

Use of prophylaxis in patients with hemophilia and its relationship with medical expenditure in urban China

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Research

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Abstract

Background

The advantage of prophylaxis treatment has been proved to significantly improve the average life expectancy and quality of life in patients with hemophilia (PWH). However, few studies have examined the use of prophylactic treatment in PWH in China. Our study aims to investigate the prophylactic treatment use of PWH and its association with medical costs in China.

Methods

The study population included 815 patients with hemophilia between 2010 and 2016. The chi-square test was used to analyze the factors influencing usage of prophylactic treatment. Univariate analysis was used to analyze the influencing factors of treatment costs for hemophilia A and hemophilia B.

Results

The proportion of hemophilia A patients and hemophilia B patients using prophylactic treatment in urban China was 3.2% and 3.4%. PWH in urban China have a heavy financial burden. The total annual per capita medical expenses for hemophilia A patients were ¥31022, of which 69.0% (¥21400) was caused by hemophilia. And the total annual per capita medical expenses for hemophilia B patients were ¥46084, of which 91.5% (¥42055) was caused by hemophilia. The out-of-pocket (OOP) costs from hemophilia account for more than 30% of per capita disposable income. Besides, we found that there was a statistically significant difference in total annual costs between patients who took prophylactic treatment and those who did not. ($P < 0.001$)

Conclusion

The proportion of PWH receiving prophylaxis treatment in China is very low due to the high cost of medical treatment and the shortage of medicines. There was a statistically significant difference in total annual costs between patients with and without prophylactic treatment.

Background

Hemophilia is an inherited bleeding disorder caused by a deficiency of coagulation factor VIII (hemophilia A) or factor IX (hemophilia B).[1] It is characterized by the spontaneous bleeding of the joints, muscles, viscera and deep tissues and difficulty in stopping the bleeding.[2] According to the World Hemophilia Federation (WFH), there are 400000 people living with hemophilia worldwide.[3] China has a population of 1.33 billion and an estimated of 100000 people with hemophilia.[4]

The rate of diagnosis and treatment of hemophilia is low. The WFH estimates that approximately 70% of patients with hemophilia (PWH) are underdiagnosed and untreated.[5] As the 2012 annual survey from the WFH reported, China's National Hemophilia Information Management Center had registered 10652 cases nationwide, which means only approximately 10% have been diagnosed and registered. [6] This figure is even lower than the average level in developing countries, where 85 percent of PWH are not treated.[7]

The treatment of hemophilia is mainly to supplement clotting factor, and many countries recommend prophylaxis treatment for PWH.[8, 9] Prophylaxis treatment has been administered to PWH for 4 decades.⁸ It can result in an improvement of the medical and social situation of patients, which can significantly reduce the bleeding frequency and hospitalization rate of PWH, as well as the incidence of hemophilic arthropathy. Evidence suggests that prophylactic treatment can prevent initial joint damage and decrease the frequency of joint hemorrhages in PWH.[10] The hospitalization rates of patients who receive prophylactic treatment are approximately 50% lower than those who receive on-demand treatment.[11] With the improvement of medical insurance and drug supply conditions, the basic conditions for hemophilia prevention and treatment have been established in China. The Chinese government and hemophilia organizations are actively promoting prophylactic treatment to reduce the disability rate and improve the quality of life of PWH.[12]

PWH usually require life-long treatment, which brings a huge social and economic burden.² The price of hemophilia drugs is very high due to the high cost of research and development, the high costs of drug storage and the low number of PWH.[13] Hemophilia has become a serious health problem in China because of the high cost of treatment.[14] According to a study on the cost of hemophilia treatment in Guangdong Province in 2008, 18.2% of PWH spent more than ¥118259 on treatment, which was about 120 times that of China's per capita health expenditure (¥972).[15] The quality of life of children with hemophilia is significantly lower than that of healthy children. Moreover, their treatment costs are nearly five times higher than those of healthy families, and more than half of hemophilia families in China cannot fully afford treatment costs.[16]

Currently, hemophilia has been included in the National Reimbursement Drug List (NRDL), which will greatly improve drug access for PWH.[17] In addition, with the continuous development of China's society and economy, PWH can gradually afford the cost of drug treatment. An increasing number of PWH have the ability of taking prophylactic treatment to improve their quality of life, enabling them to live as healthy people. Nevertheless, few studies have examined the use of prophylactic treatment in PWH in China. This study aims to investigate the prophylactic treatment use and the relationship between prophylactic treatment and medical costs for PWH in mainland China. Our research will help the public understand the current situation of the treatment of PWH in China.

Methods

Data source

The data used in this study were from the National insurance database operated by the China Medical Insurance Research Association (CHIRA). By the end of 2018, Basic Medical Insurance (BMI) covered more than 94 percent of Chinese citizens. Medical service utilization information of every Urban Employee Basic Medical Insurance (UEBMI) and Urban Resident Basic Medical Insurance (URBMI) (hereafter jointly referred to as BMI) beneficiary in hospitals and BMI designated drugstores is routinely collected in BMI databases at city level.[17] The CHIRA employs a two-stage systematic sampling design to obtain a national representative sample of BMI beneficiaries and extracts cross-sectional medical service utilization data annually from the city-level BMI databases. The percentage of sampled BMI beneficiaries is 2% in the centrally administered municipalities and provincial capitals, 5% in the prefecture-level cities, and 10% in the counties. The extract forms the unique national health insurance database known as the CHIRA database.[17]

Our study was based on the CHIRA database from 2010 to 2016, which included inpatient and outpatient diagnostic and medical service utilization data of 37.3 million BMI beneficiaries from 82 cities across the country, accounting for about 2% of the total population in mainland China. A total of 815 patients diagnosed and documented with hemophilia between 2010 and 2016 were included in the study.

Variables

Our study focused on the use of prophylactic treatment in PWH and its influencing factors. The independent variables included age, gender, insurance type and area. In addition, we also focus on the annual medical costs of PWH and its influencing factors, which are used to reflect the financial burden of PWH.

In this study, prophylactic treatment was defined as the regular use of clotting factor supplements for PWH over a one-year period, and the total dose of clotting factor supplements was not less than the minimum dose specified in The Chinese guidelines for hemophilia treatment. According to the recommendation of Chinese hemophilia treatment guidelines, PWH should take prophylactic treatment with the minimum amount of clotting factor preparation 43200IU per year. And the medical expenditure was defined as the total direct costs of seeking healthcare services for a PWH, which was the sum of treatment cost of each visit in a year. Indirect costs, such as the costs of transportation and special diets and wages lost due to illness, were not considered in this study. Furthermore, medical expenditure was categorized into two components—expenses within and beyond the reimbursement coverage of basic health insurance in China. Expenses beyond the reimbursement coverage of basic health insurance paid by a person is referred to as the out-of-pocket costs (OOP).

Statistical analysis

The chi-square test was used to analyze the factors influencing usage of prophylactic treatment in PWH. The independent variable is gender, insurance types, age, and area. Similarly, univariate analysis was used to analyze the influencing factors of treatment costs for hemophilia A and hemophilia B. Differences in means were tested using the Mann-Whitney U test. And the Kruskal-Wallis test was used to

compare more than two groups. These non-parametric tests were used because the data on medical expenses were not normally distributed. Statistical analysis was performed using the statistical software Stata/MP V.16.0. Statistical significance was considered at $p < 0.05$.

Results

Characteristics of participants

Our study included a total of 815 PWH in the CHIRA database, among which 696 (85.4%) were hemophilia A and 119 (14.6%) were hemophilia B. 22 (3.2%) hemophilia A patients were treated with prophylactic therapy. And 4 (3.4%) hemophilia B patients were treated with prophylactic therapy. Among hemophilia A patients, 613 (88.5%) were male and 80 (11.5%) were female. There were 200 (28.7%) teenagers, 285 (41.0%) aged 18-44 and 211 (30.3%) over 45. And 354 (50.9%) hemophilia A patients were covered by UEBMI, while the remaining 342 (49.1%) were covered by URBMI. The eastern region has a population of 377 (54.2%), the midland 172 (24.7%), and the western region 147 (21.1%). Among hemophilia B patients, 110 were male (92.4) and 9 were female (7.6%). There were 41(34.5%) children, 40 (33.6%) of those aged 18-44, and 38(31.9%) aged 45 and over. Among which 60 (50.4%) were covered by UEBMI and 59 (49.6%) were covered by URBMI. There are 62 (52.1%) in the eastern region, 44 (37.0%) in the midland and 13 (10.9%) in the western region.

The rate of prophylactic treatment of patients with hemophilia

3.6% of male PWH used prophylactic treatment, while none of the women PWH used prophylactic treatment. There was no significant correlation between the gender of PWH and their use of prophylactic treatment ($p=0.09$). In addition, there was no significant relationship between the age of PWH and their use of prophylactic treatment ($p=0.94$). Whether people with hemophilia A receive prophylactic treatment was significantly related to the area in which they live ($p=0.15$). 4.8% of hemophilia A patients living in the eastern China were treated with prophylactic treatment, which is higher than those living in the midland and western China. As for hemophilia B, the use of prophylactic treatment was related to the type of their insurance. Hemophilia B patients with UEBMI (6.8%) are more likely to use prophylactic treatment ($p=0.04$). (Table 2)

Medical expenses of patients with hemophilia

The overall healthcare annual costs are shown in Table 3. The total annual per capita medical expenses for hemophilia A patients were ¥31022, of which ¥21400 was caused by hemophilia. And the annual per capita OOP expenses were ¥8404 for Hemophilia A patients, of which ¥5714 was caused by hemophilia. The total costs and OOP caused by hemophilia A accounted for 69.0% and 68.0% respectively. The co-payment rate of total expenses for hemophilia A patients was 27.1%, among which the co-payment rate caused by hemophilia was 26.7%. Among them, the total annual per capita medical expenditure accounts for 73.3% of China's annual per capita GDP. OOP medical expenditure accounts for 36.6% of annual per capita disposable income in urban China. Medical expenses and OOP expenses caused by hemophilia A

account for 99.5% of GDP and 36.1% of annual per capita disposable income in urban China, respectively.

The total annual per capita medical expenses for hemophilia B patients were ¥46084, of which ¥42055 was caused by hemophilia. And the annual per capita OOP expenses were ¥9045 for Hemophilia B patients, of which ¥8298 was caused by hemophilia. The total costs and OOP caused by hemophilia B accounted for 91.3% and 91.8% respectively. The co-payment rate of total expenses for hemophilia B patients was 27.1%, among which the co-payment rate caused by hemophilia was 26.7%. Among them, the annual per capita total medical expenses accounted for 109.1% of China's annual per capita GDP, OOP medical expenses accounted for 34.1% of China's annual per capita disposable income. Medical expenses and OOP expenses caused by hemophilia B account for 99.5% of GDP and 36.1% of annual per capita disposable income in urban China.

The determinants of prophylactic treatment costs of patients with hemophilia

We found there was a statistically significant difference in total annual costs between PWH with and without prophylactic treatment. Among hemophilia A patients, the per capita annual medical cost of patients who used prophylactic treatment was ¥234637, 16 times that of those who did not use it ($P<0.01$). The annual per capita OOP expenditure for hemophilia A patients using prophylactic treatment was ¥45408, 10 times that of patients who not using it ($P<0.01$). Male (¥23287) hemophilia A patients had higher per capita annual medical expenditure than females (¥6867). There was no significant difference between the annual per capita medical expenditure of UEBMI (¥23354) patients and URBMI patients (¥19080), but the OOP expenditure of UEBMI patients (¥4199) was lower than URBMI patients (¥7282). The total costs of medical treatment and OOP for hemophilia A patients living in the eastern China were higher than those living in the midland and western China ($P<0.01$).

The annual per capita medical expenditure of hemophilia B patients using prophylactic treatment was ¥70167, and the annual per capita OOP expenditure was ¥13609. There was no significant difference in the annual per capita medical expenditure and OOP expenditure between patients with and without prophylactic treatment ($P>0.05$). The annual per capita OOP expenditures of hemophilia B patients with URBMI (¥11143) were higher than those of UEBMI (¥5521) patients ($P<0.05$), but the difference in total expenditures was not statistically significant ($P>0.05$), which is similar to that of hemophilia A. What's more, the total costs of medical care for hemophilia B patients is related to the area in which they live, and OOP costs are related to their age ($P<0.05$). (Table 4)

Discussion

Our study is the first to use CHIRA database to study the use of prophylactic treatment in PWH in China and its relationship with treatment costs. We found that the proportion of hemophilia A patients and hemophilia B patients using prophylactic treatment in urban China was 3.2% and 3.4%, respectively. In addition, PWH in urban China have a heavy financial burden. The total annual per capita medical expenses for hemophilia A patients were ¥31022, of which 69.0% (¥21400) was caused by hemophilia.

And the total annual per capita medical expenses for hemophilia B patients were ¥46084, of which 91.5% (¥42055) was caused by hemophilia. OOP costs from hemophilia account for more than 30% of per capita disposable income. Meanwhile, we found that there was a statistically significant difference in total annual costs between patients with and without prophylactic treatment. The cost of medical care for PWH who used prophylactic treatment is 16 times that of those who did not use it.

We found that the rate of prophylactic treatment in hemophilia was as low as less than 4%, which is close to the figure (3.6%) in a previous study in Shanxi province, China. Between 1999 and 2010, prophylaxis use in the US increased from 31% to 59%, and 75% of children and youths (<20 years) received prophylaxis treatment in 2010. Besides, a study in the Netherlands showed that 29% of Dutch PWH received prophylactic treatment in 2001.⁹ Thus, the proportion of hemophilia patients receiving prophylactic treatment in China is far lower than that in some developed countries. The reasons for the low proportion of prophylactic treatment maybe as follows. Firstly, at present China's domestic production of clotting factor α products far cannot satisfy the needs of patients. In addition, because of the high drug storage requirements, most blood products and injectable drugs are only available in the tertiary hospitals.[14] This may result in high indirect costs, including the time spent waiting in the hospital, the costs of travelling to and from the hospital, etc. Furthermore, according to the current regulations of medical insurance, injections are not allowed to be discharged with drugs, and the requirements for blood products are more stringent.[13] So if a patient needs prophylactic treatment they should go to the hospital every time.

The total annual per capita medical expenses for hemophilia A patients and hemophilia B patients were ¥31022 and ¥46084, of which 69.0% and 91.5% was caused by hemophilia, respectively. A European study estimated the mean per-patient annual direct cost of severe hemophilia ranges from EUR 116963 to EUR 313068, approximately 34 to 87 times higher than the mean per-capita health expenditure.[18] And the clotting factor replacement therapy accounted for 99% of the total costs.[18] WHO reported that the average annual cost of prophylaxis for PWH is USD100000 per individual, with prophylactic consumption of pdFVIII being 1900-8200 IU/kg/year in developed countries.[19][20] While according to a report by the WHF, the annual per capita consumption of coagulation factors by PWH in China is more than six-times lower than that of the minimum adequate treatment levels as established by the WFH.[12] The medical costs and the proportion of clotting factor usage of hemophilia patients in China are lower than those in developed countries, which may indicate that most hemophilia patients in China have not been adequately treated.

The general superiority of prophylactic treatment over on-demand treatment has been demonstrated that prophylactic treatment can greatly improve the average life expectancy and quality of life of hemophilia patients. [16] But due to the high cost, most PWH in China cannot afford the prophylactic treatment, resulting in their poor quality of life. Although hemophilia treatments are covered by China's medical insurance coverage, under the pressure of the control assessment of drug proportion and total medical insurance amount, doctors' prescription of drugs is constrained, and the reimbursement policy of drugs is almost useless.[13] However, on January 30, 2019, China abolished the single drug proportion

assessment. With the elimination of the assessment of drug proportion, the pressure on hospital procurement and physician prescription of hemophilia drugs will be further alleviated.

In fact, hemophilia is a rare disease with a clearly effective treatment. And once hemophilia patients get effective prevention and treatment, their life expectancy and quality of life will be greatly improved. Therefore, we hope that Chinese pharmaceutical companies can accelerate the development of domestic hemophilia drugs, and medical institutions can increase the reserves of hemophilia drugs to ensure that hemophilia patients can have drugs available. In addition, we call on the Chinese government to further increase the reimbursement level for hemophilia, so that hemophilia patients can afford routine treatment for hemophilia. With the socio-economic development of China, we also believe that through the joint efforts of all parties, more and more PWH can gradually understand the benefits of prophylactic treatment and use prophylactic treatment.

Limitation of this study

Due to our small sample size, the extension of the study to PWH nationwide may be limited. The CHIRA only included patients with URBMI and UEBMI, while PWH covered by the NRCMS were excluded because our data did not provide relevant information. Because hemophilia is a rare disease with small number of patients, it is difficult to obtain sufficient sample size data. And the definition of prophylactic treatment may introduce some bias. We determined whether PWH used prophylaxis by observing their medication behavior and the dose of coagulation factors. The results obtained by this method may not be accurate.

Conclusion

The proportion of PWH receiving prophylaxis treatment in China is very low. Most patients choose to be treated on demand or choose not to use any treatment. Although prophylactic treatment is considered to be the best way to improve the quality of life of PWH, the choice of prophylactic treatment means a higher financial burden. Therefore, government should improve the treatment status of PWH by further improving the reimbursement level of hemophilia and improving the accessibility of hemophilia drugs. Further research is needed to study the socio-economic factors of prophylactic treatment and the impact of prophylactic treatment on the quality of life of PWH.

Declarations

Acknowledgments

Not applicable.

Authors' contributions

SC and PH participated in the study concept and design; SC performed the statistical analysis and drafted the first version of the manuscript; XY, DZ and RD performed critical revision of article for

important intellectual content. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Tables

Table 1 Characteristic of people with hemophilia(N=815)

Characteristic	Hemophilia A(n=696)		Hemophilia B(n=119)	
	number	Proportion (%)	number	Proportion (%)
Treatment				
On-demand	674	96.8	113	96.6
Prophylactic	22	3.2	4	3.4
Gender				
Female	80	11.5	9	7.6
Male	613	88.5	110	92.4
Age				
0-17	200	28.7	41	34.5
18-44	285	41.0	40	33.6
≥45	211	30.3	38	31.9
Insurance				
UEBMI	354	50.9	60	50.4
URBMI	342	49.1	59	49.6
Area				
East	377	54.2	62	52.1
Midland	172	24.7	44	37.0
West	147	21.1	13	10.9

Table 2 Univariate analysis of prophylactic treatment of hemophilia (N=815)

	Hemophilia A(n=696)			Hemophilia B(n=119)		
	Prophylactic	Proportion (%)	P-value	Prophylactic	Proportion (%)	P-value
Gender			0.09			0.56
Male	22	3.6%		4	3.6%	
Female	0	0.0%		0	0.0%	
Insurance			0.73			0.04
UEBMI	12	3.4%		4	6.8%	
URBMI	10	2.9%		0	0.0%	
Age			0.94			0.06
0-17	8	4.2%		2	5.0%	
18-44	8	2.7%		2	4.9%	
≥45	6	2.8%		0	0.0%	
Area			0.02			0.27
East	18	4.8%		1	1.6%	
Midland	4	2.3%		3	6.8%	
West	0	0.0%		0	0.0%	

Table 3 Annual per capita medical expenses of hemophiliac in China (¥, CNY) (SD)

	Hemophilia A(n=696)		Hemophilia B(n=119)	
	All	Caused by hemophilia	All	Caused by hemophilia
total costs	31022(76947)	21400(55160)	46160(54564)	42131(54038)
OOP	8404(20526)	5714(14264)	9055(10977)	8308(10534)
OOP / total costs	27.1%	26.7%	19.6%	19.7%
total costs / GDP	73.3%	50.6%	109.1%	99.5%
OOP / disposable income	31.6%	21.5%	34.1%	31.3%

† From 2010 to 2016, the per capita GDP and disposable income in urban China were ¥42326 and ¥26583 respectively.

‡1 USD ≈ 6.4 CNY.

Table 4 Univariate analysis of annual per capita medical expenses for prophylactic treatment in hemophilia (¥, CNY) (SD)

	Hemophilia A(n=696)				Hemophilia B(n=119)			
	Total	P-value	OOP	P-value	Total	P-value	OOP	P-value
Treatment		0.00		0.00		0.78		0.60
On-demand	14440(26078)		4418(10892)		41156(54657)		8124(10367)	
Prophylactic	234637(172374)		45408(35029)		70167(15916)		13609(15544)	
Gender		0.00		0.23		0.13		0.22
Male	23287(58266)		6146(15004)		44579(55368)		8551(10646)	
Female	6867(14661)		2310(5522)		12213(14584)		5339(9048)	
Insurance		0.10		0.00		0.34		0.00
UEBMI	21367(54585)		4199(10615)		41382(64023)		5521(7471)	
URBMI	21436(55788)		7282(17123)		42893(42073)		11143(12360)	
Age		0.00		0.94		0.06		0.00
0-17	23259(65028)		6315(13669)		46986(44375)		13181(13927)	
18-44	23070(60059)		5377(13348)		58011(71422)		7601(8056)	
≥45	17391(34553)		5467(15979)		19888(30159)		3942(5787)	
Area		0.00		0.00		0.02		0.14
East	27190(69535)		7185(17619)		37780(54818)		6839(8680)	
Midland	21733(36656)		5908(9581)		55481(57256)		10457(11750)	
West	6053(11295)		1683(6269)		17700(17145)		8046(13610)	

†P-value was computed using the Mann-Whitney U test and the Kruskal-Wallis test.

‡1 USD ≈ 6.4 CNY.