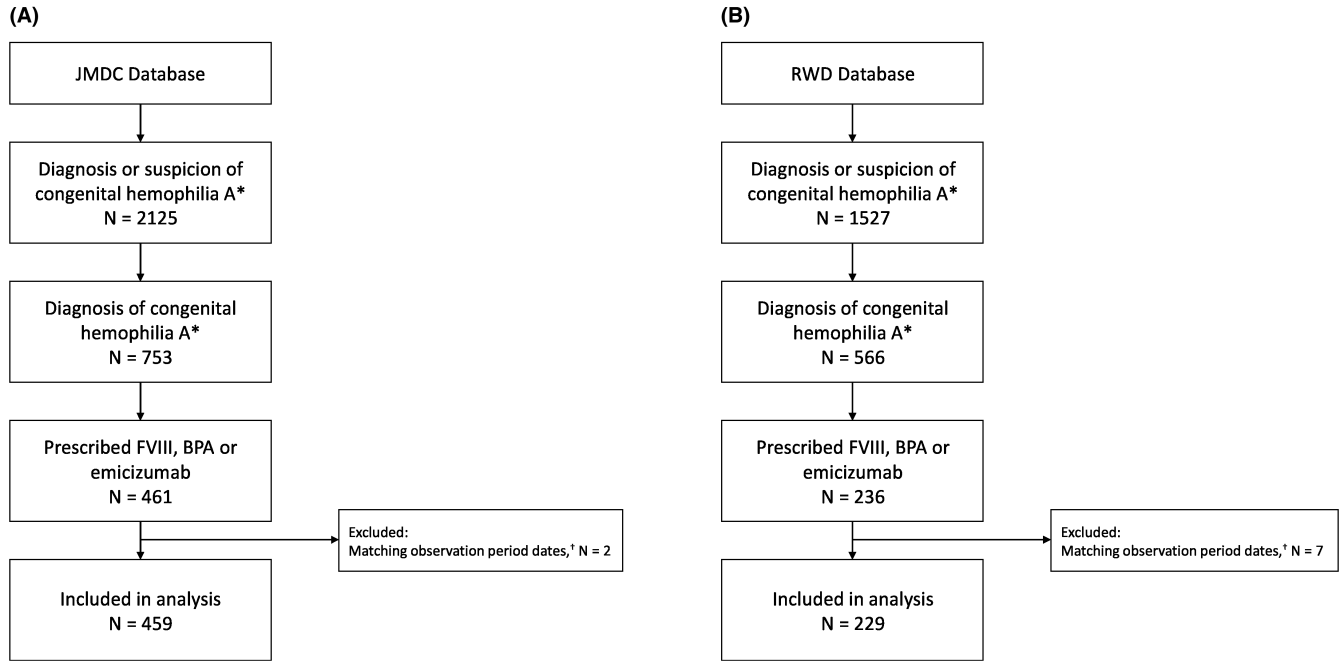


FIGURE 1 Subject flow diagram for (A) the JMDC database and (B) the RWD database. *ICD-10 category code D66. †People with HA were excluded from the JMDC database if the start and end months of the period for which records were available were the same. People with HA were excluded from the RWD database if the start and end months of the period for which records were available were the same or if they were hospitalized on the start date of the record period and died within 1 week. BPA, bypassing agent; F, factor; HA, hemophilia A; ICD-10, International Classification of Diseases, Tenth Revision; RWD, Real World Data Co., Ltd.

in the JMDC database, respectively, and 31.9% and 27.1% of those in the RWD database, respectively. The specific neurological diseases were not reported; however, the ICD-10 codes include inflammatory diseases, systemic atrophies, demyelinating diseases of the central nervous system, extrapyramidal and movement disorders, other degenerative diseases of the nervous system, and diagnoses of pain. The third most common comorbidity observed in both databases was essential hypertension, which was diagnosed in 9.6% and 13.5% of individuals in the JMDC and the RWD databases, respectively. In the JMDC database, 5.7% of people with HA had comorbid HIV (HIV records are not included in the RWD database because they are deemed sensitive information) (Figure S2).

3.2.2 | Clinical outcomes

The incidences of ICH, a significant risk for younger people with HA, and IHD, a growing risk in elderly people with HA, were investigated in the JMDC and RWD databases across the age groups (Table 3).

The proportion of people with HA who experienced an ICH associated with hospitalization was 2.6% (95% CI, 1.4–4.5) in the JMDC database. All except two cases occurred in the 0- to 9-year age group, in which 9.4% (95% CI, 4.6–16.7) of children with HA had one or more ICH events with hospitalization. In the RWD database, 4.4% (95% CI, 2.1–8.0) of people with HA experienced an ICH with hospitalization, with the majority of cases occurring in the 0- to 9- and 10- to 19-year age groups. Individuals aged 10–19 years had the highest proportion, with incidences of ICH with hospitalization being reported for 13.0% (95% CI, 2.8–33.6) of adolescents over the data collection period.

There were no cases of IHD with hospitalization among people with HA of any age in the JMDC database, and only two claims in one individual in the RWD database (0.4%).

3.3 | Treatment burden

3.3.1 | Drug prescriptions for hemophilia-related products, analgesics, and anticoagulants

Evaluations of medical practice were reported only for the JMDC database, which has high patient-tracking capabilities. The mean (95% CI) proportion of prescriptions for hemophilia-related products among eligible people with HA was 96.1% (93.9–97.7) for FVIII products, 2.0% (0.9–3.7) for activated prothrombin complex concentrate (aPCC), 5.2% (3.4–7.7) for activated recombinant FVII (rFVIIa), 0.7% (0.1–1.9) for activated FVII (FVIIa)/FX, and 13.7% (10.7–17.2) for emicizumab over the entire period (Figure 2). This proportion is calculated from all people with HA in the database, including those who only had records available before the approval of some products.

The mean (SD) monthly dose of FVIII products per person was 10,526 (11,260) IU across the whole period, and a steady increase was seen during this time, from 2201 (2148) IU in 2005 (n = 8) to 8239 (8020) IU in 2013 (n = 93) to 11,377 (10,993) IU in 2019 (n = 294) (Figure 3). The proportion of people with HA in the database prescribed standard half-life FVIII products was highest at

TABLE 2 Patient demographic data

Characteristics	JMDC database	RWD database
Number of people with HA	459	229
Sex, *n* (%)		
Male	446 (97.2)	218 (95.2)
Female	13 (2.8)	11 (4.8)
Health insurance plan type,[a] *n* (%)		
Individual insurance plan	247 (53.8)	–
Family insurance plan	212 (46.2)	–
Age at start of first record, years		
Mean (SD)	25.0 (16.8)	19.2 (20.3)
Median	24.0	13.0
Q1–Q3	11.0–37.0	1.0–34.0
Minimum, maximum	0, 68	0, 87
Age groups, *n* (%), years		
0–9	106 (23.1)	108 (47.2)
10–19	82 (17.9)	25 (10.9)
20–29	92 (20.0)	35 (15.3)
30–39	82 (17.9)	22 (9.6)
40–49	60 (13.1)	15 (6.6)
50–59	25 (5.4)	11 (4.8)
60–69	12 (2.6)	9 (3.9)
70–79	0 (0.0)	4 (1.7)
Record period, months		
Mean (SD)	48 (36)	156 (102)
Median	37	154
Q1–Q3	24–62	75–220
Minimum, maximum	2, 186	0, 409

Abbreviations: HA, hemophilia A; Q, quartile; RWD, Real World Data Co., Ltd.; SD, standard deviation.

[a]Japanese health insurance plans are primarily split into two types. Individuals who are full-time employees of medium to large companies will be enrolled through their employer (social health insurance), and this type of insurance includes their family. Individuals who are self-employed or who work for small companies will be covered by national health insurance, which does not include their family.

86.7% in 2008 and decreased after the approval of extended half-life (EHL) FVIII products, to 44.1% in 2019. The prescription of EHL FVIII products can be seen upon their introduction in 2015, and the mean monthly dose per person has gradually increased since then, from 5175 IU in 2015 to 11,597 IU in 2019. The proportion of people with HA in the database prescribed EHL products has risen dramatically over that time, from 2.7% in 2015 to 40.8% in 2019.

The mean (SD) monthly dose of bypassing agents prescribed was 6203 (6981) IU per person for aPCC (n = 9), 16 (32) mg for rFVIIa (n = 24), and 12 (17) mg for FVIIa/FX (n = 3). No trend or change was observed in the subgroup analysis by age group across the data collection period.

The mean (SD) monthly dose of emicizumab was 116 (113) mg (n = 63). The mean dose volume and the number of people with HA prescribed emicizumab have been increasing year on year since the approval of emicizumab in Japan in 2018. Analysis by age group showed that the proportion of prescriptions was highest in the 0- to 9-year age group (45.5% in 2018, 38.0% in 2019, and 30.2% in quarter [Q]1, 2020), compared with the other age groups.

Over the data collection period, 83.9% of people with HA were prescribed analgesics for a mean (SD) of 2.5 (7.0) days per month. The mean (SD) number of days per month of analgesic prescription was lowest in the 0- to 9-year age group, at 0.3 (0.3), and highest in the 50- to 59-year age group, at 6.3 (16.6). There were no trends or changes across the data collection period. Only four individuals were prescribed anticoagulants for thrombotic disorders over the duration of the data collection period. One person received ethyl icosapentate (WHO-ATC code: B01AC); one received edoxaban-tosilate hydrate (WHO-ATC code: B01AF03) and heparin sodium (WHO-ATC code: B01AB01), and the other two people received heparin sodium (WHO-ATC code: B01AB01) only.

3.3.2 | Medical expenses

The median (interquartile range) annual cost per person for the entire period was 14.51 (5.12–62.40) USD for surgery and procedures, 259,589.93 (44,815.30–563,604.42) USD for drug products, and 1013.75 (434.50–2343.69) USD for laboratory tests (Figure 4). Median (interquartile range) drug product expenses per person showed an increasing trend year on year, from 3805.87 (1052.57–26,098.84) USD in 2005 to 106,361.06 (22,901.30–195,651.66) USD in 2019.

3.3.3 | Clinical visits

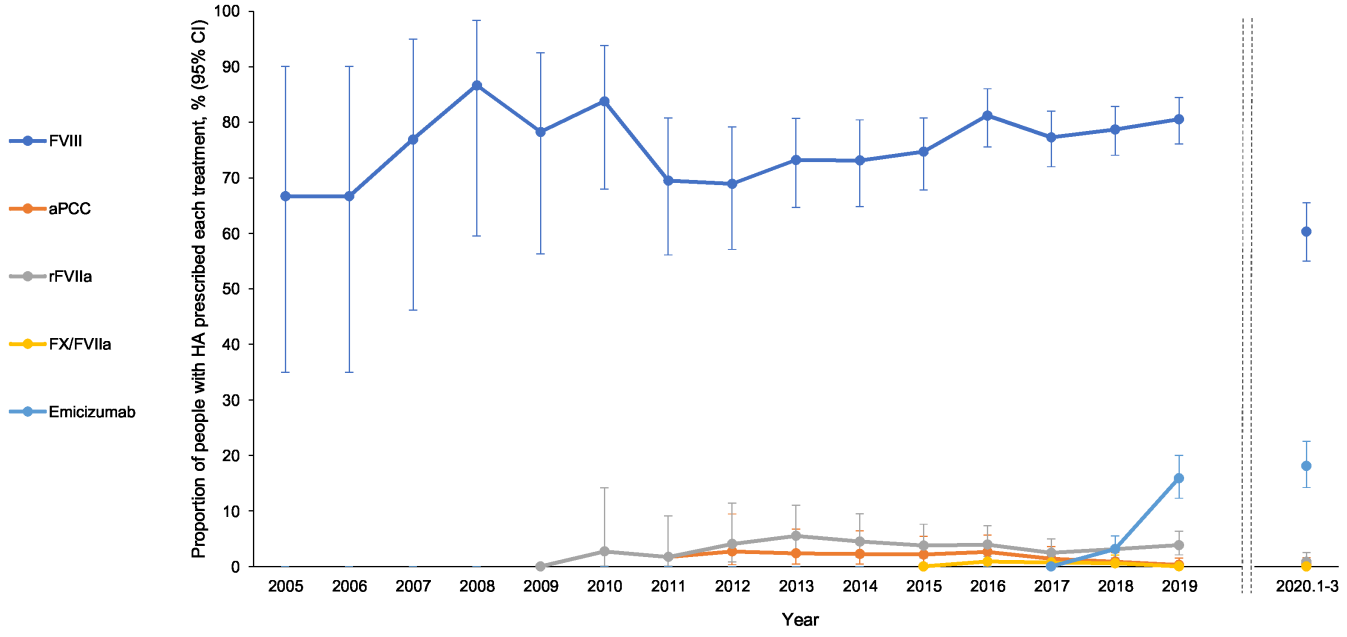
The mean (95% CI) number of outpatient and out-of-hours visits per person decreased slightly between 2013 and 2019 (outpatient visits: from 22.9 [16.8–29.0] to 14.3 [12.6–16.1] per person; out-of-hours visits: from 1.3 [0.2–2.5] to 0.6 [0–1.4] per person; Figure 5A). The number of outpatient visits per person per year was highest in children aged 0 to 9 years (Figure 5B). There was no change in the mean number of hospitalizations per person over time. The mean (SD) length of stay per hospital stay was 9.2 (10.7) days. There were no annual changes or differences by age.

A small proportion of people with HA had joint replacements (1.1%) and synovectomies (0.9%) recorded in the JMDC database. Likewise, 4.8% had a record of central venous access device insertion and 2.2% had a central venous access device removed. A total of 15.5% (n = 71) of people with HA in the JMDC database had received rehabilitation. For most people (n = 51/71; 741 instances), these related to physical therapy for the purpose of restoring basic movement skills. Some codes were recorded more frequently in the database because of continuous use, but corresponded to fewer

TABLE 3 Clinical outcomes for ICH and IHD in the JMDC database and the RWD database

		ICH with hospitalization			IHD with hospitalization		
Age (years)	No. of people with HA	Number of people with HA with event	Number of events	Proportion of people with HA with event (95% CI)	Number of people with HA with event	Number of events	Proportion of people with HA with event (95% CI)
JMDC database							
All	459	12	40	2.61 (1.36–4.52)	0	0	0.00 (0.00–0.80)
0–9	106	10	38	9.43 (4.62–16.67)	0	0	0.00 (0.00–3.42)
10–19	82	0	0	0.00 (0.00–4.40)	0	0	0.00 (0.00–4.40)
20–29	92	0	0	0.00 (0.00–3.93)	0	0	0.00 (0.00–3.93)
30–39	82	0	0	0.00 (0.00–4.40)	0	0	0.00 (0.00–4.40)
40–49	60	1	1	1.67 (0.04–8.94)	0	0	0.00 (0.00–5.96)
50–59	25	1	1	4.00 (0.10–20.35)	0	0	0.00 (0.00–13.72)
60–69	12	0	0	0.00 (0.00–26.46)	0	0	0.00 (0.00–26.46)
≥70	0	0	0	–	0	0	–
RWD database							
All	226	10	18	4.42 (2.14–7.99)	1	2	0.44 (0.01–2.44)
0–9	108	4	5	3.70 (1.02–9.21)	0	0	0.00 (0.00–3.36)
10–19	23	3	10	13.04 (2.78–33.59)	0	0	0.00 (0.00–14.82)
20–29	35	0	0	0.00 (0.00–10.00)	0	0	0.00 (0.00–10.00)
30–39	22	2	2	9.09 (1.12–29.16)	0	0	0.00 (0.00–15.44)
40–49	15	1	1	6.67 (0.17–31.95)	1	2	6.67 (0.17–31.95)
50–59	11	0	0	0.00 (0.00–28.49)	0	0	0.00 (0.00–28.49)
60–69	8	0	0	0.00 (0.00–36.94)	0	0	0.00 (0.00–36.94)
≥70	4	0	0	0.00 (0.00–60.24)	0	0	0.00 (0.00–60.24)

Abbreviations: CI, confidence interval; HA, hemophilia A; ICH, intracranial hemorrhage; IHD, ischemic heart disease; RWD, Real World Data Co., Ltd.



	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020.1-3
N	12	12	13	15	23	37	59	74	127	134	186	229	286	352	365	348
FVIII	8	8	10	13	18	31	41	51	93	98	139	186	221	277	294	210
aPCC	0	0	0	0	0	<4	<4	<4	<4	<4	4	6	4	<4	<4	<4
rFVIIa	0	0	0	0	0	<4	<4	<4	7	6	7	9	7	11	14	<4
FX/FVIIa	0	0	0	0	0	0	0	0	0	0	0	<4	<4	<4	0	0
Emicizumab	0	0	0	0	0	0	0	0	0	0	0	0	0	11	58	63

FIGURE 2 Proportion of people with HA treated with FVIII, aPCC, rFVIIa, FX/FVIIa, and emicizumab in the JMDC database. Data are for people with HA from the JMDC database ($N = 459$). Data for the year 2020 are only available for Q1 (through March 2020) and are included for reference only. Years with data for $n = 10$ and below are not shown. When the number of people with HA is three or below, the data point is shown as $n < 4$ to preserve anonymity. *N* indicates the total number of people with HA in the database for that year. a, activated; aPCC, activated prothrombin complex concentrate; CI, confidence interval; F, factor; HA, hemophilia A; Q, quarter; r, recombinant

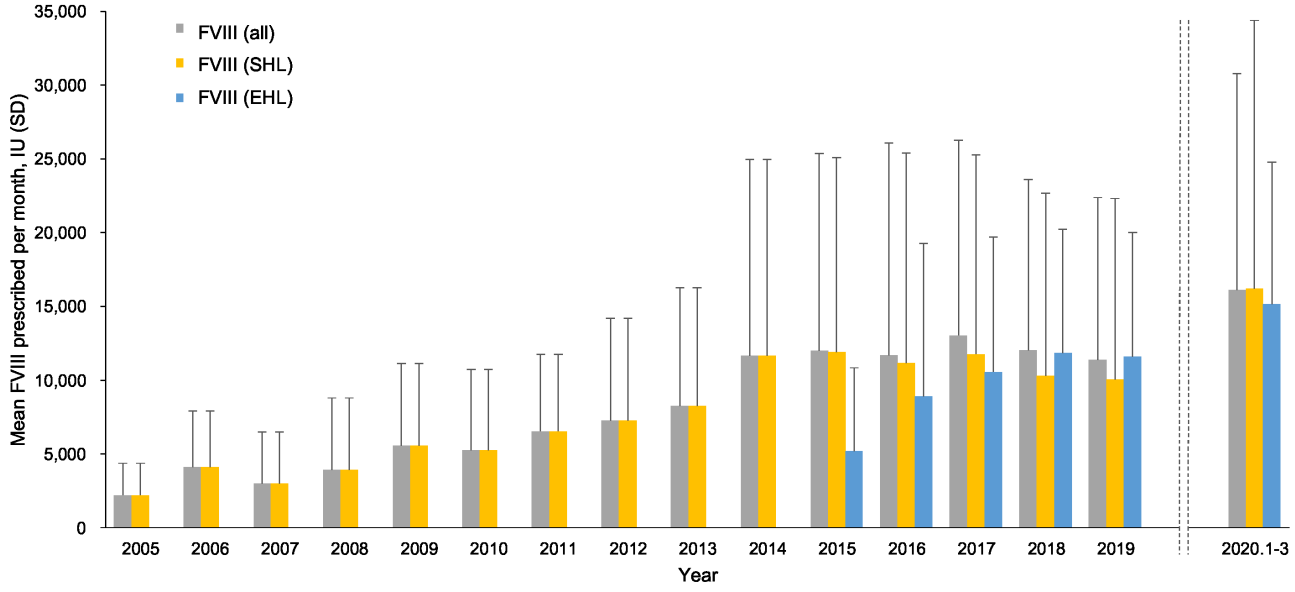
people, for example those indicating physical or occupational therapy for disability ($n = 3$; 940 instances).

4 | DISCUSSION

The HIKOBOSHI study found that the mean monthly dose of FVIII concentrates prescribed per person increased throughout the period of data collection, but a significant disease burden remains, including drug prescriptions, outpatient visits, and hospitalizations.

Although the RWD database includes more patient records than the JMDC database, fewer individuals were included from the RWD database because most medical institutions did not treat any people with HA. It was expected that most people with HA identified in this study would be male because of its inheritance pattern, but the striking lack of females may be due to underrecognition of the symptom burden of being a "carrier" of HA.[14] Identified people with HA were also relatively young, which could be due to the many specialized pediatric hospitals in the RWD database. A relatively high proportion of people with HA had received physical rehabilitation, in line with recommendations in the 3rd edition of the World Federation of Hemophilia guidelines.[1] Perhaps surprisingly, the second most common diagnosis reported was neurological disease; however, pain diagnosis and prescription of analgesics and sleeping pills are encompassed within the codes for neurological diseases, and it has been well established that many people with HA experience pain from their disease.[15]

The proportion of people with HA who experienced ICH with hospitalization was much lower than historical rates,[16] as expected because of extensive use of prophylaxis today.[17] However, due to the differing definitions of ICH, it is difficult to make direct comparisons with past reports. This study may also slightly underestimate the incidence since it is limited to events involving hospitalization. If the event was immediately fatal or not recognized as an ICH, this would not be captured. In seven individuals with ICH with hospitalization in the JMDC database, ICH occurred in spite of hemophilia-related medications being prescribed in the previous month. The frequency of IHD with hospitalization in this study was similar to, albeit slightly higher than, a recent observational study describing ischemic events in people with hemophilia aged 30 years or older ($N = 711$), which reported ischemic events in just two individuals (0.3%).[5] It is unclear if these events are particularly rare in people of Japanese ethnicity.[5] Although IHD with hospitalization was only recorded in one person in this study, four were prescribed anticoagulants for thrombotic disorders over the data collection period; these people may have experienced other thrombotic events, such



	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020.1-3
N	12	12	13	15	23	37	59	74	127	134	186	229	286	352	365	348
FVIII (all)	8	8	10	13	18	31	41	51	93	98	139	186	221	277	294	210
FVIII (SHL)	8	8	10	13	18	31	41	51	93	98	138	171	184	187	161	104
FVIII (EHL)	0	0	0	0	0	0	0	0	0	0	5	30	68	119	149	112

FIGURE 3 Monthly average dose of prescribed FVIII concentrates. Data are for people with HA from the JMDC database (*N* = 459). Data for the year 2020 are only available for Q1 (through March 2020) and are included for reference only. *N* indicates the total number of people with HA in the database for that year. EHL, extended half-life; F, factor; HA, hemophilia A; IU, international unit; Q, quarter; SD, standard deviation; SHL, standard half-life

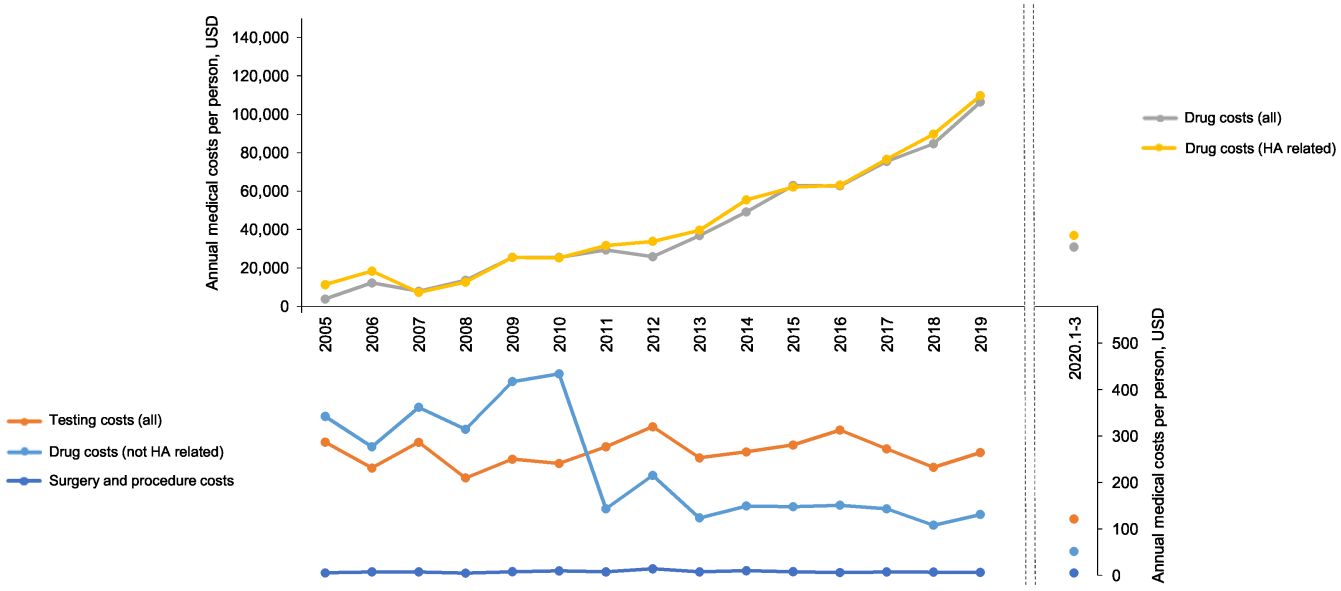


FIGURE 4 Medical expenses for people with HA in the JMDC database. Data shown are the median values. Data are for people with HA from the JMDC database (*N* = 459). Data for the year 2020 are only available for Q1 (through March 2020) and are included for reference only. Drug costs (all) and drug costs (HA related) are shown on the top section of the graph using the left-hand y axis and testing costs (all), drug costs (not HA related) and surgery and procedure costs are shown on the bottom section of the graph using the right-hand y axis, due to differences in the scale of costs. $1 USD = approximately ¥170.65 JPY or €0.90 EUR (March 2020). EUR, Euros; HA, hemophilia A; JPY, Japanese yen; Q, quarter; USD, United States dollars

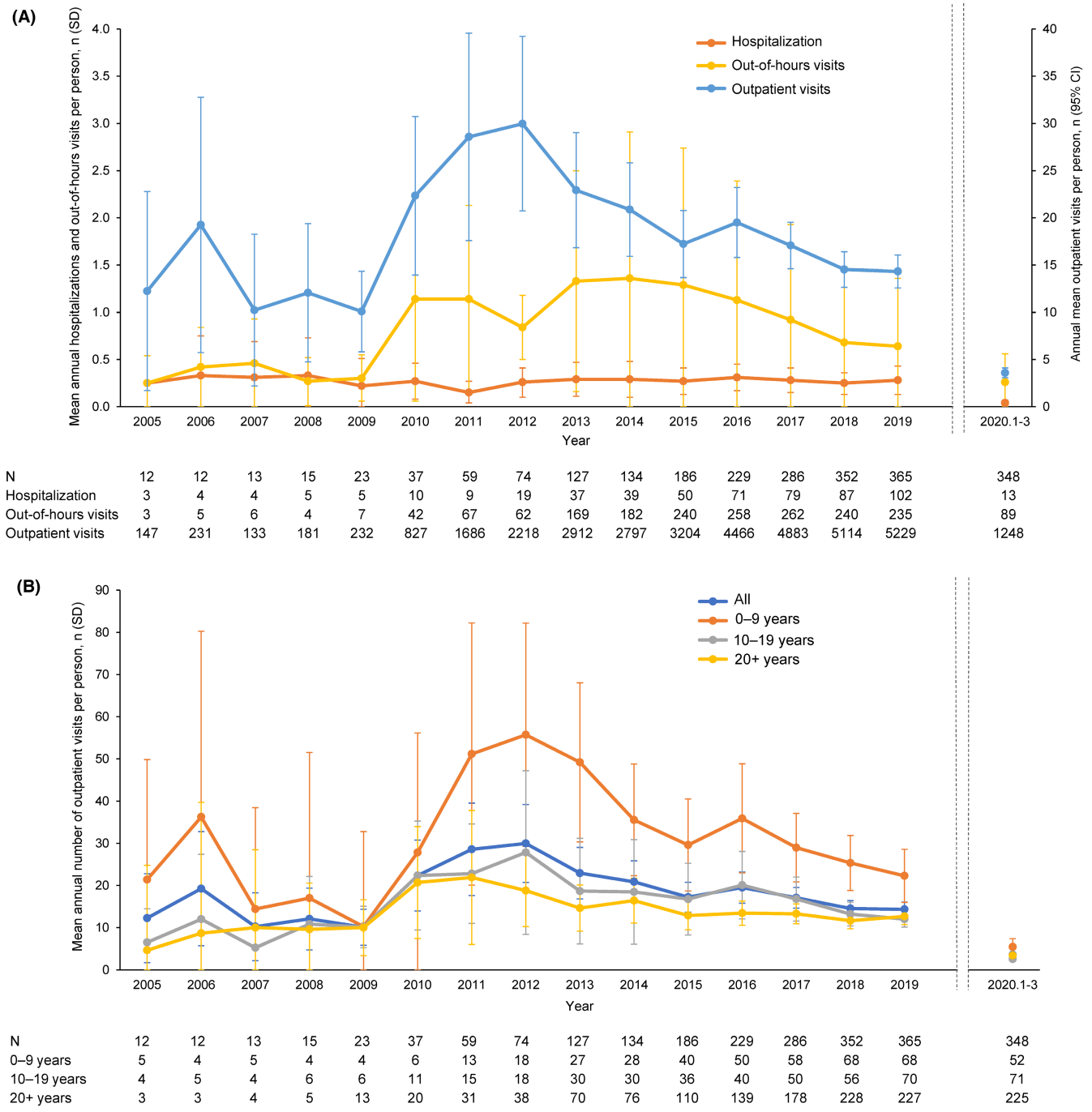


FIGURE 5 Annual incidence of (A) hospitalization, out-of-hours visits, and outpatient visits per person, and (B) outpatient visits per person by age group in the JMDC database. Data are for people with HA from the JMDC database (*N* = 459). Data for the year 2020 are only available for Q1 (through March 2020) and are included for reference only. For (A), hospitalizations and out-of-hours visits are shown using the left-hand y axis, and outpatient visits are shown using the right-hand y axis, due to differences in scale. *N* indicates the total number of people with HA in the database for that year. From 2005 to 2012, the total number of times for each medical consultation corresponding to "out-of-hours visit" was obtained for each patient in monthly units, and the maximum obtained was defined as the number of occurrences of an out-of-hours visit in a particular month. From 2013 onward, the total number of consultation dates was defined as the number of occurrences of an applicable medical consultation for each patient. CI, confidence interval; HA, hemophilia A; Q, quarter; SD, standard deviation.

as pulmonary embolism or deep vein thrombosis. As the frequency of ICH and IHD with hospitalization was low in this study, the data do not allow for consideration of change across time. Other bleeding events typically occurring in hemophilia, such as joint bleeding, were not captured or analyzed during this study because these events are usually treated by self-injection without visiting a doctor.

Since the rate of regular FVIII concentrate administration has been rising every year in Japan, from 664/1321 (50.3%) people with

severe HA surveyed in 2009 to 1578/1805 (87.4%) in 2020,[10] the increase in mean monthly dose of FVIII products per person observed in this study can be attributed to the increasingly widespread use of regular FVIII prophylaxis. In the authors' experience, higher doses have become more favored since measurement of FVIII levels has shifted toward targeting peak levels and a higher area under the curve.[18] Another possibility is that this increase is associated with changes in apparatus, such as the large vials that are now widely used to distribute FVIII, containing up to 4000 IU, or improvements in delivery devices.

We expected that the widespread use of prophylactic FVIII concentrates would reduce outpatient visits and hospitalizations by reducing bleeding events and preventing serious bleeding. In fact, although the number of people with HA in the JMDC database increased greatly over time, the calculated CIs indicated no change in hospitalizations. As this study was not designed to detect differences, we did not adjust for the baseline demographics or disease characteristics of the people included; these considerations may change the results. The stable rate of hospitalizations may be due to a growing population of elderly people with HA, hospitalized with pneumonia or other infectious diseases, cirrhosis following hepatitis C virus infection, or other medical issues associated with aging. Younger people with HA may be admitted to a hospital because of the increased capabilities for arthroplastic procedures. In contrast, outpatient visits showed an increasing trend until 2012 and a decreasing trend after 2013. One reason for this may be a temporary increase in education on the implementation of prophylactic FVIII concentrates according to the changing guidelines at that time, then a gradual decrease as people became accustomed to this. Some outpatient visits may be due to the administration of medication. In Japan, as in other countries, home injection/infusion is learned and implemented at the age of 2–3 years, but this study did not capture whether medications were administered at home or in the hospital, and the reasons for outpatient visits were not specified. It is difficult to examine the reduction in burden caused by regular FVIII concentrates because hemophilia- and non-hemophilia-related visits cannot be distinguished in the JMDC database, and it is not possible to determine whether FVIII prescription is for prophylaxis or on-demand use. Nevertheless, it is thought that the decrease in out-of-hours visits reflects extensive adoption of prophylactic therapy and comprehensive medical care.

The authors acknowledge that this analysis is subject to the usual pitfalls of secondary use data, such as incomplete records, inaccuracies in coding that misrepresent the circumstances of the individual, and variable adherence to prescribed treatments.[19] For example, the intended use of the anticoagulants prescribed to four individuals and the results of their use cannot be determined. Moreover, the accuracy of the definitions for the outcome measures may be limited because it has not been possible to validate these using true information, although a validation study using data from a single hospital has been attempted.[20] In that study, the ICD-10 D66 code in the electronic medical records in combination with administration of FVIII products without administration of FIX products had a positive predictive value of 95.2% (95% CI, 76.2–99.9) and sensitivity of 64.5% (95% CI, 45.4–80.8) for identifying HA.[20] The predictive values for identifying ICH and IHD could not be confirmed because of insufficient incidence, and the presence of FVIII inhibitors and FVIII activity levels were not very reliable definitions.[20] Additionally, major joint bleeding or arthropathy could not be accurately identified; the positive predictive values for these outcomes, plus FVIII product prescription, were 27.8% and 42.9%, respectively. Nevertheless, it would be difficult to conduct a large-scale prospective study in this population because of the rarity of the condition; thus, medical information databases offer a valuable means of scrutinizing real-world disease burden of people with HA to highlight remaining unmet needs. A prescription for FVIII, bypassing agents, or emicizumab in addition to congenital HA diagnosis was required for study eligibility, so females and people with nonsevere HA are less likely to be included, and the study population may be biased toward those with severe disease. Race and ethnicity of the participants were unknown, but this is not expected to impact the findings.

A further limitation of the JMDC and RWD databases is the difficulty in tracking individuals and their outcomes, and the bias that this may introduce. Matching of the medical information between the two databases was not possible as the data are anonymized, so it is possible that a person could be included in both databases; however, because the datasets were analyzed separately, this would not affect the conclusions of the study. Patient tracking in the JMDC database is possible if the subscriber does not withdraw from the health insurance association. However, bias toward a less severe population could occur in some instances; for example, if people withdraw from an insurance association from disease aggravation, but this reason is unknown. Moreover, the JMDC database does not include people older than 75 years of age.[12] In the RWD database, data are collected from discrete medical institutions and information from other hospitals is not taken into account. Therefore, if a treatment or prescription is received at another hospital, clinical outcomes and demographic data may not be collected correctly. Along with the varied record periods for each individual, lack of patient tracking complicated the authors' aim of examining the relationship between comorbidities, laboratory test results, and clinical outcomes.

Finally, the authors recognize that the people with HA whose records were examined in this analysis represent only a minority of the people with HA in Japan, as the JMDC and RWD databases do not cover the entire population and many medical institutions in Japan do not use electronic medical records.

In conclusion, the HIKOBOSHI study, one of the first database studies in Japan in the field of HA,[21] was designed to investigate real-world treatment patterns in people with HA and quantify their disease burden. The mean monthly dose of FVIII concentrates prescribed per person increased over time to the present day, presumably as FVIII prophylaxis in the clinical setting has become more common. Widespread use of prophylaxis has brought many benefits for people with HA, including prevention of joint damage; however, they still endure a considerable disease burden, encompassing the need for multiple drug prescriptions, outpatient visits,

and hospitalizations. Although it is important to evaluate the treatment burden of people with HA, there are limitations when using the current databases. An appropriate method such as prospective epidemiological studies, including a national registry, is required.

AUTHOR CONTRIBUTIONS

A. Ioka, T. Nakamura, Y. Murakami, M. Makishima, and N. Okada designed and conducted the study. A. Nagao and M. Sakai analyzed and interpreted the data. All authors revised the manuscript critically and provided final approval of the version to be published. All authors agree to be accountable for all aspects of the work.

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RELATIONSHIP DISCLOSURE

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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