Rare Disease Curative Care Expenditure- Financing Scheme-Health Provider- Beneficiary Group Analysis — An Empirical Study in Sichuan Province, China

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Research Article

Keywords: Rare diseases, Curative care expenditure, SHA2011, Healthcare security system

Posted Date: November 30th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-1090833/v1

Rare disease curative care expenditure- financing scheme-health provider- beneficiary group analysis

—An empirical study in Sichuan Province, China

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Abstract

Background: Rare diseases impose heavy economic burdens on patients' families and society worldwide. This study has used the samples from Sichuan Province of China to estimate the curative care expenditure(CCE) of ten rare diseases to provide reference and support for the prioritization of rare disease health policies.

Methods: The multi-stage cluster sampling method was adopted to conduct a survey of 9714 rare disease patients from 1,556 medical institutions in Sichuan Province in 2018. Based on System of Health Accounts 2011, the study estimated the total curative care expenditure on rare diseases and identified financing sources and their allocation among different health institutions and the patient population.

Results: In 2018, the total CCE of the ten rare diseases in Sichuan Province was 19.001 million US dollars; the top three rare diseases in terms of CCE were Hemophilia ($4.3786 million), Young-onset Parkinson Disease ($2.9627 million) , and Systemic

Sclerosis ($2.4457 million); household out-of-pocket expenditure (86.00% for outpatients, 41.60% for inpatients) and social health insurance (7.85% for outpatients; 39.58% for inpatients) were the main sources of financing. The out-of-pocket expenditures for patients with Young-onset Parkinson Disease, Congenital Scoliosis, Autoimmune accounted for more than 60% of the total CCE. More than 80% of the rare disease CCE was incurred in general hospitals. The 40-59 age group consumed the highest percentage of CCE (38.70%) while men spent slightly more (55.37%) than women (44.64%).

Conclusions: Since rare disease treatment is costly and household out-of-pocket expenditure is high, we suggest taking steps to include rare disease drugs in the National Reimbursement Drug List, scientifically design insurance coverage range. It is also necessary to explore a multi-tiered Healthcare Security System to pay for the CCE of rare diseases and to reduce the economic burdens of patients.

Keywords: Rare diseases, Curative care expenditure, SHA2011, Healthcare security system

Introduction

Rare diseases refer to diseases that have a low prevalence rate and are extremely rare. As defined by the World Health Organization (WHO), a disease is considered to be rare when the number of affected patients accounts for 0.65‰-1‰ of the total population [1]. The definition of rare disease differs among countries, and there is no implicit official definition for rare disease in China [2-4]. In 2018, China issued *the Catalog of the First Group of Rare Diseases,* which included 121 rare diseases including Systemic Sclerosis (SSc) and Young-onset Parkinson Disease (YOPD)[5].

There are currently 6000-8000 internationally acknowledged rare diseases, which account for about 10% of human diseases and affect approximately 475 million people. Eighty percent of the rare diseases are genetic, and fifty percent of which start in childhood. However, only 5% of them have treatment methods[6,7]. Since rare diseases are serious and difficult to diagnose and treat, most of them affect all the systems and organs in the human body, which can easily result in disability, mental disorders, deteriorated quality of life, and even death, causing extremely heavy burdens on patient's families and the society while posing immense challenges to the construction and improvement of the global public health service system [8-10]. Researches have

shown that the annual curative care expenditure(CCE) of Hemophilia in the United States is US$80,811-632,088; European patients with Multiple Sclerosis (MS) spend an average of US$47,888 per year on curative care [11,12]; in Australia, CCE for rare diseases accounts for 4.60%-10.50% of the total inpatients' curative care expenditure, equivalent to that of diabetes or asthma in 2010[13]. Rare disease CCE accounted for 4.30% of the total inpatient expenditures in Hongkong in 2016[14]; Researchers in Taiwan found that health expenditures for patients with rare diseases grew sharply from US$18.65million in 2003 to US$137million US dollars in 2014[15].

As a huge country with a population of 1.411 billion, rare diseases are, indeed, not rare in China. It is estimated that there are at least 20 million rare disease patients in China, which is the largest population of rare disease patients in the world [16]. The huge number of rare disease patients will inevitably result in more economic burdens and a series of social problems [17]. In this background, a large number of studies have been carried out in China to respond to the challenges of rare diseases; to the best of our knowledge, most of the prior researches focused on prevention and clinical research while relatively few studies involved curative care expenditures and medical insurance system payment information of rare diseases[18]. A lack of information will make it hard to measure the overall disease burden of rare diseases in China. Hence, there is an urgent need to establish an expenditure calculation framework that can help to accurately estimate the CCE of rare diseases in China and enable international comparative studies.

The System of Health Accounts 2011 is considered to be the global standard framework for national health accounts and has been widely adopted by the European Union, member states of the Economic Cooperation Organization, and other countries [19]. Application of this system in research on rare diseases can not only help in the understanding of the CCE financing sources and its distribution among health care service providers of rare disease CCE but also provide information about health spending by beneficiary characteristics. We used the samples from Sichuan Province, which has a medium level of economic and medical development in China to calculate the CCE of the top ten high costing rare diseases in Sichuan Province. The research results are expected to provide references for policy making concerning the effective control of rare diseases and rational allocation of

medical resources in order to reduce the economic burdens of patients and protect their rights.

Methods

Data sources

The official statistical data was obtained from the *Sichuan Province Statistical Yearbook (2018)*, *Sichuan Health Financial Statistical Yearbook(2018)*, and *Sichuan Health Statistical Yearbook(2018)*. Most of the medical expenditures were indexed from Hospital Information System form from 1,556 hospitals in Sichuan Province.

Study sample

A multi-stage stratified sampling method was used to collect samples. The first stage was to choose sample cities. Based on the economic development level, population size, geographic location in Sichuan Province, seven cities including Chengdu, Mianyang, Meishan, Guang'an, Zigong, Yibin, and Liangshan Zhou were selected. In stage two, four districts or counties were selected from the sample cities and four to six communities and towns were selected as sample regions. In stage three, public health institutions and medical institutions were randomly chosen. As a result, 1,556 medical institutions (including general hospitals, traditional Chinese medicine hospitals, specialized hospitals, maternal, and child care hospitals and primary medical health institutions) were selected. Finally, patient information (gender, age, length of hospital stay, disease name, ICD-10 code, curative care expenditure, and insurance) retrieved from the above-mentioned institutions was sorted out and standardized, thus forming the sample database of this study.

The rare diseases defined in this study were derived from the 2018 edition of *Compendium of China's First List of Rare Disease*, which covered 121 rare diseases. This research targets ten rare diseases with the highest curative care expenditures: Hemophilia-D66.01, YOPD-G20, SSc-M34.0, Neuromyelitis Optica (NO)-G36.0, Autoimmune Encephalitis (AE)-G04.8, Idiopathic Pulmonary Fibrosis (IPF)-J84.1, Multiple System Atrophy (MSA)-G90.3, MS-G35.0, Amyotrophic Lateral Sclerosis (ALS)-G12.2 and Congenital Scoliosis (CS)-Q76.3.

Accounting and statistical methods

Based on the SHA2011 theoretical framework, we have adopted top-down accounting principles to estimate the CCE of rare diseases. Incorporating medical income, government basic expenditure subsidies, and project subsidies in the accounting scope while excluding expenditures not directed related to health care services such as basic construction costs, equipment costs, and depreciation. The preventive care costs of medical institutions have been excluded as well.

The calculation process was divided into three steps, which is exemplified in the case of the outpatient medical service:

The first step was to determine the total CCE of medical institutions in Sichuan Province.

$$\mathrm{CCE}= \mathrm{CI}+\mathrm{BS}+\mathrm{PS} \quad (1)$$

CCE in formula (1) represents the total curative care expenditure of medical institutions in Sichuan Province. CI refers to curative income (excluding preventive service fees); BS stands for the basic curative expenditure fiscal subsidy provided to medical institutions in Sichuan province by the government; PS derived from the government health input monitoring data, represents the provincial project subsidy, including central government financial subsidies and local government specialized funds, such as maternal and childbirth subsidies and basic drug subsidies.

Among them: CI and BS are obtained with the following formula:

$$CI=TOI \times (1 - POI/OI) \quad (2)$$

$$\mathrm{BS} = \mathrm{BCS} \times \left(1 - \frac{IBD}{IBD+COV \times K}\right) \quad (3)$$

$$\mathrm{COV}=\mathrm{TOV} \times (1 - POV/OV) \quad (4)$$

In formula (2): TOI stands for the total outpatient income in Sichuan Province in the year 2018; POI refers to the preventive outpatient income of sample medical institutions; OI represents the total outpatient income of sample medical institutions.

In formula (3), BCS is the total basic curative expenditure subsidy in Sichuan Province in 2018; IBD represents the number of inpatient bed days in the sample medical institution; COV refers to the number of curative outpatient visits in the sample medical institution, and K takes a constant of 0.1, meaning that 10 outpatient visits are equivalent to 1 inpatient bed day. Among them, COV is calculated by the formula (4), in which TOV represents the total number of outpatient visits in Sichuan Province in 2018; POV stands for the number of outpatient visits for preventive services in sample medical institutions, and OV refers to the total number of outpatient visits in sample medical institutions.

Step two: calculation of the CCE per patient

In line with the "top-down" approach, the curative care expenditure per patient among medical institutions in Sichuan was calculated with the following formula:

$$S_{CI} = CI \times \frac{EOI}{\sum_{i=1}^{n} EOI_i} \text{（i=1,2,3.....n）} \quad (5)$$

$$S_{BS} = BS \times \frac{EOV}{\sum_{m=1}^{n} EOV_m} \text{（m=1,2,3.....n）} \quad (6)$$

$$S_{PS} = PS \times \frac{EOI}{\sum_{w=1}^{n} EPS_w} \text{（w=1,2,3.....n）} \quad (7)$$

In formulas (5), (6), and (7), S_{CI}, S_{BS}, and S_{PS} represent the curative care expenditure, basic expenditure subsidy, and project subsidy per patient. EOI represents the outpatient cost of each patient in different types of sample medical institutions; EOV represents the number of visits for each patient in different types of sample medical institutions.

Step three: summary of the CCE with different characteristics

Formula (8) represents the summary of curative expenditures of patients with the same characteristics such as age, gender, and disease in the region.

$$\sum_{i=1}^{n} S_{CCE} = \sum_{i=1}^{n} S_{CI} + \sum_{i=1}^{n} S_{BS} + \sum_{i=1}^{n} S_{PS} \quad (i = 1，2，3....n) \quad (8)$$

Finally, different dimensions of the rare disease curative expenditure in Sichuan Province in 2018 were obtained based on classification and summary of financing source, health service providers and health spending by beneficiary characteristics.

This study used stata14.0 (Stata Corporation, College Station, TX, USA) for data entry, accounting, and analysis.

Results

General statistics of patients with 10 rare diseases

In 2018, there were 9714 cases of the top ten high CCE rare diseases in Sichuan Province, including 7,188 outpatients and 2,526 inpatients. Among them, patients with SSc totaled 2534 (26.09%), and patients with YOPD and Hemophilia totaled 1935 (19.92%) and 1504 (15.48%) respectively. The average age of the patients with 10 rare diseases was 42.80,of which the average age of patients with CS was the smallest(13.28) and IPF patients was the oldest (67.91). In terms of gender distribution, the percentage of women (55.12%) was slightly higher than that of men (44.88%). Five diseases including SSc and NO mainly inflicted females, while the male patients were usually diagnosed with the other five diseases, such as Hemophilia and IPF.

Table 1 The general statistics of patients with 10 rare diseases in Sichuan Province in 2018 (n/%)

Disease	Total Number of patients	Average age（$\bar{x}\pm s$）	Gender		Service function	
			Male	Female	Outpatients	Inpatients
SSc	2534（26.09）	49.02±15.26	565（22.30）	1969（77.70）	2180（86.03）	354（13.97）
YOPD	1935（19.92）	42.83±9.50	1030（53.23）	905（46.77）	1744（90.13）	191（9.87）
Hemophilia	1504（15.48）	18.10±17.03	1437（95.55）	67（4.45）	954（63.43）	550（36.57）
NO	1340（13.79）	46.32±14.4	178（13.28）	1162（86.72）	1017（75.90）	323（24.10）
MS	682（7.02）	41.35±13.92	195（28.59）	487（71.41）	416（61.00）	266（39.00）
MSA	571（5.88）	62.77±9.34	311（54.47）	260（45.53）	397（69.53）	174（30.47）
ALS	415（4.27）	57.27±10.99	241（58.07）	174（41.93）	172（41.45）	243（58.55）
AE	323（3.33）	33.47±18.49	158（48.92）	165（51.08）	131（40.56）	192（59.44）
IPF	280（2.88）	67.91±10.31	186（66.43）	94（33.57）	103（36.79）	177（63.21）
CS	130（1.34）	13.28±10.28	57（43.85）	73（56.15）	74（56.92）	56（43.08）
Total	9714（100.00）	42.80±19.06	4358（44.86）	5356（55.14）	7188（74.00）	2526（26.00）

Curative care expenditure and average expenditure per visit of the ten rare diseases

The CCE of the ten rare diseases totaled US$19.001 million, with outpatient CCE of US$5,686,600 (29.93%) and inpatient CCE of US$13,314,500 (70.07%). The top three high CCE rare diseases were Hemophilia (US $4,378,600), YOPD (US $2,964,700) and SSc (US $2,445,700). The average expenditure per visit of outpatients for ten rare diseases was 109.33$. The top three diseases were AE ($308.36), Hemophilia (221.54$), and NO (120.04$). The average expenditure per visit of outpatient for

rare diseases except CS was mainly spent on drugs. The average CCE per visit of inpatients was 2411.64$, of which CS expenditure ranked the highest per visit($10491.82), which was 3.08 times the per capita disposable income of residents. (table 2)

Table 2 The CCE, average expenditure and drug cost per visit for 10 rare diseases in Sichuan Province in 2018

Disease	Outpatients			inpatients			Total
	CCE $Million(%)	Average expenditure per visit（$）	Average drug cost per visit（%）	CCE $Million(%)	Average expenditure per visit（$）	Average drug cost per visit（%）	CCE $Million(%)
Hemophilia	154.73（35.34）	221.54	86.76	283.13（64.66）	2112.22	45.35	437.86（23.04）
YOPD	102.07（34.35）	74.5	87.12	194.2（65.55）	5141.82	6.57	296.27（15.59）
SSc	144.35（59.02）	88.78	70.03	100.22（40.98）	1180.98	35.54	244.57（12.87）
NO	80.65（34.92）	120.04	89.11	150.29（65.08）	2104.93	30.65	230.94（12.15）
AE	25.63（14.47）	308.36	51.78	151.49（85.53）	3766.57	33.14	177.12（9.32）
IPF	6.67（5.42）	82.97	77.38	116.28（94.58）	2781.55	33.86	122.95（6.47）
MS	16.75（15.82）	52.02	64.76	89.15（84.18）	1481.66	31.32	105.91（5.57）
CS	4.06（4.14）	82.96	0.01	93.99（95.86）	10491.82	5.15	98.05（5.16）
MSA	27.86（28.45）	110.31	86.82	70.06（71.55）	1515.47	19.78	97.93（5.15）
ALS	5.89（6.65）	49.3	75.91	82.64（93.35）	1601.52	16.21	88.53（4.66）
Total	568.66（29.93）	109.33	79.5	1331.45（70.07）	2411.64	26.65	1900.11（100.00）

Health financing schemes for the ten rare diseases

As shown in Fig.1, 86% of outpatient CCE was financed from the household out-of-pocket expenditure(OOP), while social health insurance, the secondary source, only accounted for 7.85% of CCE. For outpatient CCE, the OOP of CS was the highest (97.73%) while the OOP of YOPD was the lowest(71.64%,). The household out-of-pocket expenditure, which was still the primary source of financing, accounted for 41.60% of inpatient expenditures, and social health insurance (39.58%) was the secondary financing source. In contrast to outpatients, inpatients had access to six common financing sources, which were relatively more diversified. Among inpatient services, the OOP for CS was the highest (79.6%), while OOP for YOPD and AE were also more than 50%, all of them caused heavy economic burdens for patients.

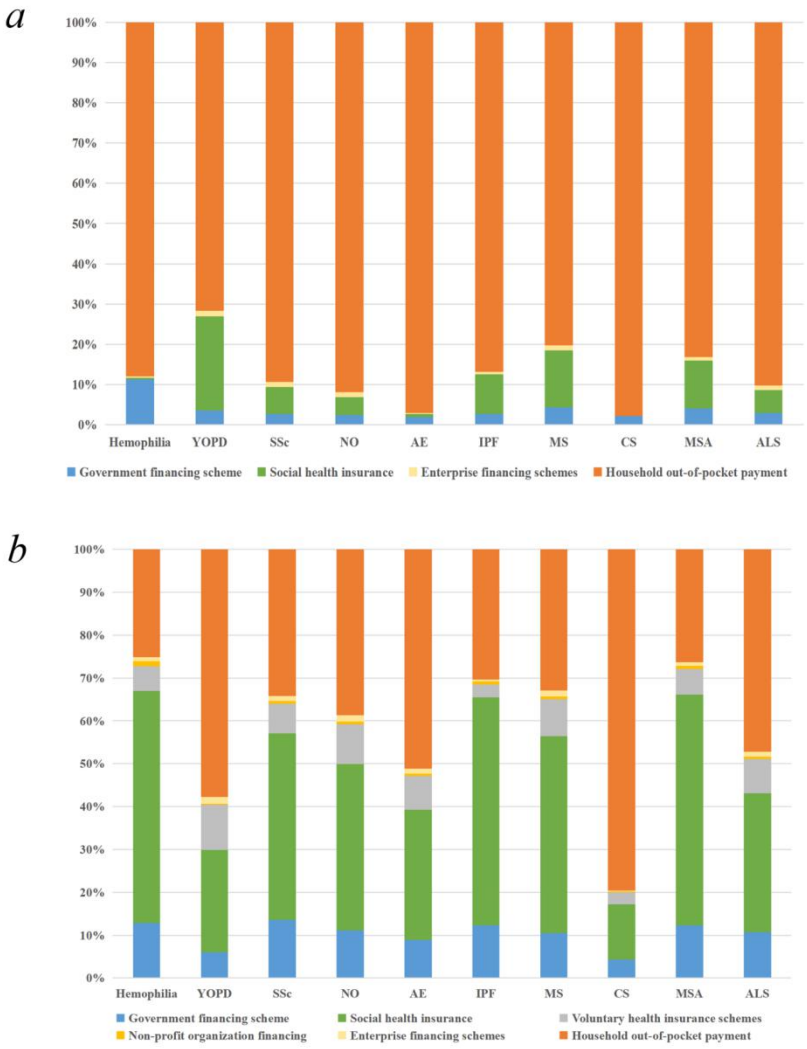

Fig.1 Outpatient (a) and inpatient (b) CCE financing schemes for the 10 rare diseases in Sichuan Province in 2018 (%)

Allocation of CCE in different medical institutions for the ten rare diseases

Fig.2 shows that more than 80% of the rare disease CCE was distributed to general hospitals; the second destination was specialized hospitals (outpatient 11.70%, inpatient 8.81%); and the third destination was Chinese traditional medicine hospitals (outpatient 3.55%, inpatient 7.74%). The outpatient CCE of three diseases (Hemophilia, YOPD, and MS)and the inpatient CCE of two diseases (CCE of SSc and NO) were distributed to primary medical institutions, indicating that such institutions also undertook some rare disease treatment services.

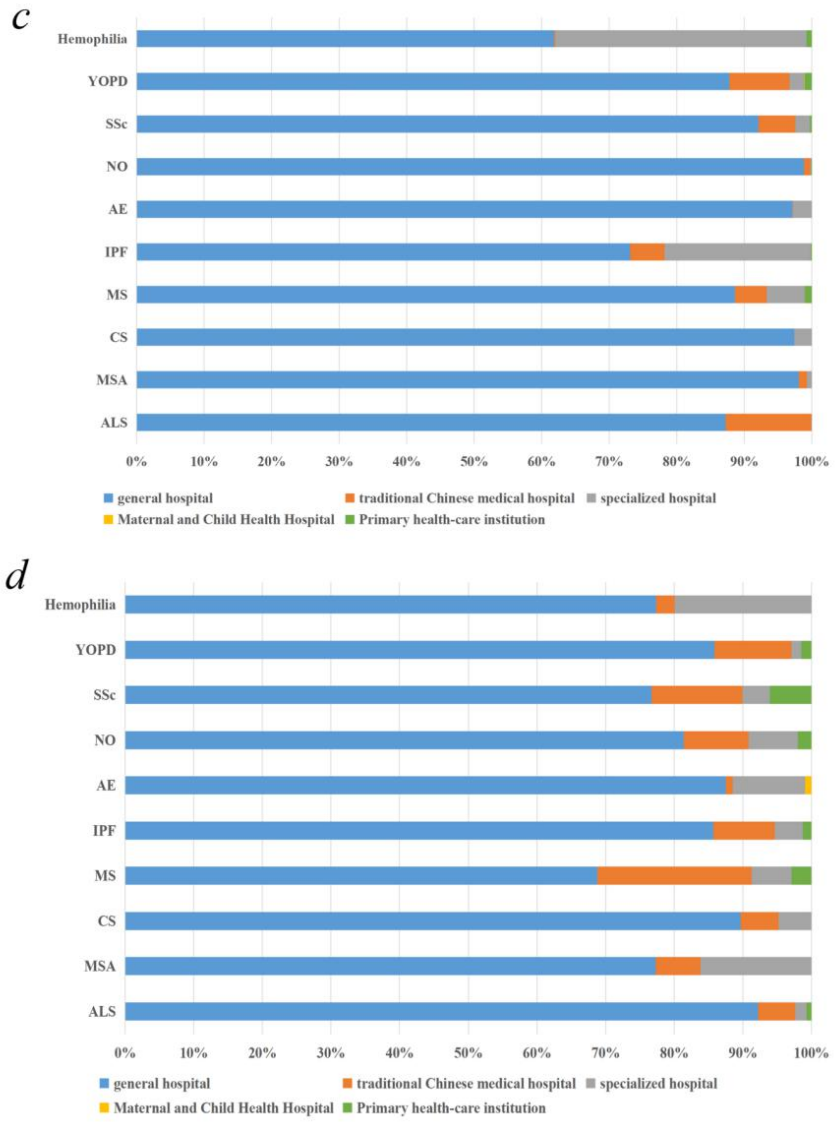

Fig.2 Allocation of outpatient (c) and inpatient (d) CCE in different medical institutions in Sichuan Province in 2018 (%)

The CCE of ten rare disease by beneficiary characteristics

The CCE of Hemophilia and CS mainly occurred in children and adolescents; CCE of YOPD, SSc, NO, and MS were mainly distributed among people aged 40~years, and the CCE of IPF and MSA were mainly distributed among people aged 60~years. Almost all the CCE of Hemophilia, IPF, and MSA were consumed by men.(Table 3)

Table 3 The CCE of ten rare diseases by beneficiary characteristics in Sichuan Province in 2018

Disease	0~		20~		40~		60~		Total	
	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
Hemophilia	46.34	0.17	24.34	0.39	23.03	0.94	4.59	0.20	98.30	1.70
YOPD	1.87	1.93	12.90	9.76	43.99	29.56	0.00	0.00	58.76	41.24
SSc	0.77	1.39	2.26	9.97	13.20	40.26	10.01	22.14	26.24	73.76
NO	2.03	1.93	3.64	16.67	6.08	42.78	4.06	22.80	15.82	84.18
AE	17.68	8.79	12.71	29.57	12.24	10.37	3.69	4.94	46.32	53.68
IPF	0.00	0.00	0.00	0.12	10.49	2.71	54.69	31.99	65.18	34.82
MS	1.22	2.08	15.50	19.45	11.65	32.25	3.81	14.05	32.17	67.83
CS	31.89	54.79	3.28	8.27	0.00	1.76	0.00	0.00	35.17	64.83
MSA	0.00	0.00	0.20	1.06	20.79	11.53	47.03	19.39	68.01	31.99
ALS	0.00	0.00	2.10	1.96	22.27	14.87	31.55	27.27	55.91	44.09
Total	14.68	4.52	10.68	9.34	19.18	19.52	10.83	11.25	55.37	44.63

Discussion

In this study, the CCE of ten rare diseases in Sichuan Province in the year 2018 was estimated based on the SHA 2011 accounting framework. The results have shown that the CCE of the ten rare diseases totaled US$19.011 million, accounting for 0.06% of the CCE in Sichuan Province in 2018; the average outpatient expenditure per visit was 109.33$, accounting for 3.22% of the per capita disposable income in Sichuan Province in 2018 and 1.40% of per capita GDP. The average inpatient expenditure per visit was $2411.64, accounting for 70.99% of per capita disposable income and 30.93% of GDP per capita. These research results are incomparable with prior research done in other countries due to the fact that few studies were based on the SHA2011 accounting framework and used such a "top-down" approach to calculate rare disease CCE, and that definition of rare diseases differs from country to country [20,21]. Nevertheless, our research has provided not only a new approach for the calculation of rare disease curative care expenditures but also important policy making support for concerned government departments.

High average CCE per visit, and high level of OOP, especially outpatient OOP, indicate that patients and their families bear high economic burdens caused by rare diseases, which can easily result in poverty[22]. In China, high R&D costs and low returns of rare disease drugs(orphan drugs) have caused pharmaceutical companies to be reluctant to invest in these drugs. Most rare disease drugs on the Chinese market are imported and therefore extremely expensive, posing a great economic challenge for rare disease patients and hence the high CCE [23,24]. Consequently, adopting effective measures to ensure that rare disease patients could afford drugs is the key to alleviating the economic burdens of these patients. In recent years, the Chinese government has issued a raft of policies in an effort to improve the accessibility to health services of rare disease patients [25-27]. In 2017, the National Healthcare Security Administration of China included recombinant human coagulation factor VIIa for injection for the treatment of Hemophilia, recombinant human interferon β-Ib for the treatment of MS, and pirfenidone for the treatment of IPF in the Medicine List for National Basic Medical Insurance and Employment Injury Insurance and Maternity Insurance (hereinafter referred to as "The National Reimbursement Drug List"). The inpatient OOP of these three rare diseases was found to be low in this study, indicating that the policies may have been effective [28]. However, the outpatient OOP of rare disease is still high and the proportion of reimbursement in the medical insurances is too low. Studies have found that there are still many restrictions on medical insurance coverage for outpatients [29,30], Another issue worth noting is the fact that the medical insurance reimbursement policy in China focuses more on rare disease drug cost-sharing, while non-drug treatment-based rare diseases cost more but less noticed by policymakers. This explains the high OOP in CS households, which depend mainly on surgeries for treatment. Therefore, the policymakers should also be concerned about how to reduce the disease burden of rare disease patients who rely on non-drug treatments.

We suggest exploring newer and more diversified medical security systems for rare diseases and co-paid by different parties in order to effectively alleviate the economic burdens of rare disease patients. On the one hand, the social health insurance system should play a basic role, and more rare disease treatment drugs should be incorporated into the National Reimbursement Drug List. On the other hand, a Multi-tiered Healthcare Security System covering critical illness insurance, medical assistance, commercial

insurance, and social assistance should be established so that the rare disease patients could get access to multiple channels of cost-sharing [31]. Most importantly, when formulating health insurance payment standards and multi-party co-payment mechanisms, we should fully consider the restrictions on rare disease reimbursement. For example, it is necessary to set a proper threshold,an annual limit of health insurance payment, and the top limit of annual out-of-pocket curative expenditures based on the actual CCE levels for different rare diseases in different regions to ensure that patients can truly benefit from the policies.

As is true to most diseases, rare disease treatment services are mainly provided by general hospitals because of their competence in diagnosis and treatment. China's primary medical institutions are limited in their technology levels and therefore focused on the diagnosis and treatment of common and frequently-occurring diseases. However, our research found that primary medical institutions had also undertaken the treatment of some rare diseases. For example, they provided outpatient services for SSc and MS patients as well as inpatient services for YOPD patients. This shows that it is feasible to improve doctors' expertise in the diagnosis and treatment of rare diseases in primary medical institutions. We recommend providing more training for primary medical workers to identify rare diseases and enable to acquire abilities to screen for, refer and even treat rare diseases, thus effectively shortening the diagnostic cycle of rare diseases, and reducing health care resource consumption and disease induced economic burdens [32,33].

The CCE distribution trend of various rare diseases in the population is approximately the same as its prevalence trend in this study [34-39]. For example, the prevalence rate of Hemophilia is relatively high, and its onset is mainly in boys. YOPD, IPF and MSA are more common in middle-aged and elderly people, while NO, and MS are more common in women. Consequently, these groups consume more CCE. Since rare diseases are mostly genetic, effective prevention is more important than treatment[40]. We need to focus on women of childbearing age and newborns with rare disease family histories. Tertiary prevention before, during and, after pregnancy are essential for the reduction of rare diseases. Firstly, it is necessary to carry out genetic screening before pregnancy and make appropriate reproductive choices based on genetic counseling, pathogenic gene carrier screening, and risk

assessment. Secondly, it is also important to carry out prenatal screening and prenatal diagnosis to avoid the birth of defective babies as much as possible. For newborns with a family history of rare diseases, genetic diseases screening, early diagnosis, early treatment, and enhanced lifetime follow-up management and drug control are of great significance to improvement of the patient's quality of life. IPF is the only respiratory disease among the ten rare diseases. Raghu found that the disease is more common in elderly men with a history of smoking [41]. Evidently, educating people to maintain a healthy lifestyle is also essential for the prevention and control of rare diseases [42,43].

It is undeniable that this study may have certain limitations. We may have underestimated the actual scale of rare disease CCE. When selecting hospitalized patients, this study uses the first diagnosis as the data extraction standard, and there may be a small number of rare disease patients not included in the calculation. In addition, we did not include misdiagnosed rare disease patients and those who were not diagnosed or not clearly diagnosed. Nevertheless, this study is a rare comprehensive report covering the financing scheme of rare disease CCE, health provider distribution, and beneficiary groups. It can help to improve the understanding of the impacts of rare diseases on Chinese society by providing empirical evidence for rare disease research in China.

Conclusions

The high CCE of rare diseases has always been a widely debated topic in the world, posing great challenges to patients, health policymakers, health care providers, and society. So far, there has neither been an internationally agreed-upon standard to access the scale of rare disease curative care expenditures nor research based on the financing structure of rare disease curative care expenditures. Under the SHA2011 framework, this study calculated the CCE scale of top ten high CCE rare diseases in Sichuan Province on both macro and micro levels and systematically answered the questions about the total amount of CCE, financing schemes, health providers, and beneficiary groups of the top ten rare diseases. As is shown by our research results, the total curative care expenditure of the 10 rare diseases is US$19,001,100; the average CCE per visit is high and the patients' out-of-pocket economic burdens are heavy. Curative care expenditures occurred mainly in general hospitals and distributed among

the 40-59 age group, indicating that the financing structure of rare disease CCE needs to be optimized and that a rare disease prevention and treatment model based on multi-party collaboration and financing should be explored to improve the level of medical security for rare disease patients. In addition, it is essential to enhance primary medical institutions' abilities to diagnose common rare diseases and to build a trio-tiered rare disease prevention system.

Abbreviations

CCE: curative care expenditure; OOP: out-of-pocket; SHA2011: System of Health Accounts 2011; YOPD: Young-onset Parkinson Disease; SSc: Systemic Sclerosis; NO: Neuromyelitis Optica; AE: Autoimmune Encephalitis; IPF: Idiopathic Pulmonary Fibrosis; MSA: Multiple System Atrophy; MS: Multiple Sclerosis; ALS: Amyotrophic Lateral Sclerosis; CS: Congenital Scoliosis

Acknowledgement

The authors express thanks to China National Health Development Research Center for their help with SHA 2011 analysis.

Author contributions

LJ and YL were involved in the study design and data interpretation. ZYT, LHL and MY developed the protocol and data collection materials.SQ was involved in the statistical analysis. This manuscript was prepared by LJ. YL was the director for the fund and designed ideas of research.All the authors participated in revising the report and commenting on the drafts of the manuscript, and approved the final report.

Funding

The authors received financial support of National Natural Science Foundation of China (NO.72174032).

Availability of data and material

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

Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

Consent for publication

Not applicable.

Conflicts of Interest

None of the authors has financial interest related to this study to disclose.

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References

1. Taruscio D, Capozzoli F, Frank C. Rare diseases and orphan drugs. Ann Ist Super Sanita. 2011;47(1):83-93. https://www.iss.it/documents/20126/45616/ANN_11_01_17.pdf

2. Song P, Gao J, Inagaki Y, Kokudo N, Tang W. Rare diseases, orphan drugs, and their regulation in Asia: Current st atus and future perspectives. Intractable Rare Dis Res. 2012 Feb;1(1):3-9. https://doi.org/10.5582/irdr.2012.v1.1.3

3. Arnold RJ, Bighash L, Bryón Nieto A, Tannus Branco de Araújo G, Gay-Molina JG, Augustovski F. The role of globalization in drug development and access to orphan drugs: orphan drug legislation in the US/EU and in Latin America. F1000Res. 2015 Feb 27;4:57.https://doi.org/10.12688/f1000research.4268.1

4. Hayashi S, Umeda T.35 years of Japanese policy on rare diseases.Lancet.2008 Sep 13;372(9642):889-90. https://doi.org/10.1016/S0140-6736(08)61393-8

5. 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 May;7(2):145-147.https://doi.org/10.5582/irdr.2018.01056

6. Tillet Y, Maillols-Perroy AC. Les médicaments orphelins : des opportunités méconnues pour les développeurs en Eur ope [Orphan Drugs: Underrated Opportunities for The Developers in Europe]. Therapie. 2015 Jul-Aug;70(4):351-7. Frenc h.https://doi.org/10.2515/therapie/2015021

7. The Lancet Neurology. Rare neurological diseases: a united approach is needed. Lancet Neurol. 2011 Feb;10(2):109.h ttps://doi.org/10.1016/S1474-4422(11)70001-1

8. Feng S, Liu S, Zhu C, Gong M, Zhu Y, Zhang S. National Rare Diseases Registry System of China and Related Cohort Studies: Vision and Roadmap. Hum Gene Ther. 2018 Feb;29(2):128-135. https://doi.org/10.1089/hum.2017.215

9. B Rupasinghe,A Gilbane,CR Schlegel,K Walsh, R Degun .Launching Combination Therapies In Rare Diseases: Is High Cost Burden Restricting Access?Value in Health,2017;20(9).https://doi.org/10.1016/j.jval.2017.08.859

10. Tasdemir E, Magestro M, Griner BP, Cummins G, Van EA, Kreeftmeijer J, Niemira J, Tao C. Prevalence-Based Me asurement of the Economic Burden of Rare Diseases: Case Review To Determine the Annual Cost of Acromegaly In Fr ance. Value Health. 2014 Nov;17(7):A527. https://doi.org/10.1016/j.jval.2014.08.1666

11. Buckner TW, Bocharova I, Hagan K, Bensimon AG, Yang H, Wu EQ, Sawyer EK, Li N. Health care resource utili zation and cost burden of hemophilia B in the United States. Blood Adv. 2021 Apr 13;5(7):1954-1962.https://doi.org/10. 1182/bloodadvances.2020003424

12. Paz-Zulueta M, Parás-Bravo P, Cantarero-Prieto D, Blázquez-Fernández C, Oterino-Durán A. A literature review of c ost-of-illness studies on the economic burden of multiple sclerosis. Mult Scler Relat Disord. 2020 Aug;43:102162.https:// doi.org/10.1016/j.msard.2020.102162

13. Walker CE, Mahede T, Davis G, Miller LJ, Girschik J, Brameld K, Sun W, Rath A, Aymé S, Zubrick SR, Baynam GS, Molster C, Dawkins HJS, Weeramanthri TS. The collective impact of rare diseases in Western Australia: an estima te using a population-based cohort. Genet Med. 2017 May;19(5):546-552.https://doi.org/10.1038/gim.2016.143

14. Chiu ATG, Chung CCY, Wong WHS, Lee SL, Chung BHY. Healthcare burden of rare diseases in Hong Kong - adopting ORPHAcodes in ICD-10 based healthcare administrative datasets. Orphanet J Rare Dis. 2018 Aug 28;13(1):147. https://doi.org/10.1186/s13023-018-0892-5

15. Hsu JC, Wu HC, Feng WC, Chou CH, Lai EC, Lu CY. Disease and economic burden for rare diseases in Taiwan: A longitudinal study using Taiwan's National Health Insurance Research Database. PLoS One. 2018 Sep 21;13(9):e0204206. https://doi.org/10.1371/journal.pone.0204206

16. China Daily. Rare Disease Medicine Debuts in China. Available online: http://www.gov.cn/xinwen/2019-03/02/content_5369882.htm. (accessed on 28 February 2020).

17. Xiang Yan,Dong Dong,Shenjing He,Chris Webster. Examining Trans-Provincial Diagnosis of Rare Diseases in China: The Importance of Healthcare Resource Distribution and Patient Mobility. Sustainability.2020;12(13).https://sci-hub.st/10.3390/su12135444

18. Xin XX, Guan XD, Shi LW. Catastrophic expenditure and impoverishment of patients affected by 7 rare diseases in China. Orphanet J Rare Dis. 2016 Jun 6;11(1):74.https://doi.org/10.1186/s13023-016-0454-7

19. Mueller M, Morgan D. New insights into health financing: First results of the international data collection under the System of Health Accounts 2011 framework. Health Policy. 2017 Jul;121(7):764-769.https://doi.org/10.1016/j.healthpol.2017.04.008

20. Boycott KM, Rath A, Chong JX, Hartley T, Alkuraya FS, Baynam G, Brookes AJ,Brudno M, Carracedo A, den Dunnen JT, et al. International Cooperation to Enable the Diagnosis of All Rare Genetic Diseases. Am J Hum Genet. 2017 May 4;100(5):695-705. https://doi.org/10.1016/j.ajhg.2017.04.003

21. Chiu ATG, Chung CCY, Wong WHS, Lee SL, Chung BHY. Healthcare burden of rare diseases in Hong Kong - adopting ORPHA codes in ICD-10 based healthcare administrative datasets. Orphanet J Rare Dis. 2018 Aug 28;13(1):147.https://doi.org/10.1186/s13023-018-0892-5

22. He J, Song P, Kang Q, Zhang X, Hu J, Yang Y, Tang M, Chen D, Hu S, Jin C. Overview on social security syste

m of rare diseases in China.Biosci Trends.2019 Sep 17;13(4):314-323.https://doi.org/10.5582/bst.2019.01209

23. Gong S, Wang Y, Pan X, Zhang L, Huang R, Chen X, Hu J, Xu Y, Jin S. The availability and affordability of orp han drugs for rare diseases in China. Orphanet J Rare Dis. 2016 Feb 27;11:20.https://doi.org/10.1186/s13023-016-0392-4

24. Luzzatto L, Hyry HI, Schieppati A, Costa E, Simoens S, Schaefer F, Roos JCP, Merlini G, Kääriäinen H, Garattini S, Hollak CE, Remuzzi G; Second Workshop on Orphan Drugs participants. Outrageous prices of orphan drugs: a call f or collaboration. Lancet. 2018 Sep 1;392(10149):791-794.

https://doi.org/10.1016/S0140-6736(18)31069-9

25. Zhang S, Chen L, Zhang Z, Zhao Y. Orphan drug development in China: progress and challenges. Lancet. 2019 Se p 28;394(10204):1127-1128.https://doi.org/10.1016/S0140-6736(19)32179-8

26. Fei L, Jing Z, Ming H. Analysis on the medical insurance policy and medical insurance catalog for rare diseases in China. Chinese Health Econ. 2018;37(3):71-76.https://kns.cnki.net/kcms/detail/detail.aspx?FileName=WEIJ201803027&DbN ame=CJFQ2018

27. Dong D, Wang Y. Challenges of rare diseases in China. Lancet. 2016 May 7;387(10031):1906.https://doi.org/10.1016/ S0140-6736(16)30418-4

28. the Ministry of Human Resources and Social Security.The Ministry of Human Resources and Social Security issued the National Basic Medical Insurance, Work Injury Insurance and Maternity Insurance Drug Catalog (2017 Edition).2017.

http://www.mohrss.gov.cn/SYrlzyhshbzb/dongtaixinwen/buneiyaowen/201702/t20170223_266787.html

29. Peng Haoran,Yue Jinglun.Integration of China's Basic Medical Insurance System:Theoretical Debate, Practical Progres s and Future Prospects.Academic Monthly.2020;52(11):55-65.https://kns.cnki.net/kcms/detail/detail.aspx?dbcode=CJFD&dbna me=CJFDLAST2021&filename=XSYK202011007&uniplatform=NZKPT&v=0zBciryLGJRH1usPr2qXGGNbdSHY4PrlBYhoG zkTrIRVPvqDTLZISH4CId9eSNbX

30. Huang Rufang,Shao wenbin.China rare disease Healthcare Security City Report(2020).CORD.2020.http://www.cord.org.

cn/#page1

31. R. Ma,L. Huang,D. Zhao,L. Xu. Commercial health insurance- a new power to push china healthcare reform forwar d? Value in Health.2015;18(3).https://doi.org/10.1016/j.jval.2015.03.601

32. Müller T, Jerrentrup A, Schäfer JR. Computerunterstützte Diagnosefindung bei seltenen Erkrankungen [Computer-assis ted diagnosis of rare diseases]. Internist (Berl). 2018 Apr;59(4):391-400. German.https://doi.org/10.1007/s00108-017-0218-z

33. Gong L, He Q. Establishing a rare diseases center: Experiences from Western China. Intractable Rare Dis Res. 2021 Feb;10(1):60-61.https://doi.org/10.5582/irdr.2020.03091

34. M. Cavazza, P. Armeni, M. De Santis, J. López-Bastida, R. Linertová, J. Oliva-Moreno, et al.Social/economic costs and quality of life in patients with haemophilia in Europe. Eur J Health Econ. 2016 Apr;17 Suppl 1:53-65.https://doi.org /10.1007/s10198-016-0785-2

35. Y.Kodra,M.Cavazza,A.Schieppati,M.De Santis,P.Armeni,R.Arcieri,et al.The social burden and quality of life of patients with haemophilia in Italy. Blood Transfus. 2014 Apr;12 Suppl 3(Suppl 3):s567-75.https://doi.org/10.2450/2014.0042-14s

36. Kleijn, E.P. Mauser-Bunschoten, K. Fischer, C. Smit, H. Holtslag, C Veenhof.Evidence for and cost-effectiveness of physio therapy in haemophilia: a Dutch perspective. Haemophilia. 2016 Nov;22(6):943-948.https://doi.org/10.1111/hae.13076

37. D.E. Furst, A.W. Fernandes, S.R. Iorga, W. Greth, T. Bancroft.Furst DE, Fernandes AW, Iorga SR, Greth W, Bancroft T. Annual medical costs and healthcare resource use in patients with systemic sclerosis in an insured population. J Rheum atol. 2012 Dec;39(12):2303-9.https://doi.org/10.3899/jrheum.120600

38. Chevreul K, Brigham KB, Gandré C, Mouthon L; BURQOL-RD Research Network. The economic burden and healt h-related quality of life associated with systemic sclerosis in France. Scand J Rheumatol. 2015 May;44(3):238-46.https:// doi.org/10.3109/03009742.2014.976653

39. Fischer A, Zimovetz E, Ling C, Esser D, Schoof N. Humanistic and cost burden of systemic sclerosis: A review of the literature. Autoimmun Rev. 2017 Nov;16(11):1147-1154. https://doi.org/10.1016/j.autrev.2017.09.010

40. Huang R, Wei Y, Hu J, Kong F, He J, Yang Y, Tang M, Jin C, Kang Q. The progress of, challenges faced by, and future of rare disease patient organizations in China.https://doi.org/10.5582/irdr.2019.01069

41. Raghu Ganesh,Remy-Jardin Martine,et. Diagnosis of Idiopathic Pulmonary Fibrosis. An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. Am J Respir Crit Care Med. 2018 Sep 1;198(5):e44-e68.https://doi.org/10.1164/rccm.201807-1255ST

42. Baker JR, Riske B, Voutsis M, Cutter S, Presley R. Insurance, home therapy, and prophylaxis in U.S. youth with severe hemophilia. Am J Prev Med. 2011 Dec;41(6 Suppl 4):S338-45.https://doi.org/10.1016/j.amepre.2011.09.002

43. Post B, van den Heuvel L, van Prooije T, van Ruissen X, van de Warrenburg B, Nonnekes J. Young Onset Parkinson's Disease: A Modern and Tailored Approach. J Parkinsons Dis. 2020;10(s1):S29-S36.https://doi.org/10.3233/JPD-202135