

The Treatment Pattern and Economic Burden of Homozygous Familial Hypercholesterolemia in China: A Study based on a Patient-Survey

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Research

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Abstract

Objective: The study aimed to investigate the treatment pattern and economic burden of homozygous familial hypercholesterolemia (HoFH) in China, and to evaluate the incidence rate of catastrophic health expenditure (CHE) of HoFH patients and their families.

Methods: Patients with HoFH diagnosed and treated in Beijing An'Zhen Hospital was included. A questionnaire was developed to investigate and capture the relevant variables of the participants.

Results: A total of 120 HoFH patients were investigated, and the number of children (age under 18) was 1.2 times more than adults (age above 18). There were 113 patients with basic medical insurance (including 61 patients with new rural cooperative medical insurance), 4 patients with commercial insurance and 3 patients without any insurance. There were 35 patients with atherosclerotic cardiovascular disease (ASCVD), including 29 adults and 6 children. Only 6 pediatric patients achieved their low-density lipoprotein cholesterol (LDL-C) treatment targets, and all 54 adult patients did not achieve it. The most commonly used treatment method was diet control with lipid-lowering drugs (16.67%), followed by diet control and lipid-lowering drugs using separately (16.67%). The proportion of patients whose annual personal income reached GDP per capita in 2019 was only 2.5%. The total economic burden of disease was 5,529,100 CNY / year, including direct medical costs of 3,427,200 CNY / year, direct non-medical costs of 1,504,500 CNY / year and indirect costs of 611,300 CNY / year; the per capita economic burden of disease was 46,100 CNY / year, including direct medical costs of 28,600 CNY / year, direct non-medical costs of 12,500 CNY / year and indirect costs of 5,100 CNY / year. There were 32 families with CHE due to the disease, accounting for 26.67%.

Conclusion: Patients with HoFH in China are generally at young age, and the economic burden of disease for the family is heavy. The existing treatment is not effective, and it is easy to cause premature death due to ASCVD.

Introduction

Homozygous familial hypercholesterolemia (HoFH) is an autosomal dominant genetic rare disease, characterized by elevated plasma low-density lipoprotein cholesterol (LDL-C) concentration levels (>13 mmol/L)[1]. It is caused by the occurrence of mutations in genes such as the low-density lipoprotein receptor (LDLR), apolipoprotein B (apoB), proprotein convertase subtilisin/kexin type 9 (PCSK9), which all impair LDL-C levels ultimately[2]. HoFH has been recognized as a cause of premature atherosclerotic cardiovascular disease (ASCVD), which may lead to myocardial infarction or premature death[3][4]. There is a lack of epidemiology study on HoFH. The prevalence of HoFH is generally considered as 1/1,000,000, which could be higher among specific populations such as French Canadians and Transvaal Afrikaners[5][6]. However, there is currently no epidemiological data of the patients with HoFH in China.

A combination of dieting management, lipid-lowering therapy (LLT), LDL apheresis and liver transplantation are available alternatives to treat HoFH[7]. However, a considerable part of patients still has difficulty in achieving the target level for plasma LDL-C[1]. The curative effect of the conventional pharmacotherapy such as high-dose statins (with or without ezetimibe) is very limited. In recent years, innovative pharmaceuticals, such as Lomitapide (an oral inhibitor of the microsomal triglyceride transport protein (MTP)), mipomersen (a

second generation antisense oligonucleotide) and Evolocumab(monoclonal antibody therapies targeting PCSK9), have been developed approved by different authorities[7].

In 2018, HoFH was included in the included in the first batch of Nation Rare Diseases List in China (NRDL)[8]. A series of policies have been issued to improve the accessibility of drugs for rare diseases in China[9]. After that, the Chinese government has published a series of policies to improve comprehensive healthcare security of rare diseases, including constructing the diagnosis and treatment network, registering rare disease patients, publishing guidelines for diagnosis and treatment, improving the accessibility, reducing the import tax, accelerating the market authorization process of drugs for rare diseases, and bring the drugs for rare diseases into the National Drug Reimbursement List. Meanwhile, Evolocumab has been approved by the China National Medical Products Administration (NMPA) in 2018. However, the utilization of different pharmaceuticals for HoFH remains unknown in China.

The study aimed to investigate the treatment pattern of patients with HoFH in China and further measure the cost-of-illness and the incidence of catastrophic health expenditure of the patients. Thus, policy recommendation could be provided to policy-makers to improve the healthcare security of the patients.

Materials & Methods

Study design

The study of economic burden of disease is also called study of cost-of-illness, it is a partial economic evaluation approach which measures the economic burden or total costs attributable to a particular disease and can help improve the accessibility of diagnosis and treatment for patients, put forward policy recommendations of enhancing the relevant healthcare systems of the disease, and effectively alleviate the economic burden suffered by patients [10][11].

The study surveyed patients with HoFH who were diagnosed and treated in Beijing Anzhen Hospital from September 2017 to December 2019. All patients or their family members completed a self-made questionnaire survey designed according to the family health questionnaire of the fifth National Health Services Survey (NHSS) in China[12]. Respondents answered questions on their own demographics, clinicopathological characteristics, household healthcare expenditures and medical insurance status.

Cost calculation

Three types of costs are included in this study: direct costs, indirect costs and intangible costs. Depending on the different expenditures, direct costs included direct medical costs and direct non-medical costs[13].

Direct medical costs referred to financial expenditures incurred by patients during the healthcare services, including inpatient costs and outpatient costs as follows: inpatient bed costs, physician diagnostic costs, inpatient nursing costs, drug costs including Traditional Chinese Medicine and other medications, laboratory testing costs, surgery costs, and other related expenses.

Direct non-medical costs are related to the consumption of non-medical resources during the healthcare services, such as lodging costs, diet costs, transportation costs, and assistant service costs. Direct non-

medical costs were calculated as follows:

Direct non-medical costs = (average transportation costs paid per visit + average accommodation costs paid per visit + average sick leave costs per visit...) * number of visits per year

Indirect costs reflected to efficiency or productivity losses of working caused by premature death or disability related to the disease, as well as the lost working time of the relatives due to the care of the patient.

Intangible costs refer to the anxiety, sadness, pain and other mental losses of patients and their families caused by diseases. Currently, no certain approach is quantified due to high subjectivity and measurement difficulties of the indicator, thus no calculations of intangible costs were performed in this study[14].

Evaluation indicators

Individual economic burden of Patients with HoFH

The evaluation indicators of individual economic burden include annual direct medical costs, annual direct non-medical costs, and annual indirect costs.

Catastrophic health expenditure

Household catastrophic health expenditure (CHE) is defined as the proportion of out-of-pocket (OOP) payments for healthcare exceeds a certain level of household capacity to pay, which poses a catastrophic threat to the family. Generally, the global threshold is 40% as a threshold[15].

Statistical Methods

Means and standard deviations (SD) were used for continuous variables, and percentages and frequencies were used for categorical variables as descriptive statistics. Comparison of two age groups were performed using chi-square test and Fisher's exact test. EpiData 3.1 was used for double data entry, and SPSS was used to perform the analyses. Estimates with P-values < 0.05 were considered statistically significant.

Ethical statements

Informed consents were attained by all the participants before the formal survey started. The participants' privacy, including any individual information they provided in the survey, would be protected. This study was approved by the ethics committee of Beijing An'zhen Hospital (Approval No.2017035).

Results

Demographic and characteristics

A total of 120 patients were included in the study, and a maximum of 17 patients came from Hebei Province. Most of the other patients were from East China, with more than 10 patients coming from Anhui, Jiangsu, Shandong, and Zhejiang, respectively (Figure1).

Among the patients, 59 were males and 61 were females. There were 66 children (age<18) and 54 adults (age≥18), accounted for 55% and 45%, respectively. The mean age of children was 8.13 years old, and the

mean age of adults were 31.06 years old (Table 1). There were 113 patients participating basic medical insurance (including Urban Employee Basic Medical Insurance, Urban Resident Basic Medical Insurance, and New Rural Cooperative Medical Insurance), 4 patients participating only commercial insurances, and 3 patients without any insurance. Among the patients with basic medical insurance, NRCMI was the majority (50.83%).

Table 1. Demographic characteristics of HoFH patients

Variable/ Characteristics	Number	Percentage (%)
Total	120	100
Age		
<18	66	55.00
≥18	54	45.00
Gender		
Male	59	49.17
Female	61	50.83
Medical insurance		
NCMS*	61	50.83
Basic insurance for urban residents	34	28.33
Basic insurance for urban employees	18	15.00
Commercial insurance	4	3.33
No insurance	3	2.50
Chinese average GDP per capita in 2019		
Reached	3	2.5
Not reached	117	97.5

New rural cooperative medical care system, NCMS.

Clinical Characteristics and Treatment Patterns of Patients with HoFH

35 patients (29.17%), including 29 adults and 6 children were diagnosed with ASCVD. According to the treatment target levels of LDL-C established by Chinese Society of Cardiology (CSC), 6 of the children patients achieved the target level, while none of the adult patients achieved it. When compared ASCVD status and LDL-

C levels by age groups, it indicated that adults were more likely combined with ASCVD (82.26%) and children patients were probably more likely achieved the LDL-C levels, the results were both statistically significant (Table 2, $P < 0.05$). The dietary management + lipid-regulating drugs treatment were mostly used by patients (62.50%), following by the dietary management and lipid-regulating drugs using separately, each accounting for 16.67%.

Table 2. Clinical characteristics of HoFH patients by age groups

Variable/ Characteristics	Number	Children (age<18)	Adults (age≥18)	P-value
Total	120			
Combined ASCVD				<0.0001
Yes	35	6 (17.14%)	29 (82.26%)	
No	85	60 (70.59%)	25 (29.41%)	
LDL-C target level*				0.03194
Achieved	6	6 (100%)	0 (0%)	
Not achieved	114	60 (52.63%)	54 (47.37%)	

*Target level of LDL-C for children (age<18) is <3.4mmol/L (<130 mg/dL), for adults (age≥18) is <2.6 mmol/L (<100 mg/dL), for adults with ASCVD is <1.8 mmol/L (<70 mg/dL).

Table 3. Treatment Patterns of Patients with HoFH

Treatment	Number	Percentage (%)
Dietary management	20	16.67
Dietary management + Lipid regulating drugs*	75	62.50
Dietary management + Lipid regulating drugs + LDL apheresis	2	1.67
Lipid regulating drugs	20	16.67
Lipid regulating drugs + Plasma exchange	1	0.83
Traditional Chinese medicine treatment	1	0.83
No treatment	1	0.83

*:PCSK9 Inhibitors were not included.

The Economic burden of the patients with HoFH

From the patients' individual perspective, the total costs of HoFH for 120 patients were 5.5291 million CNY/year, of which direct medical costs were 3.4272 million CNY/year, direct non-medical costs were 1.504 million CNY/year, and indirect costs were 611, 273 CNY/year. The total costs of HoFH per capita were 46, 076 CNY/year, of which direct medical costs were 28, 560 CNY/year, direct non-medical costs were 12, 537 CNY/year, and indirect costs were 5, 093 CNY/year . 32 families suffered CHE due to illness, and the incidence rate was 26.67%.

Table 4. The economic burden of patients with HoFH

Indicator	Number	Minimum costs (CNY)	Maximum costs (CNY)	Average costs (CNY)	SD	Total costs (CNY)
Direct medical costs	120	36	350, 000	28, 560.34	58, 176.6	3, 427, 241
Direct non-medical costs	120	0	170, 150	12, 537.39	26, 617.24	1, 504, 486
Indirect costs	120	0	103, 561.6	5, 093.95	15, 204.32	611, 273.8
Total economic burden	120	36	440, 195.9	46, 076.18	77, 776.26	5, 529, 141

Discussion

This is the first study to reveal the economic burden of patients with HoFH in China and is a key step to provide evidence for policy-makers. A total of 120 patients were surveyed and the following characteristics are mainly presented: Firstly, the number of children patients with HoFH is more than that of adults. One of the possible reasons may be that most patients with severe ASCVD complications, which is highly lethal, resulting in the low tendency of young patients to be investigated. In fact, more than 80% of rare diseases are caused by genetic defects[16], and there are common problems that need to be solved such as low diagnosis rate, lack of effective treatment methods, and drugs have not been included in the medical insurance system, which can easily cause disability or premature death of patients.

Secondly, current treatments are lack of effectiveness based on our research. According to previous studies, elevated LDL-C levels has been identified as an important risk factor for ASCVD, so decreasing LDL-C levels becomes particularly important in the treatment of HoFH. As our survey showed, one of the mostly used treatment methods was dietary management combined with lipid-lowering drugs, while serum LDL-C level of only 6 non-adult patients (5%) achieved the targets in this study, indicating the lack of effectiveness in current situation. The European Atherosclerosis Society (EAS) pointed out that lifestyle intervention and maximum tolerated dose of statin therapy are the main treatments for HoFH, adjuvant lipoprotein apheresis can be performed before 8 years old as well due to LDL-C targets are seldom achieved. The study by Hartgers et al. showed that LDL-C activity was reduced in patients treated with Alirocumab and has clinical significance. Despite Evolocumab has been approved by NMPA in China[17], it was not included in the National Drug Reimbursement List and thus had never been used among the patients investigated when maximum tolerated dosage statin were still not effective enough. There is a lack of specific treatment drugs for HoFH in China,

and it is recommended to speed up the introduction of corresponding drugs and inclusion in the medical insurance.

The third is that the patient has a heavy burden of disease, with a CHE rate of more than 26%, and the main costs were medical costs caused by recurrent cardiovascular events. Over 35 countries have included Evolocumab in the medical insurance list, and the cover rates of Evolocumab in federal insurance, medical assistance insurance and commercial insurance are 41%, 100% and 91% respectively in the United States. The U.S. Food and Drug Administration (FDA) approved the microsomal triglyceride transfer protein (MTP) inhibitors Lomitapide[18] and Mipomersen[19] respectively in 2012 for patients aged ≥ 18 years and ≥ 12 years old as the adjuvant therapy, and the European Medicines Agency also approved Lomitapide[20] as a therapeutic drug. Evinacumab[21] was also approved by FDA in 2021. As the average income of most families with HoFH is lower than that of China's GDP in 2019, it is hard for them to afford the novel treatment, and the lack of effective treatment may aggravate the economic burden of patients,. Although the high cost of these treatments may be a problem, due to their rarity, the total costs of adequate treatment of HoFH is still relatively low. According to Chinese expert consensus on screening, diagnosis and treatment of FH, the prevalence of HoFH in China was from 1/1 million to 3/1 million, and the total population of mainland China was 1.4 billion at the end of 2019[22]. Therefore, the number of patients in China was estimated to be 1,400 to 4,200, and the total economic burden of disease was estimated to be from 64,506,700 CNY to 193,520,000 CNY. Besides the conventional treatment for HoFH, it is necessary and urgent to approve more innovative drugs in medical insurance list in China.

It is also reported that early detection, early diagnosis, and early treatment play an important role in improving the prognosis of the disease, preventing the occurrence of related complications, reducing medical costs, and reducing the burden on patients. Clinicians should raise awareness of familial hypercholesterolemia and improve the ability in the field of diagnosis and treatment. It is also suggested that the introduction of advanced medications and effective therapeutic drugs should be accelerated, and a multi-channel fee payment mechanism should be established to reduce the burden on patients, delay the progression of atherosclerosis, and prolong the life cycle.

Our study also has some limitations. Firstly, the patients were only recruited from Beijing Anzhen hospital, which may cause selection bias. Secondly, intangible costs were omitted, as it is difficult to calculate precisely. Further research is needed in this field.

Conclusion

In summary, as a rare disease, the economic burden of HoFH is heavy in China, and it is very easy to cause premature death of patients due to ASCVD, more attention is needed in this field.

Declarations

Ethics approval and consent to participate

This study was approved by the ethics committee of Beijing An'zhen Hospital (Approval No.2017035).

Consent for publication

Not applicable

Availability of data and materials

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

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

Shanlian Hu, Yan Yang and Mi Tang designed the survey questionnaire. Ya Yang, Wenhui Wen and Lvya Wang managed and coordinated the patient survey. Ya Yang, Wenhui Wen, Lvya Wang and Yan Yang were in charge of collecting survey data and quality control. Jiangjiang He, Shanlian Hu and Yan Yang analyzed and interpreted the survey data. Yan Yang and Mi Tang contributed to writing the manuscript. All authors read and approved the final manuscript.

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Conflicts of interest

The authors report no conflicts of interest in this work.

References

1. Turgeon RD, Barry AR, Pearson GJ. Familial hypercholesterolemia review of diagnosis, screening, and treatment. *Can Fam Physician*. 2016;62:32–7.
2. Benito-Vicente A, Uribe KB, Jebari S, Galicia-Garcia U, Ostolaza H, Martin C. Familial hypercholesterolemia: The most frequent cholesterol metabolism disorder caused disease. *Int J Mol Sci*. 2018;19.
3. Gidding SS, Champagne MA, De Ferranti SD, Defesche J, Ito MK, Knowles JW, et al. The Agenda for Familial Hypercholesterolemia: A Scientific Statement from the American Heart Association. *Circulation*. 2015;132:2167–92.
4. Santos RD, Gidding SS, Hegele RA, Cuchel M, Barter PJ, Watts GF, et al. Defining severe familial hypercholesterolemia: Implications for clinical management. *Lancet*. 2016;1–36.
5. Seftel HC, Baker SG, Sandler MP, Forman MB, Joffe BI, Mendelsohn D, et al. A host of hypercholesterolaemic homozygotes in South Africa. *Br Med J*. 1980;281:633–6.

6. Moorjani S, Roy M, Gagne C, Davignon J, Brun D, Toussaint M, et al. Homozygous familial hypercholesterolemia among French Canadians in Quebec province. *Arteriosclerosis*. 1989;9:211–6.
7. Cuchel M, Bruckert E, Ginsberg HN, Raal FJ, Santos RD, Hegele RA, et al. Homozygous familial hypercholesterolaemia: New insights and guidance for clinicians to improve detection and clinical management. A position paper from the Consensus Panel on Familial Hypercholesterolaemia of the European Atherosclerosis Society. *Eur Heart J*. 2014;35:2146–57.
8. He J, Kang Q, Hu J, Song P, Jin C. China has officially released its first national list of rare diseases. *Intractable Rare Dis Res*. 2018;7:145–7.
9. He J, Song P, Kang Q, Zhang X, Hu J, Yang Y, et al. Overview on social security system of rare diseases in China. *Biosci Trends*. 2019;13:314–23.
10. Jo C. Cost-of-illness studies: concepts, scopes, and methods. *Clin Mol Hepatol*. 2014;20:327–37.
11. Rabarison KM, Bish CL, Massoudi MS, Giles WH. Economic evaluation enhances public health decision making. *Front Public Heal*. 2015;3:1–5.
12. National Health Commission. Fifth National Health Service Survey Programme [Internet]. 2013. Available from:
<http://www.nhc.gov.cn/mohwsbwstjxxzx/s8211/201610/9f109ff40e9346fca76dd82cecf419ce.shtml>
13. Ibrahim N, Pozo-Martin F, Gilbert C. Direct non-medical costs double the total direct costs to patients undergoing cataract surgery in Zamfara state, Northern Nigeria: A case series. *BMC Health Serv Res*. ???; 2015;15:1–7.
14. Yousefi M, Assari Arani A, Sahabi B, Kazemnejad A, Fazaeli S. Household health costs: Direct, indirect and intangible. *Iran J Public Health*. 2014;43:202–9.
15. Xu K. Distribution of health payments and catastrophic expenditures Methodology. FER/EIP Discuss Pap; 2005;11 p.
16. February 29 is Rare Disease Day in Europe. 2011.
17. Centre for Drug Evaluation National Medical Products Administration. Evolocumab [Internet]. Available from: http://app1.nmpa.gov.cn/data_nmpa/face3/base.jsp?tableId=36&tableName=TABLE36&title=%BD%F8%BF%DA%&bclId=152904858822343032639340277073
18. Food and Drug Administration. FDA Approved Drugs-Lomitapide [Internet]. Available from: https://www.accessdata.fda.gov/scripts/cder/ob/search_product.cfm
19. Food and Drug Administration. FDA Approved Drugs-Mipomersen [Internet]. Available from: <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=BasicSearch.process>
20. European Medicines Agency. Human medicine European public assessment report (EPAR): Lojuxta [Internet]. Available from: <https://www.ema.europa.eu/en/medicines/human/EPAR/lojuxta>
21. Food and Drug Administration. FDA Approved Drugs-Evinacumab [Internet]. Available from: <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=BasicSearch.process>
22. Atherosclerosis and Coronary Heart Disease Group CA of C. Chinese experts' consensus on screening and diagnosis and treatment of familial hypercholesterolemia. *Chinese J Cardiovasc Dis*. 2018;46:99–103.

Figures

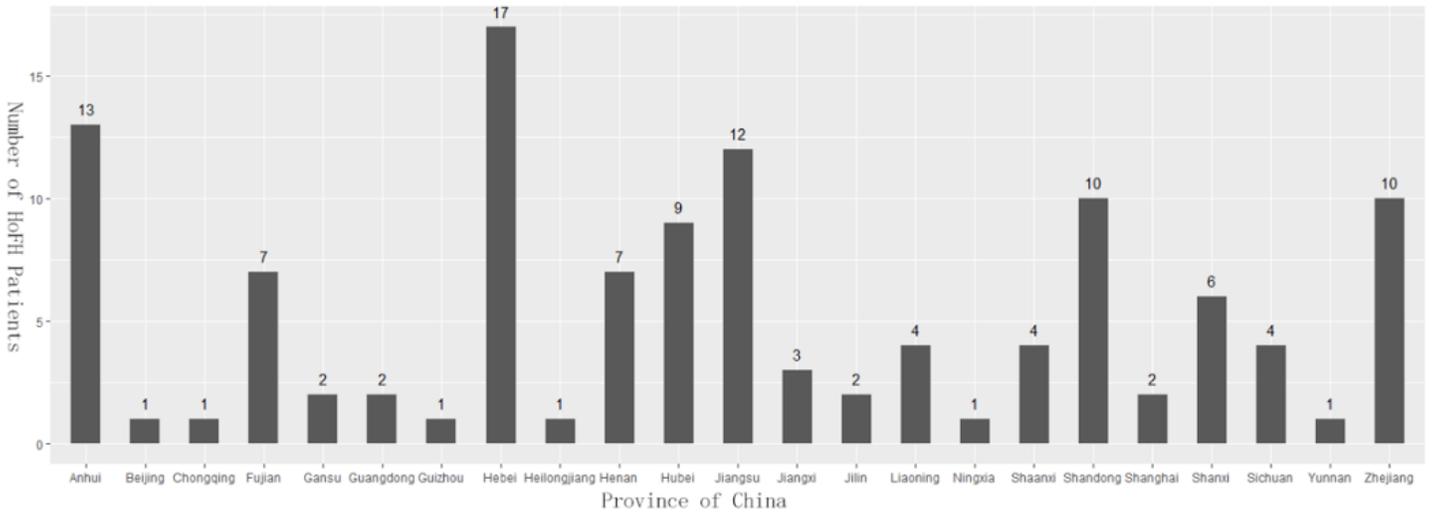


Figure 1

Province of HoFH patients in China