

ORIGINAL ARTICLE

Analysis of hospitalization of people with hemophilia—12 years of experience in a single center

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Abstract

Background: To what extent hospital use and medical resources are used on hemophilia care in China's health care system is unknown.

Objectives: This study was based on a single center in China and was conducted to comprehensively assess the resource use for hospitalization of people with hemophilia.

Methods: We analyzed clinical characteristics, diagnosis, inhibitor status, reasons, length of stay, and hospital costs of 323 hospitalizations in which hemophilia must be considered as the main factor for hospitalization from January 2009 to December 2020 at the Institute of Hematology and Blood Diseases Hospital in Tianjin, China.

Results: There were 265 hospitalizations for people with hemophilia A (HA) and 58 with hemophilia B (HB). Seventy-eight hospitalizations (24%) were for patients with inhibitor (INH+). Minor bleeding (eg, hemarthrosis, hematuria) was the most common reason for hospitalization. The cost of clotting factor concentrates was the major burden of inpatients with hemophilia. Total cost in a single hospitalization of a person with HA (median, 21,281 Chinese yuan [¥]) was about twice that for HB (median, ¥11,060). Expenditure of drugs in HA (median ¥14,157) was two to three times more than that in HB (median, ¥5707). Total cost and drug cost in hospitalizations of people with inhibitors were about two times more than these without (INH-) (median cost in INH+ hospitalizations: total cost, ¥27,303; drug cost, ¥20,445. Median cost in INH- hospitalizations: total cost, ¥17,743; drug cost, ¥11,973.).

Conclusions: For hemophilia, the most dominant cost during hospitalization was on clotting factor concentrates. Diagnosed HA and inhibitor positivity increased the global cost.

KEYWORDS

hemophilia, hospital costs, hospitalization, inhibitor, length of stay, reasons

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Essentials

- Hospital use in hemophilia care in China is unknown.
- We analyzed 323 hospitalizations, the main reason for which was hemophilia.
- Clotting factor concentrates accounted for the majority of the total costs.
- Diagnosed HA and inhibitor positivity increased the global cost.

1 | INTRODUCTION

Hemophilia is a group of inherited bleeding disorders caused by deficiency or dysfunction of the coagulation proteins factor VIII (FVIII), leading to hemophilia A (HA), and factor IX (FIX), leading to hemophilia B (HB). Since these plasma glycoproteins have an essential role in coagulation, their defects will cause defects in clot formation, resulting in hemorrhagic diathesis, affecting mucosa, soft tissue, vital organs, joints, and muscles and even fatal intracranial hemorrhage. Repeated joint hemorrhages result in chronic arthropathy, even loss of joint movement.¹

As a group of rare X-linked recessive disorders, hemophilia affects mainly males. The prevalence is around 17.1 and 3.8 per 100,000 male births for HA and HB globally.² Being the country with the largest population in the world, China has an estimated hemophilia population of at least 130,000.³

Before the 1990s, the development of hemophilia management in China was stagnant.⁵ The formation of the Hemophilia Treatment Center Collaborative Network of China (HTCCNC) in 2004 led to the gradual buildup for hemophilia care capacity throughout China. The gradual coverage of coagulation products for hemophilia treatment by the National Medical Insurance System greatly reduces the economic burden of people with hemophilia. Importantly, in 2007, hemophilia was included in “outpatient special diseases,” allowing for insurance coverage for treatment of bleeding in people with hemophilia not only in the inpatient setting but also in the outpatient setting.⁶ Low-dose prophylaxis for hemophilia in China that began in 2007 has been shown to reduce bleeding rates by 75%–80%, with substantial gains in life quality.^{8,9}

With the nationwide improved hemophilia care, severe hemorrhage has decreased, with a decrease in hemophilia-related hospitalizations. At this time, there are few real-world data about the hospital use and medical resource usage for people with hemophilia in China. As one of the core members of HTCCNC, the Institute of Hematology and Blood Diseases Hospital (IHBDH), Chinese Academy of Medical Sciences (CAMS), and Peking Union Medical College (PUMC), serves patients from all over the country. We retrieved patients' medical records between January 2009 and December 2020 to conduct an investigation on hospitalization of people with hemophilia.

2 | METHODS

2.1 | Patients

People with a confirmed diagnosis of HA or HB who were hospitalized in IHBDH between January 2009 and December 2020 were included. Those who were enrolled for clinical trials were excluded. Excluded were also people with hemophilia A and B whose hospitalization diagnosis was non-hemophilia related, for example, those with a primary diagnosis such as acute leukemia, lung infection, or allergic purpura. This study was approved by the Ethics Committee at Institute of Hematology and Blood Diseases Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College (IHBDH, CAMS & PUMC).

IHBDH is a tertiary hospital specializing in blood diseases. The mean number of visits by people with hemophilia at IHBDH was 4192 (standard deviation [SD], 1524; median, 4748; range, 1289–5925; interquartile range [IQR], 3104–5421) per year with an increasing trend from 2009 to 2020. Most visits (60%–80%) were from people with hemophilia in Tianjin. The vast majority of patient visits and treatments were on an outpatient clinic basis, and only a few patients required care as inpatients (Figure S1).

Owing to the specialty of the IHBDH, there may be admission bias in these patients. To comprehensively understand reasons for hospitalization of people with hemophilia, a questionnaire survey including name, age, diagnosis, number of hospitalizations, and reasons in the past 5 years was conducted on people in Tianjin with hemophilia through “Wenjuanxing,” a professional online questionnaire survey platform. Hospital of admission included both our hospital and other hospitals.

2.2 | Study variables and definitions

Based on the Consensus of Chinese experts (version 2017), consistent with the international definition, the severity of hemophilia was defined by clotting factor activities as mild (0.05–0.40 IU/ml), moderate (0.01–0.05 IU/ml), or severe (<0.01 IU/ml).¹⁰

Inhibitors to FVIII or FIX were screened and quantified using the Bethesda assay in our hospital coagulation laboratory. Inhibitor titer >0.6 Bethesda units (BU)/ml was defined as positive.

Patients' characteristics, diagnosis, inhibitor status, reasons and length of stay of hospitalizations, status of blood-borne infections, and hospital costs were collected. The costs analyzed in this study included total costs in a single hospitalization and costs of hemophilia-related laboratory examinations (including coagulation-related and infection-related tests), imaging (joints, hematoma-related ultrasonic, X-ray, and computed tomography), and drugs (F, FIX, prothrombin complex concentrates [PCCs] and immunosuppressants) and were expressed in Chinese yuan (CNY) (exchange rate: 1 CNY to 0.1533 USD and 0.1246 EUR in 2020). The costs were adjusted to 2020 according to the Consumer Price Index of Healthcare released by the Chinese National Bureau of Statistics.

Based on the literature¹¹ and on the actual situation of our patients, reason for hospitalization was classified into five groups: minor bleeding (eg, hemarthrosis, hematuria), major bleeding (eg, cerebral, gastrointestinal), pseudotumor, postoperative bleeding, and others.

2.3 | Statistical analysis

Statistical analysis was performed using SPSS 26 (IBM, Armonk, NY, USA). Descriptive statistics were reported using frequencies and percentages for categorical variables; mean \pm SD, 95% confidence interval (CI) of mean, median (IQR) and range were used to describe continuous variables. Extreme outlier costs referred to values greater than three times IQR. Given the skewed distribution of cost data and length of stay of hospitalizations, nonparametric statistics were used to assess differences between HA and HB, with or without inhibitors and with different reasons for hospitalization. A *p* value < 0.05 was considered statistically significant.

3 | RESULTS

3.1 | Characteristics of hospitalizations

Between January 2009 and December 2020, a total of 323 hospitalizations, 223 people, were included, 265 (82.0%) hospitalizations with HA and 58 (18.0%) with HB (Table 1). These included 318 males (98.5%) and 5 females (1.5%). The median age was 23 (IQR, 14–39; range, 0.1–66; mean, 27 \pm 16) years. The median time from first diagnosis to hospitalization in our hospital was 15 (IQR, 6–25; range, 0–53; mean, 17 \pm 13; 95% CI, 15–18) years. One hundred fifteen (35.6%) hospitalizations were for children and adolescents. The majority of hospitalizations (268; 83.0%) were for people from outside Tianjin, while Tianjin residents took up only a small proportion (55; 17.0%) (Figure S1). The number of hospitalizations per year showed a downward trend, both for Tianjin and for referrals from outside.

Seventy-eight (24.1%) hospitalizations were for patients with inhibitors, of which 30 were of low titer (<5 BU), 26 with HA and 4 with HB. Among hospitalizations for people with HA, the median titer was 8.4 (IQR, 3.1–67.1; range, 0.6–10240.0; mean,

TABLE 1 Characteristics of hospitalizations

	HA and HB	HA	HB
Total (N, %)	323 (100)	265 (82.0)	58 (18.0)
Gender (N, %)			
Male	318 (98.5)	261 (98.5)	57 (98.3)
Female	5 (1.5)	4 (1.5)	1 (1.7)
Age, median (IQR)	23 (14–39)	25 (14–41)	20 (11.8–29.3)
Severity			
Mild	78	70	8
Moderate	130	98	32
Severe	115	97	18
INH+ (N, %)	78 (24.1)	70 (26.4)	8 (13.8)
Mild	3	3	0
Moderate	22	22	0
Severe	53	45	8
Inhibitor titer, median (IQR)	8.4 (3.8–58.8)	8.4 (3.1–67.1)	10.3 (4.6–52.0)
INH- (N, %)	245 (75.9)	195 (73.6)	50 (86.2)
Mild	75	67	8
Moderate	108	76	32
Severe	62	52	10

Abbreviations: HA, hemophilia A; HB, hemophilia B; INH-, hospitalizations for people without inhibitor; INH+, hospitalizations for people with inhibitor; IQR, interquartile range.

230.1 \pm 1234.0) BU. Among hospitalizations for people with HB, the median titer was 10.3 (IQR, 4.6–52.0; range, 4.6–416.0; mean, 68.3 \pm 141.8) BU.

3.2 | Reasons and length of stay of hospitalizations

Reasons for hospitalizations were summarized in Table 2. Minor bleeding was the main reason for hospitalization, whether patients were inhibitor positive or not. Forty-seven patients had more than one hospitalization (median, 2; IQR, 2–4; range, 2–14; mean, 3 \pm 2).

The median length of hospital stay was 5 (IQR, 3–9; range, 1–745; mean, 10 \pm 42) days. There was no statistical difference in the length of stay between HA and HB, with or without inhibitor, and among different reasons for hospitalization (data not shown).

3.3 | Hospital costs

Drug costs, mainly for clotting factor concentrates, accounted for the majority of the total costs (about 70%) in almost all hospitalizations. Total costs and drug costs for each HA hospitalization (total costs: median, 21,281; IQR, (11,428–41,969); drug costs: median, 14,157; IQR, 4854–34,707) were on average higher than those for each HB (total costs: median, 11,060; IQR, 7284–23,418; drug costs: median, 5707; IQR, 3480–15,191; *p* = 0 and 0.001, respectively) (Table 3).

TABLE 2 Reasons for hospitalizations

N (%)	Minor bleed				Major bleed				Pseudo-tumor	Post-operative bleeding	Others			
	Total	Hemarthrosis	Muscle bleeding (except for iliopsoas)	Hematuria	Hematoma	Other bleeding	Total	Cerebral				Gastrointestinal	Iliopsoas	Total
Severe hemophilia without inhibitor	83	27	12	6	10	7	62	5	3	2	10	2	0	9
Moderate or mild hemophilia without inhibitor	219	60	33	10	38	23	164	3	20	5	28	9	9	9
Inhibitor patients	97	21	11	10	18	12	72	4	5	6	15	3	1	6
Total, N (%)	399	108	56	26	66	42	298 (74.7)	12	28	13	53 (13.3)	14 (3.5)	10 (2.5)	24 (6.0)

Note: Data in this table were derived from hospital records of hospitalizations of people with hemophilia.

Other costs were similar between HA and HB. Total costs and drug costs for people with inhibitors (total costs: median, 27,303; IQR, 11,359–60,604; drug costs: median, 20,445; IQR, 5234–47,688) were higher than for those without (total costs: median, 17,743; IQR, 10,071–33,650; drug costs: median, 11,973; IQR, 3610–26,330; $p = 0.005$ and 0.001 , respectively). Laboratory costs for people who were inhibitor positive (INH+) (median, 1534; IQR, 1127–2319) were lower than those who were inhibitor negative (INH-) (median, 1875; IQR, 1342–2962; $p = 0.03$). Imaging costs for people who were INH+ were similar to those who were INH- (Table 3). Costs among different reasons of hospitalization were similar (data not shown).

Total costs for adults (median, 21,680; IQR, 11,017–43,127; range, 444–226,796; mean, $32,934 \pm 35,027$; 95% CI, 28,146–37,723) were significantly higher than these for children and adolescents (median, 16,196; IQR, 8272–30,670; range, 75–448,469; mean, $27,722 \pm 47,253$; 95% CI, 18,993–36,451; $p = 0.006$). However, when normalized by weight, the mean cost (in CNY) per kilogram of body weight was 948 ± 2776 for children and adolescents (median, 477; IQR, 209–836; range, 2–28,029; 95% CI, 411–1485) and was 469 ± 493 for adults (median, 309; IQR, 156–574; range, 9–3234; 95% CI, 394–545). Costs for children and adolescents were significantly higher than for adults ($p = 0.002$).

3.4 | Blood-borne infections

Hepatitis B virus (HBV), hepatitis C virus (HCV), HIV, and syphilis were screened in 283 hospitalizations. The seroprevalence was 12.7% for HCV and 1.8% for HBV. There was only 1 HIV positivity (0.4%). None were syphilis serology positive.

3.5 | Others

There were 34 Tianjin residents in the 323 hospitalizations. Both hospitalization and outpatient visit medical records of these patients in our hospital were analyzed. The total number of hospital visits for 34 people was 73 in median (IQR, 22–206; range, 3–364; mean, 115 ± 110). The mean number of hospital visits was 10 ± 9 per patient per year (median, 8; IQR, 3–19; range, 0.2–33). Outpatient visits took up the vast majority of all medical treatment types, with a median of 71 (IQR, 20–200; range, 2–363; mean, 109 ± 106), while hospitalization only made up a small proportion, with a median of 1 (IQR, 1–3; range, 1–99; mean, 6 ± 17).

A total of 172 valid questionnaires were collected, involving 172 males from Tianjin with hemophilia, with a median age of 22 (IQR, 12–40; range, 1–84; mean, 27 ± 19) years. These included 159 males with HA and 13 males with HB. Thirty-six (20.9%) cases were mild to moderate, and 25 (69.4%) had not been admitted for inpatient care within 5 years. The average number of hospitalizations was 0.6 per patient in 5 years. Of the 136 (79.1%) severe cases, 82 (60.3%) had not been admitted for inpatient care in recent 5 years, with an average number of hospitalizations of 0.8 per patient in 5 years. Hemophilia-related

TABLE 3 Hospital costs and proportions

	Total costs (yuan)		Laboratory costs (yuan)		Laboratory proportion (%)		Imaging costs (Yuan)		Imaging proportion (%)		Drug costs (Yuan)		Drug proportion (%)		
	Median (range, IQR)	Mean ± SD	Median (range, IQR)	Mean ± SD	Median (range, IQR)	Mean ± SD	Median (range, IQR)	Mean ± SD	Median (range, IQR)	Mean ± SD	Median (range, IQR)	Mean ± SD	Median (range, IQR)	Mean ± SD	
	95%CI	95%CI	95%CI	95%CI	95%CI	95%CI	95%CI	95%CI	95%CI	95%CI	95%CI	95%CI	95%CI	95%CI	
Total, N = 323	18,755 (75–448,469, 10,167–37,436)	1772 (0–11,335, 1283–2857)	1772 (0–11,335, 1283–2857)	8.4 (0–96.4, 4.1–19.5)	15.4 ± 17.8 [13.5–17.4]	101 (0–40,042, 0–787)	0.4 (0–91.0, 0–3.8)	13,178 (0–440,499, 4024–29,790)	4.1 ± 9.7 [3.1–5.2]	71.9 (0–98.7, 45.5–84.9)	61.1 ± 30.8 [57.7–64.5]	64.8 (0–97.9, 34.6–78.0)	56.3 ± 29.3 [48.6–64.0]	69.9 (0–98.7, 34.4–82.6)	58.6 ± 31.5 [54.6–62.5]
HA, N = 265	21,281 (75–448,469, 11,428–41,969)	1783 (0–11,335, 1328–2879)	1783 (0–11,335, 1328–2879)	7.8 (0–96.4, 4.0–19.0)	15.2 ± 18.1 [13.0–17.4]	114 (0–40,042, 0–848)	0.5 (0–91.0, 0–3.6)	14,157 (0–440,499, 4854–34,707)	4.1 ± 9.6 [2.9–5.3]	74.3 (0–98.7, 48.5–85.8)	62.2 ± 31.1 [58.4–65.9]	64.8 (0–97.9, 34.6–78.0)	56.3 ± 29.3 [48.6–64.0]	69.9 (0–98.7, 34.4–82.6)	58.6 ± 31.5 [54.6–62.5]
HB, N = 58	11,060 (444–226,796, 728–23,418)	1635 (0–8461, 1146–2672)	1635 (0–8461, 1146–2672)	11.8 (0–73.1, 5.4–25.3)	16.5 ± 16.1 [12.3–20.8]	0 (0–15,187, 0–394)	0 (0–65.5, 0–4.4)	5707 (0–150,629, 3480–15,191)	4.3 ± 10.3 [1.6–7.0]	64.8 (0–97.9, 34.6–78.0)	56.3 ± 29.3 [48.6–64.0]	64.8 (0–97.9, 34.6–78.0)	56.3 ± 29.3 [48.6–64.0]	69.9 (0–98.2, 55.1–89.6)	69.1 ± 27.3 [63.0–75.3]
INH+, N = 78	27,303 (724–448,469, 11,359–60,604)	1534 (0–10,083, 1127–2319)	1534 (0–10,083, 1127–2319)	5.4 (0–96.4, 2.6–11.1)	12.0 ± 19.5 [7.6–16.4]	0 (0–8211, 0–729)	0 (0–23.3, 0–1.9)	20,445 (0–440,499, 5234–47,688)	2.2 ± 4.3 [1.2–3.2]	79.0 (0–98.2, 55.1–89.6)	69.1 ± 27.3 [63.0–75.3]	79.0 (0–98.2, 55.1–89.6)	69.1 ± 27.3 [63.0–75.3]	79.0 (0–98.2, 55.1–89.6)	69.1 ± 27.3 [63.0–75.3]
INH-, N = 245	17,743 (75–226,796, 10,071–33,650)	1875 (0–11,335, 1342–2962)	1875 (0–11,335, 1342–2962)	9.2 (0–81.2, 4.9–23.3)	16.5 ± 17.1 [14.4–18.7]	125 (0–40,042, 0–793)	0.7 (0–91.0, 0–4.7)	11,973 (0–150,629, 3610–26,330)	4.8 ± 10.8 [3.4–6.1]	69.9 (0–98.7, 34.4–82.6)	58.6 ± 31.5 [54.6–62.5]	69.9 (0–98.7, 34.4–82.6)	58.6 ± 31.5 [54.6–62.5]	69.9 (0–98.7, 34.4–82.6)	58.6 ± 31.5 [54.6–62.5]

Note: Laboratory proportion meant the proportion of laboratory examination cost to total cost in a single hospitalization; so as to imaging proportion and drug proportion. Drug costs accounted for about 70% of the total costs, while imaging costs and laboratory examination costs took up only a small part. Total cost in a single hospitalization of HA was about twice as much as HB. Total costs and drug costs in INH+ hospitalizations were about two times more than INH- ones, while laboratory costs were lower. Exchange rate: 1 CNY to 0.1533 USD and 0.1246 EUR in 2020.

Abbreviations: CI, confidence interval; HA, hemophilia A; HB, hemophilia B; INH+, hospitalizations for people without inhibitor; INH-, hospitalizations for people with inhibitor; IQR, interquartile range; SD, standard deviation.

	Severe hemophilia, N	Moderate or mild hemophilia, N	Total, N (%)
Minor bleed	32	3	35 (26.0)
Hemarthrosis	12	2	14
Muscle bleeding (except for Iliopsoas)	0	1	1
Hematuria	3	0	3
Hematoma	6	0	6
Other bleeding	11	0	11
Major bleed	13	5	18 (13.4)
Cerebral	9	0	9
Gastro-intestinal	4	5	9
Iliopsoas	0	0	0
Pseudotumor	1	3	4 (3.0)
Surgery	33	3	36 (26.9)
Knee	23	1	24
Hip	7	1	8
Head of femur	0	1	1
Synovectomy	3	0	3
Other	9	1	10 (7.5)
Non-hemophilia related	24	7	31 (23.1)
Total	112	22	134

TABLE 4 Reasons for hospitalization of hemophilia patients in Tianjin

Note: Data in this table were derived from the questionnaire survey conducted on people in Tianjin with hemophilia.

surgery accounted for the highest proportion (26.9%) of reasons for hospitalization, and most were for joint replacement, particularly for the weight-bearing joints such as knee and hip. A significant number of patients were admitted for inpatient care for non-hemophilia-related reasons, such as fractures, cholecystectomy, appendectomy, diabetes, lung infection, and so on (Table 4).

4 | DISCUSSION

The current study provided a comprehensive overview of hospital use and medical resource usage for people with hemophilia based on 323 hospitalizations in a single hemophilia treatment center in Tianjin, China. The vast majority of people could be treated on an outpatient basis, and only a few required hospitalization for uncontrolled bleeding, inhibitor, and the like. Costs of clotting factor concentrates accounted for about 70% of the total cost in a single hospitalization of a person with hemophilia. Diagnosed HA and inhibitor positivity increased the global cost. Mean costs per kilogram of body weight for children and adolescents were significantly higher than for adults.

A total of 75.9% hospitalizations in this study were for people with moderate to severe hemophilia. The overall INH+ rates in hospitalizations for people with HA and HB were 26.4% and 13.8%. INH+ rates in hospitalizations for people with severe HA and severe HB were 46.4% and 44.4%. Xuan et al¹² reported a lower inhibitor rate for in- and outpatients combined and their rate for inpatients was not provided. The higher inhibitor rate among our inpatients suggests

that people who were INH+ were more likely to be admitted for inpatient care. This may be attributed to people who were INH+ being more prone to bleedings that were more difficult to control as outpatients. Some of these people who were INH+ also needed repeat hospitalizations for immune tolerance induction (ITI) therapy in combination with rituximab. Our results are consistent with those of Valentino et al,¹³ who also showed that people who were INH+ had more frequent hospitalization than people who were INH-.

Previous studies often analyze health care costs of hemophilia on an annual basis.^{13,14} In this study, we analyzed medical costs of people with hemophilia from a single hospitalization perspective.

Total cost in a single hospitalization of HA (median, 21,281; IQR, 11,428–41,969) was about twice as much as HB (median, 11,060; IQR, 7284–23,418) in our study. Armstrong et al¹⁵ also showed the same trend expressed as cost by person-year, being \$98,334/person-year for HA and 23,265 for HB. The cheaper plasma-derived FVIII (¥540 for 300 IU) was widely used for HA bleeding treatment during hospitalization and recombinant F (¥1907 for 500IU), a 2-fold more expensive treatment option, was used in only 15.5% of hospitalizations. Activated recombinant human FVII (rFVIIa), an expensive bypassing agent (¥5500/mg), was used in 4.9% for people with HA inhibitor during hospitalization. For people with HB, PCC (¥265 for 300 UI, 75.9%) rather than recombinant FIX (rFIX, ¥2210 for 250 UI, 5.17%), an ≈10-fold more expensive treatment option, was the dominant clotting factor concentrates used for bleeding control. Recombinant FVIIa was used in just 1 (1.7%) of all HB hospitalizations. As included in “outpatient special diseases” in Tianjin, hemophilia has been entitled to 55% reimbursement rate from health

insurance at the outpatient clinic, and 75% for hospitalization. The average annual income in Tianjin was ¥43,854 in 2020.

The price differences among clotting factor concentrates and the distinct proportion of each used by people with HA and HB resulted in higher clotting factor concentrate expenditure by 2–3 times for admitted HA than that for HB. The cost of clotting factor concentrates accounting for >70% cost in most hospitalizations was the major burden for inpatients with hemophilia, as has been reported by previous studies.^{11,16} Costs of coagulation-related laboratory tests and imaging took up only a small proportion. The cost difference of clotting factor concentrates for HA and HB dictated the total cost of HA versus HB treatments. However, a study based on six French hemophilia centers⁹ reported no difference in terms of cost between treating HA and HB. The researchers ascribed this to the fact that the lower recovery of FIX was counterbalanced by its longer half-life, leading to a similar consumption of factor.

We found that total costs and drug costs in hospitalizations of people with inhibitors (median [IQR] of total cost: 27,303 [11,359–60,604]; drug cost: 20,445 [5234–47,688]; laboratory cost: 1534 [1127–2319]) were about two times more than these without (median [IQR] of total cost: 17,743 [10,071–33,650]; drug cost: 11,973 [3610–26,330]; laboratory cost: 1875 [1342–2962]), while laboratory costs were lower. The expensive bypassing agent rFVIIa was used in about one in five hospitalizations with inhibitors in our study. People with inhibitor receiving ITI would consume a large amount of FVIII, and in some patients rituximab was used in combination. The management of people who are INH+ is complicated by less predictable responses to bypassing agents compared to specific factor replacement therapy in people who are INH-. People who are INH+ have more frequent hospitalization than people who are INH- and account for more than three times the annual cost for people with HA and six times that for people with HB.¹⁵ For people with inhibitor with frequent hospitalization, laboratory tests were comprehensive for the first hospitalization and were simplified thereafter, leading to the fact that laboratory costs were lower in hospitalizations of people with inhibitors. Interestingly, some analyses showed that mean cost of people who were INH+ was inflated by a small number of patients with extreme outlier costs. After adjusting for these outliers, the cost of outpatient clotting factor replacement products was not significantly greater for people who were INH+ compared to people who were INH-.¹³ In our study, after adjusting for these outliers, total costs for INH+ hospitalization (N = 76; median, 26,722; IQR, 11,232–57,179; range, 724–174,864; mean, 39,314 ± 37,657; 95% CI, 30,709–47,919) were still more than that for the people who were INH- (N = 241; median, 17,654; IQR, 9964–32,415; range, 75–92,412; mean, 23,504 ± 18,829; 95% CI, 21,114–25,893; $p = 0.006$).

When normalized by weight, total costs for children and adolescents (mean, 948 ± 2776) were significantly higher than that for adults (mean, 469 ± 493) ($p = 0.002$). As China is still a developing country, the economic condition of most patients is poor. In clinical practice, it was easier for children to use and afford a full dose of

clotting factor concentrates because they often weighed less than adults. The percentage of children with inhibitors among the ones admitted with hemophilia was 27%, slightly more than that in adults. This may also partly account for the higher treatment cost for admitted children.

A previous study in the United States showed that hemophilia-related cost for most people who were INH- was relatively stable over time, with no significant year-to-year variations.¹³ In China, however, with the introduction of new products, treatment choices have changed, as well as their costs. For example, the application of rFIX, which shows a lower recovery and a higher cost than plasma-derived FIX in PCC, may increase cost for HB. The use of rFVIIa, an expensive bypass agent, significantly increases cost for the management of people who are INH+. In our study, total cost showed a rising trend by year (Figure 1).

All five cases who were positive for HBV were diagnosed before 2014, none thereafter. This is a positive outcome from increasing uptake of HBV vaccine. In general, HIV and HCV infection rates were relatively low, suggesting that the issue of blood-borne viral infection was mitigated to some extent with the use of recombinant factor products, virus-inactivated plasma-derived factors, and the improvements in blood safety in our country.

The outpatient clinic attendance was increasing from 2009 to 2016 and then remaining stable, especially for patients from Tianjin. This is the beneficial effect from the economic development of China and improved hemophilia care nationwide.⁶ Overall, the hospitalization rate was relatively low and was decreasing by year, particularly for people from Tianjin with hemophilia. The inclusion of hemophilia in “outpatient special diseases” allowed insurance coverage of treatment of bleeding in people with hemophilia in the outpatient setting and resulted in greatly reduced hospitalizations. This policy prevented patients from being hospitalized just

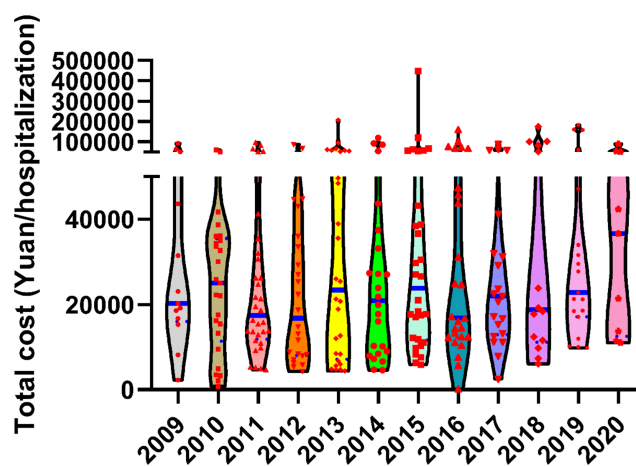


FIGURE 1 The variation of total cost by year. Total cost meant all expenses in one hospitalization. The dark blue solid line in the middle represent median, and blue dotted lines on both sides represent interquartile range (IQR). The red plot represented total cost in yuan in a single hospitalization. Exchange rate: 1 CNY to 0.1533 USD and 0.1246 EUR in 2020

for medical reimbursement and reduced the burden on doctors and hospitals.

There are some limitations in this study. As the national clinical research center for blood diseases, IHBDH serves patients with refractory and critical blood diseases from all over the country. However, as a hospital specializing in blood diseases, IHBDH has its weaknesses. It can deal only with diseases of internal medicine. Other cases, for example, surgery and rehabilitation treatment, are not provided. Hemophilia-related surgeries, such as synovectomy for hemophilia joints, pseudotumor, rehabilitation treatment, and tumor, need to be referred to a general hospital for treatment. Thus, there was admission bias. In our cohort, reason for hospitalization was confined to major or minor bleeding, inhibitors, and so on, but not hemophilia-related surgeries. To overcome this problem and to fully understand the reason for hospitalization of people with hemophilia, we conducted a questionnaire survey on people with hemophilia in Tianjin. The questionnaire survey provided an overview about reason for hospitalization of people with hemophilia, albeit the survey responses might be biased since this was conducted online. But medical costs of these patients could not be acquired and cost analysis on different surgeries and rehabilitations could not be carried out. Another limitation is that the ethnicity information is incomplete, which is a measure of social determinant of health.

5 | CONCLUSIONS

This single Chinese center study provides an overview of hospitalization of people with hemophilia. As the special outpatient disease policy implements, the number of hospitalizations for hemophilia at the hematology department has greatly reduced. The cost of clotting factor concentrates was the major burden of inpatients with hemophilia. Diagnosed HA and inhibitor positivity increased the global cost. Databases enabling record linkage across hospitals are needed to comprehensively research the cost of hemophilia-related surgeries. Future studies will be conducted in a larger patient population with various reasons for hospitalization.

AUTHOR CONTRIBUTIONS

Study conception and design: FX and RCY; data acquisition: CYQ, WL, LZ, and LLC; statistical analysis: CYQ; interpretation of the data: all authors; drafting of the manuscript: CYQ and FX; critical revision of the manuscript for important intellectual content: all authors; final approval of the manuscript: all authors.

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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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