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Differences in Major Bleeding Events Between Patients With Severe Hemophilia A and Hemophilia B: A Nationwide, Population-Based Cohort Study

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Abstract

There has been an ongoing debate as to whether hemophilia A (HA) is more severe than hemophilia B (HB), and there are studies supporting each side of the argument. The study aimed to investigate whether any differences in major bleeding events exist between patients with severe HA and HB. A nationwide, population-based retrospective cohort study using the National Health Insurance Research Database was conducted. We compared 658 patients with severe HA and 137 patients with severe HB without inhibitors from 1997 to 2013, during the period when adult patients older than 18 years old were treated with the on-demand therapy since birth. There was no significant difference between patients with severe HA and HB in the rate of major bleeding events, with an adjusted relative ratio of 0.79 (95% confidence interval [CI]: 0.36-1.71, $P = .548$). There was also no significant difference in the incidence rate of major bleeding events between adult patients with HA and HB with the on-demand therapy, and an adjusted hazard ratio (HR) of 0.82 (95% CI: 0.65-1.02). However, patients with HA had a lower incidence rate of intracranial hemorrhage, with an adjusted HR of 0.44 (95% CI: 0.25-0.79). In addition, no significant difference in the frequency of major bleeding events requiring hospitalization between patients with HA and HB was found, $P > .05$. In conclusion, the study demonstrated that patients with severe HB encountered a similar rate of major bleeding events to those with severe HA.

Keywords

epidemiology, hemophilia A, hemophilia B, hemorrhage; incidence

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Introduction

Hemophilia A (HA) and hemophilia B (HB) are X-linked recessive bleeding disorders caused by mutations in the genes encoding coagulation factor VIII (FVIII) and factor IX (FIX), respectively.[1] The severity of HA and HB is classified by the plasma level of coagulation factors, of which >5 IU/dL denotes mild, 1 to 5 IU/dL denotes moderate, and <1U/dL denotes severe hemophilia.[2] Traditionally, clinical manifestations of HA and HB were considered identical and could not be differentiated. However, more than 50 years ago, Quick et al observed less severe clinical manifestation in patients with HB compared to those in HA.[3] This finding was supported by several studies which demonstrated that patients with severe HA had higher hemophilia severity scores (HSS), required greater use of regular prophylaxis, and utilized more factor concentrate than those with severe HB.[4-6] A 3-fold higher risk of undergoing joint arthroplasty in patients with HA had also been observed.[7] Moreover, Kelly et al conducted a retrospective study using the Universal Data Collection database and

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showed that patients with HA had an increased prevalence of hip abnormality compared to those with HB.[8]

In contrast, a number of studies found a similar degree of severity between HA and HB. An analysis of a study cohort of 282 patients at the Van Creveldkliniek hemophilia treatment center in the Netherlands showed no differences in arthroplasty, prophylaxis, and annual joint bleeding frequency between patients with severe HA and HB.[9] Tagliaferri and colleagues analyzed data from a small cohort which showed similar HSS between patients with severe HA and HB.[10] Furthermore, Klamroth et al reported a higher risk of intracranial hemorrhage (ICH) in patients with severe HB than those with severe HA.[6]

These conflicting results suggest that there are no conclusive data indicating that HB is less severe than HA, and further analysis using a larger sample is warranted. As such, we conducted a population-based database study to evaluate the differences in bleeding rates and bleeding types between patients with severe HA and HB.

Methods

Data Sources

The data analyzed in this retrospective observational cohort study were obtained from Taiwan's National Health Insurance Research Database (NHIRD). Taiwan's National Health Insurance (NHI) Program is a single-payer, compulsory, and universal health insurance plan that was instituted in 1995. The NHI provides equal access to health care, including outpatient and inpatient care for 23.5 million Taiwanese citizens, with a population coverage rate of approximately 100%. Medical claims in this program, including diagnoses, invasive procedures, surgery, and detailed notes on drug prescriptions and laboratory and imaging results, are encrypted and stored in the NHIRD. The NHIRD provides a wide range of information on individual patients, including ambulatory and hospitalization care, as well as registration records and makes it available for research purposes. The accuracy of the diagnosis of severe diseases in the NHIRD has been validated.[11]

Identification of Study Cohorts

We used the Registry of Catastrophic Illness, a subset of the NHIRD, to identify severe hemophilia patients based on the *International Classification of Diseases, 9th Revision, Clinical Modifications (ICD-9-CM)* and history of previous clotting factor concentrate (CFC) treatment. Each registered hemophilia case in the registry of Catastrophic Illness must be certified by 2 hematologists, and is eligible for a total reimbursement of medical care, including the cost of CFC used. Data of patients with HA and HB (*ICD-9-CM* 286.0 and 286.1) from January 1, 1997 to December 31, 2013 were extracted. This time period was chosen for the study as the reimbursement for prophylaxis for adult (aged 18 years or older) hemophilia patients was initiated later in 2014, and all the adult patients during the study period had been treated with the on-demand therapy using CFC since birth. With respect to the selection of patients with severe hemophilia, those who received replacement therapy twice or less per year were excluded from this study.[12] Additionally, patients with inhibitors, who were assessed by determining whether there was any record of bypassing agent treatment, were excluded from the study.

Patients' Characteristics and Comorbidities

The characteristics of patients such as age, follow-up time, and comorbidity index were extracted. We used *ICD-9-CM* to identify comorbidities, including hepatitis B virus infection (0702-0704), hepatitis C virus infection (0707-0709, 07041-07042, 07044-07045, 07051-07052, and 07054-07055), human immunodeficiency virus (HIV) infection (42), hypertension (401), diabetes mellitus (250), hyperlipidemia (272), chronic obstructive pulmonary disease (490-496), ischemic stroke (401-405), ischemic heart disease (410-414), urolithiasis (592, 594), and malignancy (140-208).

Study Objectives and Statistical Analyses

The study was to compare the distribution of major bleeding events between patients with severe HA and HB. Major bleeding events included ICH(430-432), gastrointestinal bleeding (4560, 4561, 4562, 4590, 5693, and 578), hemothorax (HTX; 7863 and 51189), hemoperitoneum (56881), nontraumatic hematoma of soft tissue (NTHST) (72992), hemarthrosis (HT) (7191), and hematuria (5997). In order to prevent from the effect of prophylactic therapy on hemophilia severity, we further analyzed and compared the incidence rate of major bleeding events between adult patients with HA and HB who were treated with the on-demand therapy since birth.

Differences in demographics, clinical characteristics, and comorbidities between patients with HA and HB were analyzed using χ^2 test or Fisher exact test for categorical variables, and t test for continuous variables. Differences in major bleeding events between patients with HA and HB were evaluated by adjusted relative risk based on the logistic regression. Incidence rates of major bleeding events between patients with HA and HB were compared by adjusted hazard ratios based on the Cox regression.

In addition, the study was to compare the frequency of hospitalization resulting from major bleeding events between adult patients with HA and HB. Using hospitalization care in the NHIRD to analyze the frequency of hospitalization eliminated the bias of overcounting major bleeding events, which may occur as a result of duplicate records in the ambulatory file. All statistical analyses were performed using SAS software (version 9.2; SAS Institute Inc, Cary, North Carolina) and a P value less than .05 was considered statistically significant. This study was approved by the institutional review board of Taichung Veterans General Hospital in Taiwan.

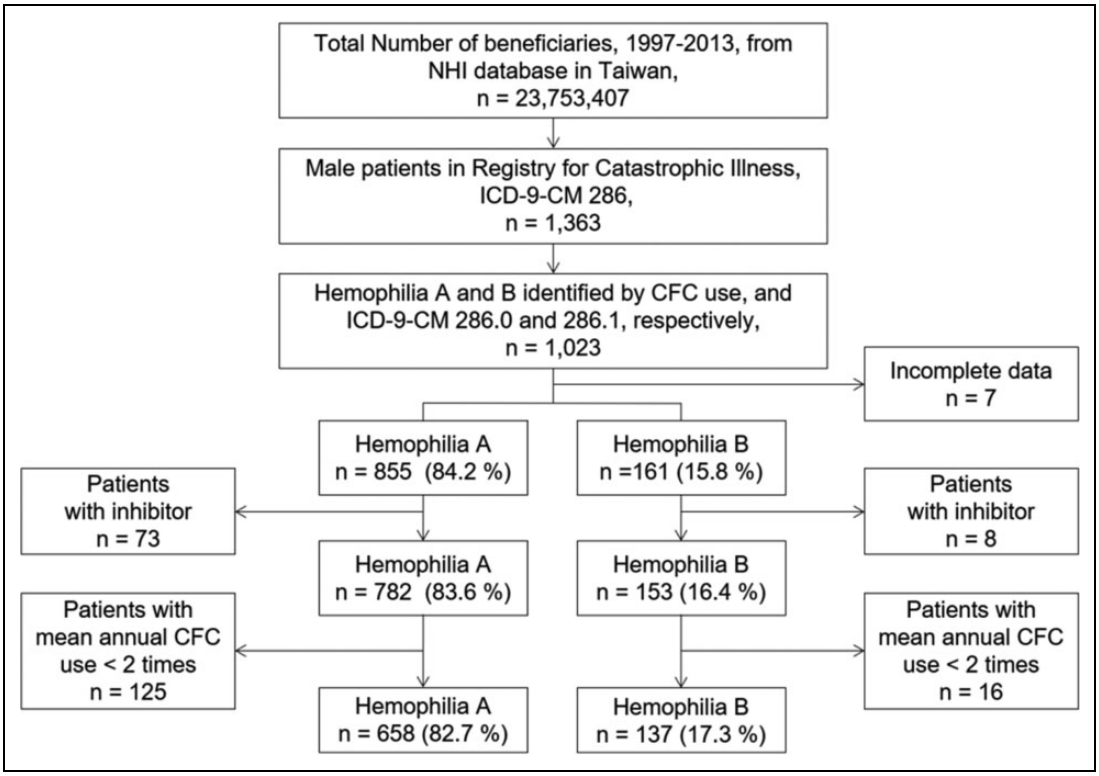

Figure 1. Retrospective study design. CFC indicates clotting factor concentrate; ICD-9-CM, International Classification of Diseases, 9th Revision, Clinical Modifications; NHI, National Health Insurance.

Results

Patient Selection and Characteristics

The total number of beneficiaries NHIRD in Taiwan from 1997 to 2013 was 23 753 407 (Figure 1). Of these, there were a total of 1363 male patients in the Registry for Catastrophic Illness with *ICD-9-CM* code 286. Patients with HA and HB (n = 1023) were identified by *ICD-9-CM* codes 286.0 and 286.1, respectively, in addition to the history of previous CFC treatment. Among these patients, 7 were excluded due to incomplete data. Furthermore, after excluding patients with inhibitors and those who received replacement therapy twice or less per year, 658 (82.7%) patients with severe HA and 137 (17.3%) patients with severe HB were included the final analysis.

Table1 presents the demographics and other characteristics of patients HA and HB in this study. Both groups were similar except for HIV infection, which was more prevalent in patients with HA (4.4% vs 0.0%, $P = .005$), and ischemic heart disease, which was more prevalent in patients with HB (2.6% vs 7.3%, $P = .005$).

Major Bleeding Events

The distribution of major bleeding events in patients with severe HA and HB between 1997 and 2013 are presented in Table 2. During the study period, 605 (92.0%) patients with HA and 129 (94.2%) patients with HB experienced at least 1 type of major bleeding events. There was no significant difference of the rate of major bleeding events in the adjusted relative ratio (RR) 0.79 (95% confidence interval [CI]: 0.36-1.71, $P = .548$) between patients with HA and HB. No significant difference was also found in various major bleeding events by types, except for NTHST which had a higher rate in HA (51.7% vs 40.9%) with an adjusted RR of 1.61 (95% CI: 1.10-2.35, $P = .014$).

Table 3 presents the incidence rate of major bleeding events per 100 person-years between patients with HA and HB, aged above 18 years and older, who were under the on-demand therapy since birth. There was no significant difference between patients with HA and HB, with an adjusted hazard ratio (HR) of 0.82 (95% CI: 0.65-1.02). However, a higher incidence rate was observed in NTHST among patients with HA, with an adjusted HR of 1.65 (95% CI: 1.14-2.37). However, in comparison with patients with HB, those with HA had lower incidence rates of ICH, with an adjusted HR of 0.44 (95% CI: 0.25-0.79), and HTX, with an adjusted HR of 0.37 (95% CI: 0.16-0.84).

In addition, no significant difference in the frequency of major bleeding events requiring hospitalization was observed in 138 patients with HA and 37 patients with HB aged 18 years and older who received the on-demand treatment since birth (Figure 2).

Table 1. Demographics and Characteristics of 795 Patients With Severe Hemophilia A or B Enrolled Between 1997 and 2013.[a]

	Both (N = 795)		Hemophilia A (N = 658)		Hemophilia B (N =137)		
	n	%	n	%	n	%	*P* Value
Age at study end (years)							
Mean ± SD	33.1 ± 16.3		33.5 ± 16.5		31.1 ± 15.4		.123
Follow-up (person-years)	11 140		9230		1910		
Follow-up (years)							
Mean ± SD	14.0 ± 3.6		14.0 ± 3.6		13.9 ± 3.5		.790
Comorbidity index							
Mean (95% CI)	0.24 (0.17-0.31)		0.27 (0.18-0.35)		0.13 (0.05-0.21)		.150
Hepatitis B virus infection	65	8.2	54	8.2	11	8.0	.945
Hepatitis C virus infection	218	27.4	185	28.1	33	24.1	.336
HIV infection	29	3.7	29	4.4	0	0.0	.005[b]
Hypertension	120	15.1	98	14.9	22	16.1	.729
Diabetes	46	5.8	40	6.1	6	4.4	.438
Hyperlipidemia	57	7.2	47	7.1	10	7.3	.949
COPD	40	5.0	34	5.2	6	4.4	.701
Ischemic stroke	29	3.7	21	3.2	8	5.8	.133
Ischemic heart disease	27	3.4	17	2.6	10	7.3	.005[b]
Urolithiasis	123	15.5	101	15.4	22	16.1	.835
Malignancy	41	5.2	34	5.2	7	5.1	.978
Mortality	89	11.2	76	11.6	13	9.5	.486

Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; SD, standard deviation.
[a] *t* Test was used for the analysis of continuous variables. χ^2 test and Fisher exact test were used for the analysis of categorical variables.
[b] Indicates a statistically significant *P* value.

Table 2. Distribution of Patients With Severe Hemophilia A and B With History of Bleeding Events by Type.[a]

	Both (N = 795)		Hemophilia A (N = 658)		Hemophilia B (N =137)		Adjusted Relative Risk	
	n	%	n	%	n	%	(95% CI)	*P* Value[b]
Patients with ≥1 bleeding event[c]	734	92.3	605	92.0	129	94.2	0.79 (0.36-1.71)	.548
Intracranial hemorrhage	90	11.3	69	10.5	21	15.3	0.66 (0.38-1.12)	.120
Gastrointestinal bleeding	623	78.4	513	78.0	110	80.3	0.94 (0.59-1.50)	.806
Hemothorax	29	3.7	20	3.0	9	6.6	0.49 (0.21-1.10)	.082
Hemoperitoneum	17	2.1	12	1.8	5	3.7	0.57 (0.19-1.67)	.303
Nontraumatic hematoma of soft tissue[d]	396	49.8	340	51.7	56	40.9	1.61 (1.10-2.35)	.014[e]
Hemarthrosis	385	48.4	313	47.6	72	52.6	0.8 (0.55-1.17)	.250
Hematuria	196	24.7	156	23.7	40	29.2	0.78 (0.52-1.19)	.246

[a] adjusted for HIV infection and ischemic heart disease.
[b] *P* value examined by logistic regression.
[c] Patients with at least one major bleeding event of intracranial hemorrhage, gastrointestinal hemorrhage, hemothorax, hemoperitoneum, nontraumatic hematoma of soft tissue, hemarthrosis, or hematuria.
[d] Nontraumatic hematoma of soft tissue and hemarthrosis may be underestimated since only severe events would be recorded in the electronic medical record.
[e] Indicates a statistically significant *P* value.

Discussion

Using NHI research database of Taiwan, we evaluated the entire Taiwanese population diagnosed with severe HA or HB from 1997 to 2013, and a substantial sample size of patients with hemophilia (PWH) without inhibitors was included in the analysis. In addition, patients with severe HA and HB with the on-demand therapy since birth were compared to evaluate any differences in major bleeding events. The results demonstrated that the incidence rate and the frequency of major bleeding events requiring hospitalization were similar in patients with HA and HB.

Mannucci and Franchini have comprehensively investigated the issue of differences in severity between HB and HA. They note 4 observations that indicate HB may be less severe than

Table 3. Incidence Rate of Major Bleeding Event in Patients With Severe Hemophilia A and B Aged 18 Years and Older.[a]

	Hemophilia A			Hemophilia B					
	Event (n)	Person-Years (PY)	Incidence Rate (Per 100 PY)	Event (n)	Person-Years (PY)	Incidence rate (Per 100 PY)	Adjusted Hazard Ratio (95% CI)		
All bleeding type events	465	2350	19.79	98	366	26.78	0.82	0.65	1.02
Intracranial hemorrhage	41	6059	0.68	17	1125	1.51	0.44[b]	0.25	0.79
Gastrointestinal hemorrhage	372	3493	10.65	82	575	14.26	0.79	0.62	1.01
Hemothorax	16	6202	0.26	9	1163	0.77	0.37[b]	0.16	0.84
Hemoperitoneum	11	6215	0.18	4	1196	0.33	0.62	0.19	2.00
Nontraumatic hematoma of soft tissue	242	4533	5.34	34	1005	3.38	1.67[b]	1.14	2.37
Hemarthrosis	226	4697	4.81	54	788	6.85	0.75	0.56	1.01
Hematuria	115	5459	2.11	24	1105	2.17	1.03	0.66	1.62

[a]Adjusted for HIV infection and ischemic heart disease.
[b]Indicates a statistically significant adjusted hazard ratio.

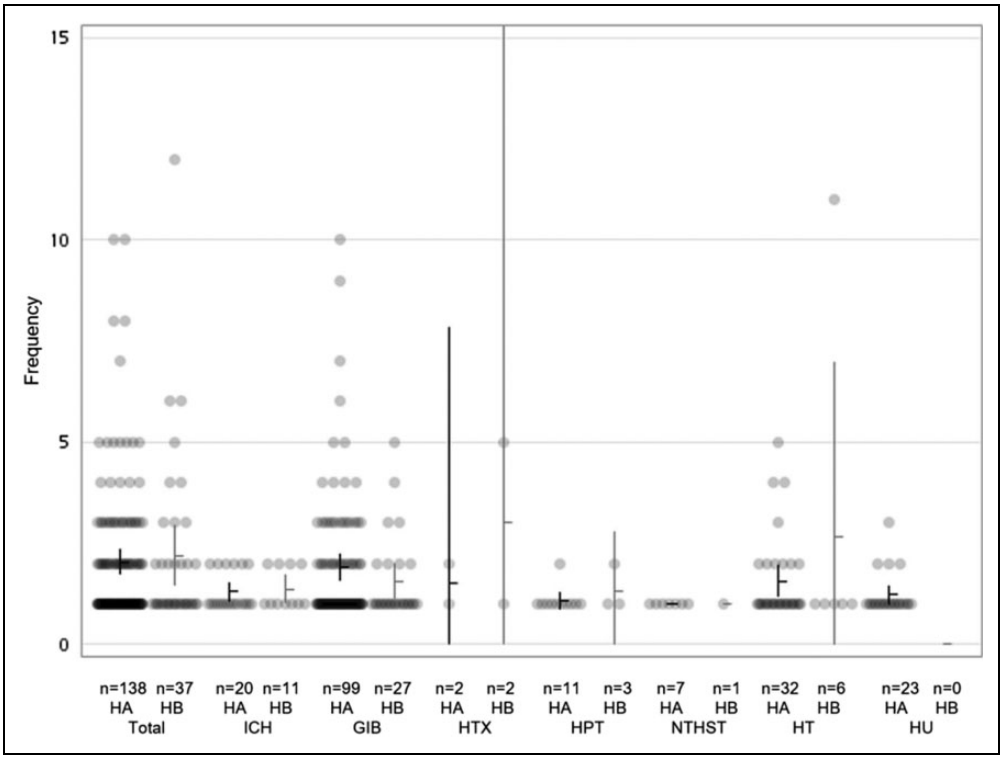

Figure 2. Frequency of hospitalization resulting from major bleeding events in patients with hemophilia A and hemophilia B above 18 years and older. GIB indicates gastrointestinal bleeding; HTX, hemothorax; HPT, hemoperitoneum; HT, hemarthrosis; HU, hematuria; ICH, intracranial hemorrhage; n, number of patients with each bleeding event; total means a total number of patients with $\geq$1 major bleeding event; NTHST, nontraumatic hematoma of soft tissue. Bar represents mean with 95% confidence interval.

HA: (1) less factor consumption, (2) less severe clinical symptoms, (3) less severe gene mutations, and (4) less need for orthopedic surgery.[13] In terms of coagulation factor consumption, various measurements were used to estimate and compare differences between patients with HA and HB. Biss et al analyzed 2161 patients with HA and 502 patients with HB in Canada and compared the proportion of patients receiving prophylaxis.[5] They found a greater proportion of prophylaxis use in HA (69%) compared to that in HB (32%). A surveillance study of 6196 patients with severe HA in the United States between 1999 and 2010 showed that the rate of prophylaxis use was 59% in patients with severe HA in 2010,[14] whereas another surveillance study between 1998 and 2011 showed that 489 (45%) of 1079 patients with severe HB received prophylaxis in 2011.[15] While it seems that a greater proportion of patients with HA used prophylaxis than those of HB, it is not known whether the difference is statistically significant. An Australian study reported rates of prophylaxis use in patients

with severe HA and HB of 82% and 75%, respectively, but again no formal analysis was conducted.[16] Another method of comparing the severity of patients with HA and HB is to evaluate average IU consumption. Nagel et al compared the IU per patient per year between 68 patients with HA (104 722 IU/patient/year) and 20 patients with HB (107 182 IU/patient/year) and concluded that there were no significant differences.[17] Klamroth et al further adjusted for the effect of body weight and reported a figure of 2109 IU/kg/year in 60 adults with severe HA on prophylaxis and 1289 IU/kg/year in 2 severe adults with HB.[6] However, several potential confounding effects need to be considered when using factor consumption to compare severity between HA and HB, such as the different pharmacological properties of FVIII and FIX. Although in vivo recovery rates of FVIII is higher than that of FIX, terminal half-lives for standard recombinant FVIII products (8-12 hours) are much shorter than FIX products (24-36 hours). Another possible confounder is patient age, which also affects the terminal half-life of FVIII, but not that of FIX.[18,19] Therefore, using factor consumption to compare disease severity may not truly reflect differences between HA and HB, and several confounding factors would need to be adjusted to perform a valid comparison. Compared to previous studies that included both PWH with the on-demand and prophylactic therapy, an advantage of our study design was that a further comparison between patients with HA and HB with the on-demand therapy was conducted. This was done in order to consider any variability due to prophylaxis adherence and associated pharmacokinetic parameters, such as the area under the curve (AUC) and time spent with the factor level below the critical threshold.

Some disagreement was found between patients with HA and HB in clinical symptoms such as bleeding rates and HSS score. Melchiorre et al reported more frequent HT, greater World Federation of Hemophilia score, and higher ultrasound score in 70 patients with severe HA compared to 35 patients with severe HB.[20] However, methodological considerations such as inclusion bias and stratification of HT frequency (<10, 10-50, and >50) have been raised.[21] Schulman et al found higher HSS scores in 37 patients with HA compared to 6 patients with HB,[4] although Tagliaferri et al did not find the same results in another small cohort.[10] Similarly, Vyas et al also reported no significant differences in all components of the HSS score between 139 patients with HA and 39 patients with HB with different levels of severity.[22] This study suggests that the incidence rate and frequency of major bleeding events were similar between HA and HB. Interestingly, in the subgroup analysis, we found a higher incidence rate of ICH in patients with HB than those with HA. This result was comparable to a previous study, in which 4 out of 12 patients with severe HB had ICH, compared to 5 out of 111 patients with severe HA.[6] Another study found no significant difference between patients with HA and HB in death rates for ICH, after adjusting for age, calendar period, and inhibitor status.[23]

Another possible reason to explain the discrepancy in clinical symptoms between patients with HA and HB may be differences in the frequency of severe genetic mutations. Mutation severity is considered to correlate with clinical phenotype.[24] Moreover, mild bleeders with severe hemophilia could be identified using the endogenous thrombin potential test, and most of these mild bleeders had non-null mutations.[25] Although less severe gene defects are more common in patients with HB than those with HA, certain missense or nonsense mutations may result in a phenotype similar to a null mutation, depending on the location of the mutation.[26] Therefore, the actual proportion of severe mutation in HB may be greater than previously reported.

With regard to orthopedic surgery in patients with HA or HB, Tagariello et al reported 328 operations in 253 patients with severe HA and 19 operations in 15 patients with severe HB who had never received prophylactic treatment, resulting in a 3-fold higher risk of undergoing joint arthroplasty after normalizing to the whole hemophilia population and adjusting for significant covariates.[7] In contrast, our previous study showed no increased risk of total joint replacement in 782 patients with HA versus 153 patients with HB (HR: 0.92, 95% CI: 0.54-1.58) after adjusting for various confounders including age, pyogenic arthritis, and HIV infection.[27]

While this national population-based study had a number of strengths, there were also some limitations. The NHI research database lacks records of laboratory data such as baseline FVIII/FIX and inhibitor level. Second, the database does not contain any information on genetic mutations. Finally, HT and NTHST are common manifestations of PWH, but not every event is recorded in the NHIRD since most instances of these 2 types of events are treated at home.

Conclusions

Whether patients with HB have less severe clinical manifestations compared to those with HA remains controversial. Here, we contribute our results which clearly demonstrated that patients with severe HB encountered a similar rate of major bleeding events to those of severe HA, and there were no differences in the frequency of hospitalization due to major bleeding events. Some previous studies have presented evidence demonstrating HA is more severe than HB, while others have found the opposite result. However, caution is warranted in the interpretation of the results of these investigations. Further studies are needed to definitively establish which form of hemophilia is more severe and to elucidate the underlying mechanisms.

Authors' Note

Jiaan-Der Wang and Ming-Yang Shih contribute equally to this work as first author.

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Declaration of Conflicting Interests

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