Why is misdiagnosis more likely among some people with rare diseases than others? Insights from a population-based cross-sectional study in China

Dong Dong
Chinese University of Hong Kong https://orcid.org/0000-0001-9784-6472
Roger Yat-Nork Chung
Chinese University of Hong Kong
Rufina Chan
Chinese University of Hong Kong
Shiwei Gong
Huazhong University of Science and Technology
Huan Xu (richardhxu@cuhk.edu.hk)
Chinese University of Hong Kong https://orcid.org/0000-0002-4720-5172

Research

Keywords: Misdiagnosis, information accessibility, social determinants of rare diseases, cross-sectional survey, China

Posted Date: November 25th, 2019

DOI: https://doi.org/10.21203/rs.2.17761/v1

Version of Record: A version of this preprint was published on October 28th, 2020. See the published version at https://doi.org/10.1186/s13023-020-01587-2.

Abstract

Background For patients with rare diseases (RD), misdiagnosis has been regarded as one of the key issues that hinder RD patients' accessibility to timely treatment. Yet, less is known about the main factors associated with RD patients' misdiagnosis. The objective of this study is to use the data from a national survey among 2,040 RD patients from China to explore the association between misdiagnosis and other factors, including patients' demographics, socio-economic characteristics, medical history, and their accessibility to RD information.

Results Three binary logistic regression analyses were performed to estimate the relationships between misdiagnosis and level of rarity of the RDs (mild, moderate and severe), demographics, health insurance levels and accessibility to disease-related information by using the total sample, and the adult and minor sub-samples.It is found that accessibility to RD information is the most critical factor influencing the patients' chances of being misdiagnosed. In other words, the greater the difficulty in accessing information on RD management, the higher the possibility of experiencing misdiagnosis.Such influences from information accessibility to misdiagnosis were repeatedly discovered when exploring the adult and the minor sub-samples. The association between perceived economic status and misdiagnosis only occurs in the total sample. The only other factor significantly associated misdiagnosis was disease complication: participants who reported no complications are less likely to experience misdiagnosis.

Conclusions Our study indicated that patients with RDs who have difficulty in accessing disease-related information have nearly two to five times higher chances of being misdiagnosed. Even after considering the patients' age, gender, economic levels and education levels, the impact of information accessibility still stands out. Our finding highlights the fact that accessibility to information is the key to reducing misdiagnosis among RD patients.

Introduction

The issue of rare diseases (RDs) has been gaining public awareness in China over the past decade. RDs are often degenerative or even life-threatening. Currently, there are nearly 7,000 RDs documented in the literature, of which 80% have genetic origins. In addition, 50% of patients with RDs are children, and 30% of them die before the age of five [1]. The global prevalence of RDs is approximately 10%, but the prevalence threshold and definition vary across countries. In the United States, an RD is defined as a condition that affects fewer than 2,00,000 people [2]. In Japan, the figure is 50,000 [3]. Currently, approximately 10 million Chinese are affected by one of 7,000 known RDs [4]. However, China lags far behind other countries in terms of knowledge about RDs, affecting prevention, diagnosis treatment, and patient protection. For most RDs, there is a lack of epidemiological data at the population level and China has yet to formulate an official definition of RDs.

Given the low prevalence and patient base of RDs, they tend to attract far less attention from medical and research professionals than common diseases. Thus, owing to the overall lack of knowledge surrounding these diseases, medical misdiagnosis among patients with RDs is common. On average, a patient with an RD has to visit 7.3 physicians and spend 4.8 years to receive an accurate diagnosis [5]. Many, however, wait decades and some never receive one. The symptoms of RDs are often uncommon and can point in many different directions, making the diagnosis even more difficult for physicians. Graber [6] has identified a number of causes for diagnostic errors. The three most common types of errors are (1) context errors, when the diagnostic possibilities for a disease are too restrictive, (2) availability errors, when a more common or more familiar diagnosis is preferred, and (3) premature closure, which means that once a probable diagnosis is identified, other options are no longer considered [7]. As a result, a definite diagnosis and treatment is often delayed, and patients experience physical and mental discomfort and increased healthcare costs.

Studies have also found that a wide range of socio-demographic and clinical factors are associated with diagnostic delay. For example, patients with low socio-economic status, low educational attainment, and those residing in rural areas experience increased diagnostic delay [9], [10]. However, there have been no relevant Chinese studies on patients with RDs. In this study, we conducted a population-based RD survey across China to explore the association between misdiagnosis and other factors, including patients' demographics, socio-economic characteristics, medical history, and their accessibility to RD information.

Method

Study design and participants

A self-administered survey on patients' understanding and experience of RDs was conducted online (www.wenjuan.com) in January and February 2018. The survey was approved by the Committee on the Use of Human and Animal Subjects in Teaching and Research of Hong Kong Baptist University (No: FRG2/15–16/052) and the Medical Ethics Committee of Tongji Medical College of Huazhong University of Science and Technology (No: S005).

Since there was no national registry or epidemiological studies on people affected by RDs in China at the time of the survey, the geographical distribution and demographic characteristics of the Chinese population with RDs were unknown, making it impossible to employ probability sampling. Therefore, a non-probability, convenience snowballing method was used to recruit participants. In collaboration with the Illness Challenge Foundation—one of the largest umbrella organisations for patients with RDs in China—the survey was advertised via its online and offline networks. Recruitment information was also shared by other patient organisations and individual patients or their friends and families through snowball sampling.

Procedure

Study information was presented to the participants on the first page of the online survey questionnaire. They had to click a button named "next page" to show their consent with the terms; they were also told, if they did not agree, that they could simply exit the survey by closing the page. After the consent, the participants were exposed to the main body of the questionnaire. At the beginning of the survey, a series of questions were used to identify the target respondents (i.e. people with RDs in China). Patients under 18 were asked to end the survey and refer the survey link to their legal guardians. Main caregivers (n = 918) and patients (n = 1,089) were identified and diverted to two different versions of the questionnaire with the same measures but customised for the two groups.

Measures

Patients' demographics (year of birth, gender, hukou or household registration, current residential district, and family size), subjective socio-economic status (measured by the respondents' perception of their own economic status in relation to others living nearby), medical history (including year of disease onset, year of diagnosis, misdiagnosis, specific names of each clinically diagnosed medical complication), and degree of difficulty in obtaining information related to the RD were asked.

Data analysis

Analyses were performed using R (R Foundation, Austria). Descriptive statistics were used to describe the study sample. Demographic characteristics were categorised as gender (male and female), hukou (dichotomised into urban and rural), and whether the participants belonged to economically developed or underdeveloped areas in China. We also reported the participants' mean age, difficulty in accessing medical information related to the RD in question (scores ranged between 1 and 5, with 1 indicating 'very easy to obtain information' and 5 indicating 'very hard to obtain information'), number of disease-related complications, and the participants' family size (number of family members)). Furthermore, considering the large income gap between developed and underdeveloped or urban and rural areas in China, it was impossible to make direct comparisons on the basis of income level. Therefore, we used another item —'perceived economic status if compared with people nearby'—as a proxy question to collect data regarding participant's subjective socio-economic level (scores ranged between 1 and 5, with 1 indicating 'much lower than average', 3 indicating 'equal to local average', and 5 indicating 'much higher than average') in the context of the place of residence. Economic level was regrouped into three categories (below average, average, and above average).

In order to consider the association of rarity of disease with misdiagnosis, depending on the known or estimated prevalence, birth prevalence, or number of total cases reported worldwide, all 94 diseases reported by the participants as their confirmed diagnoses were regrouped into three groups: mildly rare, moderately rare, and extremely rare (see Appendix 1 for detailed grouping information).

Binary logistic regression models with the dependent variable 'Have you been misdiagnosed?' were then employed. This question had two response options: 'yes' (misdiagnosis = 1) and 'no' (misdiagnosis = 0). All the models included the level of rarity, which was considered a fixed effect. The remaining characteristics were sequentially entered into the models to assess the manner in which they were associated with the relationship between misdiagnosis and the level of rarity. Five regression models were introduced to predict the variance of such relationships in three sub-samples (general participants, adults, and minors (age $\leq$ 18 years)). The first model directly explored the relationship between misdiagnosis and the level of rarity. The second model explored the relationship between

misdiagnosis and demographic characteristics. The third model explored the relationship between misdiagnosis and RD care management. The fourth model explored the relationship between misdiagnosis and economic level, household size, as well as healthcare insurance coverage. The last model was the complete model, with all the characteristics included. Fifteen models in total were presented sequentially. Moreover, the Akaike information criterion and Bayesian information criterion were reported to estimate the relative quality of statistical models. The statistical significance was set at $p < 0.05$.

Results

Figure 1 presents the distribution of participants. The study sample came from all over the mainland China, covering all 22 provinces, five autonomous regions, four direct-controlled municipalities, and two special administrative regions. Among them, nearly 10% came from Shandong Province, followed by Henan (8.2%) and Hebei (8.19%). The majority of the participants resided in Eastern and Southern China. For Macau, Hong Kong, and Tibet, only one participant was from each region. Moreover, in total and for adults or non-adults, the percentage of misdiagnosis was higher among females than males. For adults, the highest percentage of misdiagnosis was at 26–30 years (16%) and then gradually decreased to 2% by the age of 60 (Figure 2).

Table 1 displays the descriptive characteristics of the study sample. In total, 2,040 participants, with a mean age of 22.5 years, successfully completed our survey. Among them, 53.6% were male, 52.2% registered as urban hukou, 56% came from underdeveloped areas, and more than two-thirds had experienced misdiagnosis. Descriptive statistics also revealed that nearly 20% of the participants reported having an RD within the mildly rare category, and 6.2% being extremely rare. A large proportion of the participants, 73.8%, were categorised as having a moderately rare RD.

Three binary logistic regression analyses were performed to estimate the relationships between misdiagnosis and level of rarity, demographics, health insurance levels and accessibility to disease-related information by using the total sample, and the adult and minor sub-samples.

In the total sample, the level of disease rarity did not affect the chances of the participants to be misdiagnosed. Gender did not make a difference as well. When compared with adults, minors had a lower association with misdiagnosis (OR = 0.503, 95% confidence interval (CI) = 0.714- 0.610, $p < 0.001$). The factor of 'difficulty in obtaining information' revealed that the greater the difficulty in accessing information on RD management, the higher the possibility of experiencing misdiagnosis. As compared to 'a little difficult to access RD information', patients who felt 'some difficult' or 'very difficult' had a much higher probability of being misdiagnosed (OR = 2.543 for 'some difficult', 95% confidence interval (CI) = 1.697 - 2.707, $p < 0.001$; OR = 3.915 for 'very difficult', 95% confidence interval (CI) = 2.852- 4.732, $p < 0.001$). Moreover, participants who reported no complications are less likely to experience misdiagnosis in the full model (OR = 0.445, $p < 0.001$). Economic level also had some influence on the chances of being misdiagnosed. When compared with those who perceived their own family economic statuses were lower than the average local levels, those whose statuses were higher than the average were less likely to be misdiagnosed (OR = 0.778, confidence interval (CI) = 0.605- 0.999, $p <0.05$). Family size mattered too. The larger the family size was, the more likely for the patient to be misdiagnosed (OR = 1.167, 95% confidence interval (CI) = 1.040- 1.230, $p < 0.01$). However, the influence of economic level and family size disappeared in the full model (Table 2).

For the adult sub-sample (Table 3), while the 'rarity of disease' factor was non-significant in all models, 'difficulty in obtaining RD information,' 'whether having complications', and 'type of medical insurance coverage' became the strongest factors associated with misdiagnosis in partial models and the full model. Patients who had difficulties in accessing RD information were more likely to experience misdiagnosis (OR = 2.214 and 3.496, $p<0.001$), and patients with no complications were less likely (OR = 0.854, $p<0.05$). When compared with patients covered by free medical insurance, the rest who were covered by urban employee insurance, or urban resident insurance, or the new scheme rural insurance were all more likely to be misdiagnosed.

For the sub-sample of minors (Table 4), while the level of rarity did not seem to affect the probability of misdiagnosis, age did. When the patient got one year older, the chances of being misdiagnosed increased by 1.113 times (confidence interval (CI) = 1.059- 1.171, $p <0.001$) in model 2 and by 1.09 times in the full model (confidence interval (CI) = 1.03- 1.150, $p <0.01$). Besides age, the factor of 'difficulty in obtaining RD information' also significantly affected the probability of being misdiagnosed in model 3 and the full model. However, none of the rest factors, including gender, the type of Hukou, developmental status of city of living, patients' fraternal educational level, which is regarded as an important indicator of the family's social economic status, perceived family economic status in local area, or family size, made a difference on misdiagnosis.

Discussion

To the best of our knowledge, there has been no previous study investigating the issue of misdiagnosis of RDs in China, nor was such a topic being explored sufficiently in other countries. Our survey indicated that more than 66% of patients had experienced misdiagnosis (vs. 40% worldwide). Considering there are more than 20 million patients with RDs in China, the corresponding financial and social burden on the public budget is enormous.

As opposed to conventional wisdom, whether the RD was extremely or moderately or mildly rare did not increase or decrease the probability of misdiagnosis. Perhaps only when compared with 'common diseases' that the level of rarity began to matter. Partly echoing to the theories on social determinants of health, we found that patients' socio-economic characteristics might be associated with misdiagnosis. However, due to the uneven distribution of incomes and economic development in China, it was hard for us to use 'objective standards' (e.g., individual income, household income, etc.) to do the comparison. Therefore, we used 'perceived economic level' as an indicator of patients' subjective assessment on their own economic status at the local level. We found that, only patients who felt their economic status were higher than the average were less likely to be misdiagnosed. However, in the two sub-samples, such difference disappeared. Among the adult patients, the type of medical insurance coverage mattered more. Patients with free medical care, most of whom were civil servants, were much less likely to be misdiagnosed. Such findings imply that income might not be the key determinants of RD misdiagnosis; rather, the type of healthcare resources associated with individual social economic status might be more important. As seen from the data, RDs do not 'discriminate' in terms of gender, age, ethnicity, residential area, or educational levels.

The most important finding is that the accessibility to disease-related information seems to be the most critical factor influencing the patients' chances of being misdiagnosed. Our models indicate that patients with RDs who have difficulty in accessing disease-related information have nearly two to five times higher chances of being misdiagnosed, regardless of the level of rarity of their diseases. Even after considering the patients income levels and their education levels, the impact of information accessibility still stands out. This finding highlights the fact that accessibility to information is the key to reducing misdiagnosis. In the field of RDs, patients' information needs are never fully met.[10] It is difficult for them to find the right information as well as to make a detailed assessment of the quality of the information they receive. Lack of information leads to delay in diagnosis, insufficient medical and social support, as well as lowered accessibility of treatment and rehabilitation.[11]

The question is: what are the sources of RD-related information? In recent decades, the internet has become the source of choice for a growing number of patients with RDs as they seek to understand their symptoms and obtain information about possible diseases before seeking professional help.[12] At the end of 2017, in China, the number of netizens reached more than 750 million. Using the internet could be the most cost-effective way for medical professionals, patients and their families to locate information about RDs. However, in China, the online sources of RDs are scarce; over 60% of all respondents noted a general lack of available information, not to mention the questionable reliability of such information. Currently, the dominant platform for seeking and exchanging information (including experiences and knowledge) about RDs is virtual patient communities organised based on Electronic Bulletin Boards (or BBS) or social network gadgets (such as QQ or WeChat). However, such communities are relatively closed and often focus on one particular rare condition, which inevitably makes it hard for those with an ambiguous or unconfirmed diagnosis to join and find further help. Therefore, in order to reduce the chances of misdiagnosis, an aggregated RD information platform supported by patient communities might be more suitable. However, ensuring the quality[10] and suitability of information[13] remains a problem.

Another important source of information that can help patients manage their health is patient organisations (POs), which promote the needs and priorities of patients with RDs. Currently, in China, there are nearly 120 active patient groups, most of which are condition-specific groups, either led by patients with the same RD or initiated by physicians or medical specialists. The support of POs is important for patients with RDs, as demonstrated by the fact that more than 80% of our respondents indicated a desire to join. Hall indicated that POs are the most important way to provide medical information and help patients connect with each other.[14] Moreover, general support groups could provide assistance with finances and special medical equipment.[15] For patients with extremely rare diseases, POs also serve the function of disseminating information about and providing opportunities to participate in clinical trials of new drugs.[16] Furthermore, in many developed countries, POs are the backbone of efforts to advocate RD management and improve public and private awareness. Overall, POs are one of the most valuable sources of patient information. Compared with online information, information from POs is apparently more reliable, especially in the eyes of the patients. [17]

Nonetheless, the most important source of information on RD management is doctor-patient communication. Effective doctor-patient communication has the potential to help regulate patients' emotions, facilitate comprehension of medical information, and allow for better identification of patients' needs, preferences, and expectations.[18] However, we found that doctor-patient communication in the context of RDs might be problematic. First, adult patients living in rural areas and covered by the New Rural Cooperative Scheme reported a nearly 3.5 times higher probability of misdiagnosis compared with urban residents. This is not surprising, if being understood within the context of the urban-rural disparity in China. Doctors from rural areas, who have less knowledge and fewer opportunities to practice with difficult cases, are incapable of providing sufficient support for patients with RDs.

We also found that patients who reported having complications had a 44.5% higher probability of misdiagnosis; for adults, the ratio increased to 73%, and for minors, it increased to 85.4%. In China, high-quality healthcare resources are highly centralised at a few tertiary hospitals in big cities. A whitepaper indicated that more than 83% of Chinese doctors worked overtime.[19] Owing to time constraints, consultation times are limited, and doctors are unable to provide patients with all the necessary information. In fact, a large number of doctors also complain that they have very few means to access information on RDs. Freitas [20] indicated that unmet information needs harm doctors' decision-making, which may result in difficulties in making a definitive diagnosis.

In China, where there are more than 20 million people with RDs, misdiagnosis poses a huge economic and social burden on patients, families and the healthcare system as a whole. The findings of this study illustrate that improving RD patients' ability to access the required information is the key to decreasing misdiagnosis. In 2018, the China Alliance for Rare Diseases held its inaugural meeting in Beijing. About the same time, the Chinese government issued the First National List of Rare Diseases. Both events indicate the government's determination and ambition to manage RDs in China. It is hoped that this can serve as a starting point to greater public and private involvements in RD management. We hope that the next few years may see the necessary legislations, with the healthcare system supporting active patient groups, societies, and foundations to provide information and conduct research on RDs. It is also hoped that regular awareness campaigns and local RD conferences become a reality, because what patients really desire is to obtain information about living with a specific rare condition and its future impact.[21]

To our knowledge, this is the first study to explore factors associated with RD misdiagnosis based on first-hand data from patients with RDs across China. We explored the association of misdiagnosis with demographic, socio-economic, and healthcare factors. We provided evidence of the fact that accessibility of information is one of the most important risk factors associated with misdiagnosis.

The specific mechanism behind the association of increased accessibility of disease-related information with decreased misdiagnosis is complicated. Further research is required and must foster collaboration between patient communities, medical professionals, and the healthcare system. However, it is important to remember that information plays a critical role during the process of diagnosis, especially for RDs.

The study has limitations as well. The first is the non-probability sampling strategy, which limits the generalisability of the findings. The second is the cross-sectional design, which makes it difficult to make inferences regarding causality and temporality. The third is that in asking patients to self-report the situation of their misdiagnosis, the possibility of recall bias cannot be ignored. The fourth is that our investigation was centred around the phenomenon of misdiagnosis in the context of RDs in general, but the associations might vary for different RDs. Finally, as in the case of minors, the questionnaires were filled by their parents, and there is the possibility of proxy bias.

Conclusions

We found a very high rate of misdiagnosis of RDs across China. The difficulty patients experience in accessing disease-related information is the key factor leading to a high probability of misdiagnosis. There were no disparities in misdiagnosis based on gender, age, geographical region, ethnicity, or education. The importance of this study lies in the fact that it is a step towards meeting the urgent need to identify the association of patients' socio-economic, healthcare resources and social support characteristics with misdiagnosis of RDs. The findings can aid in the formulation of social and healthcare strategies to decrease the misdiagnosis of RDs in specific target populations. The epidemic of RD misdiagnosis in China is a political emergency that needs to be urgently addressed.

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Declarations

Ethics approval and consent to participate

This survey was approved by the Committee on the Use of Human and Animal Subjects in Teaching and Research of Hong Kong Baptist University (No: FRG2/15-16/052) and the Medical Ethics Committee of Tongji Medical College of Huazhong University of Science and Technology (No: S005).

Consent for publication

Not applicable

Availability of data and materials

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

Competing interests

The authors declare that they have no competing interests

Funding

This work was supported by the grants from the National Natural Science Foundation of China (No: 70903025, No: 71373089).

Authors' contributions

DD and SWG designed the survey questionnaire. DD was in charge of collecting survey data. DD and HX analyzed and interpreted the survey data. HX, DD, RYC and RC contributed in writing the manuscript. All authors read and approved the final manuscript.

Acknowledgements

The authors would like to thank the Illness Challenge Foundation and other rare disease patient organizations in China for their assistance in distributing the survey questionnaire. The authors also would like to thank all participants of the survey, including people and families affected by rare diseases in China, for their generosity in sharing their lives and experiences via the survey.

Tables

Table 1 The characteristics of study sample

	Overall		Adult		Non-adult	
	N	%	N	%	N	%
Sex						
Male	1093	53.6	492	45.2	581	63.3
Female	947	46.4	597	54.8	337	36.7
Education						
No education			47	4.3	34*	6.7
Primary and Secondary			312	28.7	172*	33.8
Senior			248	22.8	175*	34.4
College and above			482	44.3	128*	25.1
Disease Rarity level [a]						
Mildly rare	396	19.9	86	7.8	38	4.3
Moderately rare	1466	73.8	828	75.3	638	72.0
Extremely rare	124	6.2	186	16.9	210	23.7
Hukou [b]						
Urban	1061	52.2	609	56.1	432	47.3
Rural	970	47.8	477	43.9	481	52.7
Economic developed area [c]						
Develop area	898	44.0	483	44.4	402	43.8
Underdeveloped area	1142	56.0	606	55.6	516	56.2
Have been misdiagnosed						
Yes	1310	66.1	755	72.2	534	59.1
No	671	33.9	290	27.8	370	40.9
Insurance [d]						
Free medical care			42	4.7		
Urban employee medical insurance			359	40.4		
Urban resident medical insurance			130	14.6		
New rural cooperative medical care			357	40.2		
Difficult level to access Information						
A little difficult	462	23.3	269	25.6	187	20.7
Some difficult	769	38.7	416	39.7	337	37.2
Very difficult	755	38.0	364	34.7	381	42.1
Have complication						
Yes	773	70.0	433	69.3	340	70.8
No	332	30.0	192	30.7	140	29.2
Perceived economical level as compared to locals [e]						
Below average	1342	66.9	698	64.1	644	70.2
Close to average	597	29.7	353	32.4	244	26.6
Above average	68	3.4	38	3.5	30	3.3
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**
Age	22.46	17.13	36.08	10.77	6.37	4.68
Length of time to be diagnosed [f]	2.26	4.81	3.46	6.08	0.83	1.91
Family size [g]	2.73	1.14	3.27	0.87	2.08	1.08

* The patient's fraternal educational level

a. The classification of rare disease was listed in the appendix.

b. Hukou is a system of household registration in mainland China. A household registration record officially identifies a person as a resident of an area. Currently there are two categories of Hukou system: urban registration and rural registration.

c. The developed areas included Beijing, Tianjin, Hebei, Shandong, Shanghai, Jiangsu, Zhejiang, Fujian, Guangdong, Hainan, Hong Kong SAR and Macau SAR. The underdeveloped areas included Chonqing, Sichuan, Hubei, Hunan, Anhui, Jiangxi, Shaanxi, Gansu, Ningxia, Shanxi, Yunnan, Guizhou, Guangxi, Jilin, Liaoning, Heilongjiang, Inner Mongolia, Tibet, Xinjiang and Qinghai.

d. Free medical care only provides to civil servants.

e. Perceived economic level is determined by the respondent's self-assessment of their monthly family income. It is measured by a likert scale from 1-5. If the respondents think his/her family income is about the same as average level in the places where they live, they will choose 3; whereas 1-2 means lower than average local income level, and 4-5 means higher than average level

f. Length of time from symptom onset to an accurate diagnosis (years)

g. Number of many family members living under the same roof.

Table 2 Results of logistic regression models for total participant

	Model 1[a]		Model 2		Model 3		Model 4		Model 5	
	OR	95% C.I[b]	OR	95% C.I	OR	95%C.I	OR	95%C.I	OR	95%C.I
Rarity-moderate	0.764	(0.503,1.137)	0.857	(0.561,1.286)	1.162	(0.667,1.983)	0.853	(0.555,1.649)	1.329	(0.758,2.289)
Rarity-mild	0.766	(0.487,1.185)	0.901	(0.568,1.411)	0.909	(0.492,2.280)	0.839	(0.531,2.930)	1.110	(0.712,2.2)
Female			0.862	(0.721,1.067)					0.838	(0.613,1.074)
Minors			**0.503*** **	**(0.714,0.610)**					**0.615****	**(0.442,0.852)**
Rural Hukou			1.059	(0.875,1.287)					0.972	(0.73,1.294)
Underdeveloped area			1.130	(0.922,1.355)					1.043	(0.867,1.503)
Some difficult to access RD information					**2.543*** **	**(1.679,2.707)**			**2.709*** **	**(1.821,3.997)**
Very difficult to access RD information					**3.915*** **	**(2.852,4.732)**			**4.459*** **	**(3.283,5.615)**
No complication					**0.445*** **	**(0.335,0.590)**			**0.420*** **	**(0.312,0.563)**
Close to average local economic level							0.887	(0.719,1.092)	1.001	(0.756,1.411)
Above average local economic level							**0.778***	**(0.605,0.999)**	1.016	(0.537,2.904)
Family size							**1.167****	**(1.040,1.230)**	1.161	(0.999,1.334)

Reference groups are Rarity-extremely rare, male, adult, urban hukou, developed area, a little difficult to access RD information, yes complication, below average local economic level

a. Model 1 = level of rarity model; Model 2 = demographic model, Model 3 = Healthcare management model; Model 4 = social support model; and Model 5 = Full model.

b. 95% C.I = 95% confidence interval, OR = odds ratio

c. * p<0.05; ** p<0.01; ***p<0.001

Table 3 Results of logistic regression models for adult participants

	Model 1[a]		Model 2		Model 3		Model 4		Model 5	
	OR	95% C.I[b]	OR	95% C.I	OR	95%C.I	OR	95%C.I	OR	95%C.I
Rarity-moderate	0.887	(0.517,1.467)	0.956	(0.609,1.326)	0.781	(0.449,2.12)	0.981	(0.64,1.486)	0.836	(0.44,1.526)
Rarity-mild	0.854	(0.854,1.537)	0.918	(1.040,3.433)	0.751	(0.401,3.682)	0.835	(0.415,1.636)	0.809	(0.391,1.634)
Female			0.93	(0.703,1.23)					0.856	(0.619,1.179)
Age			1.001	(0.987,1.014)					0.994	(0.978,1.01)
Rural Hukou			1.275	(0.924,1.761)					1.122	(0.68,1.86)
Underdeveloped area			1.15	(0.87,1.519)					1.032	(0.744,1.428)
Primary and secondary school (9-year schooling)			1.277	(0.629,2.509)					1.515	(0.622,3.512)
High school (12-year schooling)			1.624	(0.781,3.282)					1.925	(0.764,4.647)
College and above (15-year schooling and above)			1.446	(0.706,2.869)					2.226	(0.855,5.571)
Some difficult to access RD information					**2.214*** **	**(1.732,4.133)**			**2.392*** **	**(1.635,3.513)**
Very difficult to access RD information					**3.496*** **	**(2.647,4.923)**			**3.732*** **	**(2.444,5.755)**
No complication					**0.854***	**(0.728,0.996)**			**0.828***	**(0.691,0.991)**
Close to average economic level							0.785	(0.635,1.254)	0.822	(0.526,1.273)
Above average economic level							0.699	(0.285,1.307)	0.824	(0.516,1.31)
Family size							1.005	(0.796,1.148)	1.056	(0.862,1.289)
Urban employee insurance							1.680	(0.853,3.376)	**2.085***	**(1.017,4.22)**
Urban resident insurance							**2.429***	**(1.159,4.94)**	**3.097***	**(1.361,7.044)**
New scheme rural insurance							**2.138***	**(1.064,4.05)**	**2.987***	**(1.274,6.945)**

Reference groups are Rarity-extremely rare, male, urban hukou, developed area, no education, a little difficult to access RD information, yes complication, below average local economic level, free medical insurance

Model 1 = level of rarity model; Model 2 = demographic model, Model 3 = Healthcare management model; Model 4 = social support model; and Model 5 = Full model.

a. 95%C.I = 95% confidence interval, OR = odds ratio

b. *p<0.05; ** p<0.01; ***p<0.001

Table 4 Results of logistic regression models for non-adult participants (minors)

	Model 1a			Model 2			Model 3			Model 4			Model 5	
	OR	95% C.I[b]		OR	95% C.I		OR	95%C.I		OR	95%C.I		OR	95%C.I
Rarity-moderate	0.798	(0.396,1.552)		1.535	(0.607,1.504)		1.119	(0.619,1.587)		0.801	(0.592,1.123)		2.479	(0.646,2.566)
Rarity-mild	0.932	(0.447,1.883)		1.59	(0.24,2.32)		1.298	(0.631,5.378)		0.913	(0.819,3.348)		2.63	(0.165,6.815)
Female				0.88	(0.601,1.291)								0.886	(0.485,1.573)
Age				**1.113*** **	**(1.059,1.171)**								**1.09** **	**(1.03,1.150)**
Rural Hukou				1.193	(0.765,1.858)								1.076	(0.304,1.304)
Underdeveloped area				1.074	(0.734,1.576)								0.972	(0.545,1.793)
Father - Primary and secondary school (9-year schooling)				0.796	(0.355,1.737)								0.878	(0.219,2.363)
Father - High school (12-year schooling)				0.834	(0.372,1.82)								0.777	(0.138,1.508)
Father - College and above (15-year schooling and above)				0.797	(0.332,1.85)								0.817	(0.1,1.483)
Some difficult to access RD information							**2.549*** **	**(1.746,3.709)**					**2.571*** **	**(1.535,4.516)**
Very difficult to access RD information							**5.324*** **	**(3.579,7.739)**					**5.174*** **	**(3.041,8.992)**
No complication							**0.730*** **	**(0.625,0.853)**					**0.735** **	**(0.593,0.92)**
Close to average economic level										0.885	(0.689,1.267)		1.109	(0.512,2.043)
Above average economic level										0.888	(0.589,2.754)		1.155	(0.87,40.165)
Family size										1.028	(0.893,1.146)		0.991	(0.946,1.758)

Reference groups are Rarity-extremely rare, male, urban Hukou, developed area, father-no education, a little difficult to access RD information, yes complication, below average local economic level

a. Model 1 = level of rarity model; Model 2 = demographic model, Model 3 = Healthcare management model; Model 4 = social support model; and Model 5 = Full model.

b. 95% C.I = 95% confidence interval, OR = odds ratio

c. *p<0.05; ** p<0.01; ***p<0.001

Figures

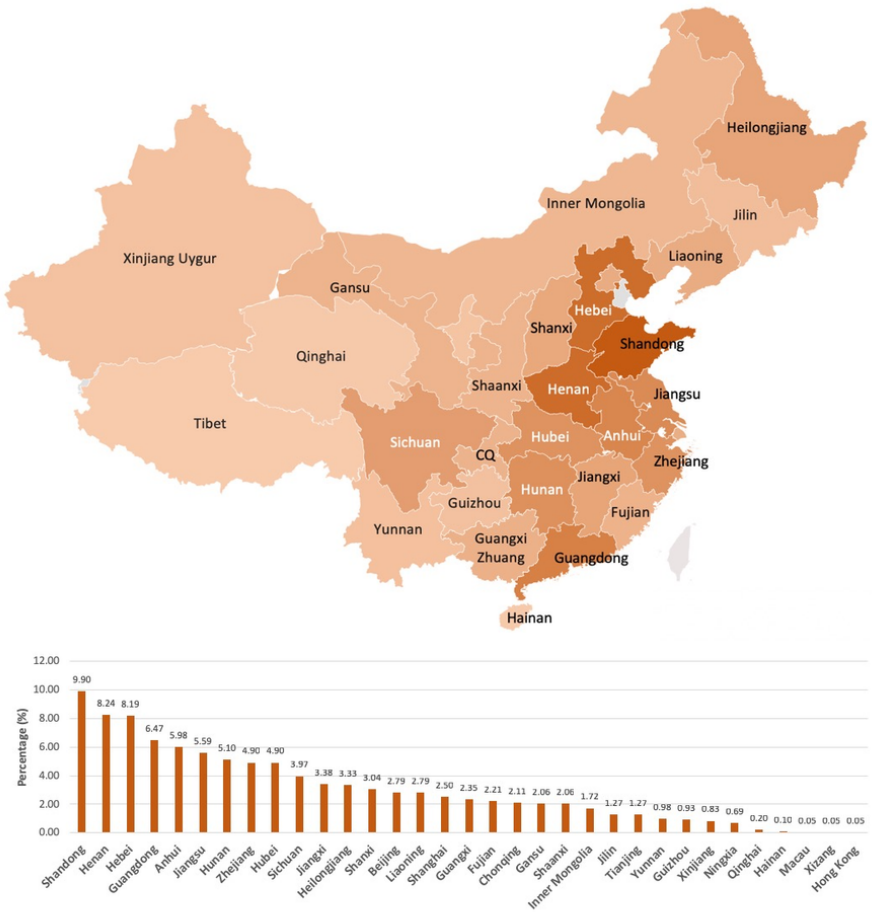

Figure 1

the distribution of participants reported of having rare disease in China • CQ = Chonqing • The dark red means the higher proportion and light red means lower proportion Note: The designations employed and the presentation of the material on this map do not imply the expression of any opinion whatsoever on the part of Research Square concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. This map has been provided by the authors.

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