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Economic burden and influencing factor analysis of outpatients with epilepsy: A cross-sectional study in Shanghai, Shanxi and Sichuan

Bing-Yu Wang¹, Yang-Mu Huang¹, Shi-Chuo Li², Yan Guo¹✉

¹School of Public Health, Peking University, Beijing 100191, PR China

²China Association Against Epilepsy, Beijing, PR China

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ABSTRACT

Objective: To better understand the economic burden of patients with epilepsy receiving outpatient services in China and to analyze potential factors influencing epileptic economic burden through a cross-sectional study. **Methods:** Using a self-designed questionnaire, we collected information retrospectively from 754 patients with epilepsy evaluated in neurology clinics in Shanghai Municipality, Shanxi Province and Sichuan Province. Descriptive analyses were used after cost variables were presented as logarithms, and multiple linear regressions were performed to explore influencing factors. **Results:** Fifty percent of the investigated patients experienced an epilepsy attack before the age of 15, and 51.3% had suffered from epilepsy for more than five years. In the past year, 87.9% of patients had visited different hospitals multiple times for evaluation (40.3%) and maintenance treatment (40.7%). The total economic burden of epilepsy was US\$ 1 143.2. The average direct economic burden and indirect economic burden were US\$ 939.0 and US\$ 110.2, respectively. Multiple linear regressions showed that patients had to bear greater economic burden if they were hospitalized, using multiple antiepileptic drugs, experiencing illness for less than 5 years, in severe seizure index or active epilepsy with drug resistance, which was statistically significant. Totally only 14.3% of patients could get reimbursement in outpatient services. **Conclusions:** Patients with epilepsy must present to hospitals regularly for satisfactory prognosis, which results in economic burden. Patients bear greater economic burden, especially direct medical costs, if they are newly diagnosed, experience severe seizures, or undergo multiple drug treatments that require more frequent monitoring. However, current insurance policy for outpatient services do not help reduce economic burden of patients efficiently.

1. Introduction

Epilepsy is a central nervous system disorder in which nerve cell activity in the brain becomes disrupted, causing seizures or periods of unusual behavior or sensations and sometimes loss of consciousness[1]. Epilepsy is one of the most common chronic neurological disorders in the world with the characteristics of

repeatability and paroxysm. The global prevalence of active epilepsy has increased from 42 million at the beginning of the 21st century to 70 million in the following decades[2].

Previous studies have shown that prevalence rates differ in areas with different economic development levels. The estimated proportion of the general population with active epilepsy is between

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First author: Bing-Yu Wang, School of Public Health, Peking University, Beijing 100191, PR China.

E-mail: bingzhao-3@163.com

✉Corresponding author: Yan Guo, School of Public Health, Peking University, Beijing 100191, PR China,

E-mail: guoyan@bjmu.edu.cn

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4 and 10 per 1000 people. The prevalence rate of epilepsy is 3.6‰ to 7.8‰ in developed countries, while it is as much as 14.0‰ to 57.0‰ in some low- and middle-income countries[3-6].

Once confirmed, epilepsy patients who receive appropriate treatment as early as possible may reduce the risk of recurrence by 30% to 60%[7]. Studies have suggested that with the help of stable antiepileptic drug (AED) therapy, seizures can be eliminated within 5 years in 50% to 70% of patients[8]. Consequently, as in other chronic diseases, patients with epilepsy must maintain regular doctor visits and long-term treatment.

Epilepsy is an economic burden on individuals and society due to the increased healthcare costs, and it causes as well as losses in employment, wages, and daily living activities. Several studies have evaluated the economic burden of epilepsy on a nationwide scale in different countries from diverse angles[9-14]. It has also been found that some patients whose conditions were more severe or complex would bear higher costs than patients whose conditions were milder[15-17].

It has been reported that approximately 10 million people in China suffer from epilepsy, 6 million patients have been diagnosed with active epilepsy, and 400 000 new cases are documented each year[18]. Expenditure on epilepsy patients is very high in China according to the investigations conducted by Hong and Mak[19-20]. Few such studies of epileptic economic burden in China have been implemented on a national level because of the limitations of national surveys, the problem of separating the cost of epilepsy from that of coexisting conditions, and the variability of the illness[21].

A better understanding of epileptic economic burden will assist decision makers in identifying focus groups in order to better allocate the limited healthcare resources in China[18]. Therefore, we conducted this study to evaluate a cross-sectional sample of patients attending the out-patient clinics of general hospitals in China and incorporate measurable indicators of economic burden to the greatest extent to determine the economic burden of Chinese patients with epilepsy, its influencing factors, and their practical need.

2. Materials and methods

2.1. Participants

According to the economic development level, we chose Shanghai Municipality, Shanxi Province and Sichuan Province of China as the investigation areas to represent high-, middle- and low-income areas. One general hospital in each area was selected respectively from a capital city and a prefecture-level city. The neurology clinics of those six hospitals were chosen as the investigation sites. Each site was investigated separately for 5 d between July and September 2014. Diagnosed patients with epilepsy or their relatives visiting the neurology clinics were enrolled in the study. Neurological physicians assisted in the estimation of the illness statuses of all the patients according to the diagnostic criteria of epilepsy.

2.2. Interview

A self-designed questionnaire was used to investigate patients with epilepsy. Detailed information was collected, including basic information of patients, development of their disease, and all possible indicators to evaluate the patients' economic burden. These indicators included health resource usage during the past year, including examination measures and antiepileptic treatment (AEDs or other kinds of treatment), numbers of medical institutions visited (in-patient and out-patient services as well as other private practices such as self-medication), and all related unit prices for the aforementioned variables. Additionally, the questionnaire collected information on the costs of transportation, accommodation, and meals for doctor visits as well as day-loss due to absenteeism and early retirement of patients and caregivers.

During the interview, the investigators attempted to help the informants recall information for the retrospective questions. Patients' medical records and the electronic medical records of the hospitals should be used to ensure the accuracy of information regarding examination and therapeutic fees.

2.3. Analyses

Each participant was assigned to one of the categories based on mild, moderate, or severe seizure severity in accordance with the following indices: ≤ 3 points as mild; 4-8 points as moderate; and ≥ 9 points as severe. Assignment of points depended on the number of seizures experienced during the last 3 months (0-3=1, 3-9=2, or 9=3 points), type of seizures (simple partial=1, complex partial=2, generalized=3, or status epilepticus=4), and interference of adverse effects of the current medication (interferes with physical activity=1, leisure and free time activities=2, or activities of daily living=3) [22]. Economic burden of patients with epilepsy were calculated in formulae based on variables collected.

Most expenditure and income variables were abnormally distributed and required presentation as logarithms. We calculated the means of logarithms and presented them with tenth in order to show the average level of economic burden components. Additionally, logarithms of economic burden components were selected as the dependent variable. Other socio-demographic and epileptic variables were treated as independent variables in the multiple linear regressions. Statistical analyses were performed on SPSS 19.0. The statistical significance level was a *P*-value less than 0.05 for all analyses. All costs were expressed in US dollars [exchange rate 1 USD = 6.134 5 Chinese Yuan (CNY), December 2014].

3. Results

3.1. Characteristics of epilepsy patients

Seven hundred fifty-four valid questionnaires were obtained in this survey. In total, the percentages of male and female patients

were 59.4% and 40.6%, respectively. Patients under the age of 24 accounted for 54.3%, and the median age was 24.0 years. Of those patients, 45.5% were urban citizens, and 27.6% were outsiders from other areas. Most of the patients were students and preschool children, which accounted for 36.6%. The percentage of unemployed patients was 22.4%. Patients under the age of 15 accounted for 50.0%.

Among the patients interviewed, 50.0% began experiencing epileptic seizures before the age of 15 years. Additionally, 51.3% had suffered from epilepsy for more than five years. Mild, moderate, and severe patients with epilepsy accounted for 30.4%, 68.0%, and 1.6% respectively. Patient characteristics in the three regions can be seen respectively in Table 1.

Table 1

Characteristics of patients [n(%)].

Characteristic	Shanghai	Shanxi	Sichuan	Total
Gender				
Male	160(62.5)	131(56.7)	157(58.8)	448(59.4)
Female	96(37.5)	100(43.3)	110(41.2)	306(40.6)
Age				
0–4	9(3.5)	7(3.0)	4(1.5)	20(2.7)
5–14	29(11.3)	40(17.3)	51(19.1)	120(15.9)
15–24	101(39.5)	72(31.2)	96(36.0)	269(35.7)
25–44	72(28.1)	63(27.3)	79(29.6)	214(28.4)
45–59	31(12.1)	34(14.7)	24(9.0)	89(11.8)
60–	14(5.5)	15(6.5)	13(4.9)	42(5.6)
Hukou type				
Urban	110(43.0)	103(44.6)	130(48.7)	343(45.5)
Rural	14(657.0)	128(55.4)	137(51.3)	411(54.5)
Source of patients				
Native	76(29.7)	223(96.5)	247(92.5)	546(72.4)
Outsiders	180(70.3)	8(3.5)	20(7.5)	208(27.6)
Occupation				
Students/preschool	96(37.5)	82(35.5)	98(36.7)	276(36.6)
Staff in institutions	72(28.1)	61(26.4)	77(28.8)	210(27.9)
Farmers	17(6.6)	23(10.0)	17(6.4)	57(7.6)
Others	12(4.7)	1(0.4)	5(1.9)	18(2.4)
Unemployed	47(18.4)	58(25.1)	64(24.0)	169(22.4)
Retirement	12(4.7)	6(2.6)	6(2.2)	24(3.2)
Age of onset				
0–4	40(15.6)	29(12.6)	44(16.5)	113(15.0)
5–14	93(36.3)	82(35.5)	89(33.3)	264(35.0)
15–24	65(25.4)	50(21.6)	78(29.2)	193(25.6)
25–44	31(12.1)	42(18.2)	39(14.6)	112(14.9)
45–59	19(7.4)	19(8.2)	12(4.5)	50(6.6)
60–	8(3.1)	9(3.9)	5(1.9)	22(2.9)
Course of disease				
0–5	117(45.7)	128(55.4)	122(45.7)	367(48.7)
6–10	47(18.4)	39(16.9)	64(24.0)	150(19.9)
11–15	37(14.5)	20(8.7)	29(10.9)	86(11.4)
16–19	20(7.8)	13(5.6)	26(9.7)	59(7.8)
20–	35(13.7)	31(13.4)	26(9.7)	92(12.2)
Seizure severity index				
Mild	100(39.1)	77(33.3)	52(19.5)	229(30.4)
Moderate	149(58.2)	149(64.5)	215(80.5)	513(68.0)
Severe	7(2.7)	5(2.2)	0(0.0)	12(1.6)
Total	256(34.0)	231(30.6)	267(35.4)	754(100.0)

3.2. Health service utilization

In the past year, 83.4% of patients received only outpatient epileptic health service, and 16.6% received inpatient healthcare. A total of 87.9% of patients had visited different hospitals, including the surveying hospital, several times for evaluation (40.3%) and treatment maintenance (40.7%). Detailed analysis of the three regions is shown in Table 2.

Table 2

Hospital visits and purpose of patients [n(%)].

Visits and purpose	Shanghai	Shanxi	Sichuan	Total
Frequency of visits ^a				
Once	34(13.3)	31(13.4)	26(9.7)	91(12.1)
2–5 times	108(42.2)	146(63.2)	174(65.2)	428(56.8)
6–10 times	51(19.9)	39(16.9)	47(17.6)	137(18.2)
11–15 times	40(15.6)	11(4.8)	13(4.9)	64(8.5)
15 times or above	23(9.0)	4(1.7)	7(2.6)	34(4.5)
Number of visits to the investigated hospital				
Once	96(37.5)	68(29.4)	65(24.3)	229(30.4)
2–5 times	101(39.5)	119(51.5)	154(57.7)	374(49.6)
6–10 times	21(8.2)	34(14.7)	33(12.4)	88(11.7)
11–15 times	29(11.3)	7(3.0)	13(4.9)	49(6.5)
15 times or above	9(3.5)	3(1.3)	2(0.7)	14(1.9)
Purpose of doctor visit				
Primary visit	21(8.2)	37(16.0)	21(7.9)	79(10.5)
Review	135(52.7)	110(47.6)	59(22.1)	304(40.3)
Maintain therapy	87(34.0)	59(25.5)	161(60.3)	307(40.7)
Other Purpose	13(5.1)	25(10.8)	26(9.7)	64(8.5)
Total	256(34.0)	231(30.6)	267(35.4)	754(100.0)

^aFrequency of visits to different health services during the past year.

With regard to therapeutic approaches, 717 cases of all the epilepsy patients interviewed were receiving AED therapy, accounting for 95.1% of patients. A total of 47.0% of the 717 cases were taking a single antiepileptic drug, and others were taking more than one kind of drug. A total of 63.0% of the patients were in the drug therapy maintenance period. 35.1% of patients were categorized as having active epilepsy without drug resistance, and 14.2% were categorized as having active epilepsy with drug resistance.

3.3. Economic burden of different patients with epilepsy

Over the past year, the average total economic burden of epilepsy was US\$ 1143.2. The average direct economic burden and indirect economic burden were US\$ 939.0 and US\$ 110.2, respectively. The direct economic burden is mainly composed of direct medical costs, with an average of US\$ 628.4, and treatment and AEDs were the most important components of the direct medical costs.

The main measurable factors influencing economic burden were put into multiple linear regressions. Few differences were found among patients' economic burden in the different investigation sites, except that patients in Shanxi Province would bear the least indirect medical cost (US\$ 49.7, $P < 0.05$). Patients interviewed in capital city

hospitals bear more in total economic burden and direct economic burden as well as its two components than those in prefecture-level hospitals ($P<0.05$). The annual indirect medical cost of the former was US\$ 106.6, while the latter was only US\$ 17.8. Compared with native patients, outsiders had to pay more in indirect medical costs (US\$ 249.2, $P<0.001$), and had a significantly greater total economic burden (US\$ 1 466.4, $P<0.001$) and direct economic burden (US\$ 1 204.3, $P<0.001$).

Economic burden was not similar among patients using different health services. During the past year, the patients who were hospitalized and their caregivers carried a significantly greater total economic burden (US\$ 3 248.2, $P<0.001$), direct economic burden (US\$ 2 799.1, $P<0.001$) and indirect economic burden (US\$ 191.8, $P<0.001$). Moreover, with the increasing number of the AEDs and the combined use of new AEDs and traditional AEDs, total economic burden, direct economic burden, and direct medical costs showed a significantly growing trend ($P<0.001$).

There were also some differences among patients with different disease statuses. For instance, total economic burden and its components were significantly higher in patients with disease courses less than 5 years than those with a longer medical history ($P<0.05$). Patients classified in the severe seizure index seemed to suffer the heaviest burden. The average total economic burden, direct economic burden, direct medical costs, and indirect economic burden were, in order, US\$ 2 981.9, US\$ 2 559.4, US\$ 1 937.6 and US\$ 549.8 which were several times higher than those of milder cases. However, no statistical significance was found in our study, except for indirect economic burden ($P<0.05$). A similar situation occurred among active epilepsy patients with drug resistance. Their total economic burden (US\$ 1 752.9, $P<0.001$) and direct economic burden (US\$ 1 284.0, $P<0.05$) were higher than those who were in remission. With the increasing number of the AEDs and the combined use of new AEDs and traditional AEDs, total economic burden, direct economic burden and direct medical cost showed a growing trend ($P<0.001$).

3.4. Medical reimbursement of patients in different areas

In such a burden condition, health insurance policy should be taken into consideration. For most patients with epilepsy payments for outpatient services had not yet been included into the reimbursement list. A total of 14.3% of patients could get reimbursement totally. What is more, only 3.7% and 10.0% of patients in Sichuan and Shanxi provinces could get reimbursement. When trans-regional doctor visits happened, outsiders had less or none insurance payments than natives in Shanghai (Table 3).

Table 3

Annual outpatient service reimbursement of patients in different areas.

Area	Total		Native		Outsiders	
	Patient number	Reimbursable number (%)	Patient number	Reimbursable number (%)	Patient number	Reimbursable number (%)
Sichuan	267	10(3.7)	247	10(4.0)	20	0(0.0)
Shanxi	231	23(10.0)	223	22(9.9)	8	1(12.5)
Shanghai	256	75(29.3)	76	49(64.5)	180	26(14.4)
Total	754	108(14.3)	546	81(14.8)	208	27(13.0)

4. Discussion

This cross-sectional study chose outpatients from epileptic clinics in 3 regions to evaluate their economic burden on epilepsy using a self-designed questionnaire. It was found that children were the main group of patients receiving outpatient services, and most epilepsy patients had to visit the hospital regularly for treatment. Epilepsy has economically influenced patients, as the average yearly cost for epilepsy is US\$ 1 143.2. Patients who were hospitalized, those using multiple AEDs, those experiencing illness for less than 5 years, those in the severe seizure index, and those in active epilepsy with drug resistance had to bear greater economic burden for epilepsy.

Epilepsy is a type of chronic neurological disease that has a life-long impact on patients. Two peak incidences of epilepsy occur in children and the elderly[23]. In this study, the median age of patients is young, and most of patients experienced epilepsy during the infantile and childhood periods. Additionally, nearly 40.0% of patients were preschool children and students. Not only does epilepsy confuse those sick children, but it also negatively influences their growth and development, resulting in long-term stress for patients and their families[24-26].

In our study, 51.3% of the patients had suffered from epilepsy for more than 5 years, but continue with regular doctor visits, which suggests that their illness has lasted for several years since epilepsy attacks began. Also, most of the patients had to visit different hospitals several times for the purpose of reviewing and regular maintenance. Like other chronic diseases, epilepsy is characterized by its long-term disease course and treatment period. The long-term outcomes of patients with epilepsy are related to the onset age, seizure type, and other factors[28-29]. Patients will benefit from timely diagnosis and treatments.

Based on the disease characteristics of epilepsy as well as the phenomena of multiple hospital visits, the epilepsy-specific economic burden, direct economic burden and indirect economic burden in our study amounted to US\$ 1 143.2, 939.0 and 110.2, respectively. A few similar studies have demonstrated epileptic economic burden and its components in China. A cross-sectional study ($n=141$) in Hubei Province showed that the median total cost,

direct cost, and indirect cost due to epilepsy were US\$ 949.29, 501.34, and 276.72, respectively[30]. Hong reported that the overall annual cost, direct cost, and indirect cost for epilepsy per patient was approximately US \$773 598, and 223, respectively, in Sichuan Province ($n=289$)[19].

Several cross-sectional studies have indicated epilepsy-specific cost or its components in other countries. In 2011, Pato had estimated that the total cost associated with epilepsy in Spain was a mean of € 5 168 for each patient (equal to US\$ 26 775 in 2011 dollars)[14]. The total annual cost per patient amounted to US\$ 344 in India in 2001[31]. A German study showed that total direct costs amounted to € 1 619 per participant during a 3-month evaluation period (equal to US\$ 8 388 per year in 2011 dollars), and direct costs are mainly due to hospitalization (47.8%), AEDs (13.2%), and ancillary treatment (9.1%)[32]. Even though the comparability of the current results with results from other countries is somewhat restricted by the differences in healthcare systems, economic status, methodological factors and the like, studies all maintain that epileptic economic burden or related cost undoubtedly cause economic pressure for patients and their families.

According to the linear regression analyses, patients should be identified so that more importance can be attached. Different health service utility makes patients' economic burden different. Visiting better developed medical institutions and trans-regional doctor visits cause greater economic burden. Additionally, hospitalization dramatically increases economic burden, even though outpatients in the present study had a relatively low hospitalization rate in the past year. Patients whose seizures are not well-controlled are likely to be hospitalized for more intensive observation or surgery, which may cause temporarily high expenditure[33-34]. Thus, those patients had to bear a greater economic burden for epilepsy than those who only used outpatient services.

AED therapy is one of the main methods for seizure control. Once diagnosed and drug therapy has started, epilepsy patients should keep taking AEDs in good adherence after the therapy plan is set. When drug combination is necessary, drug costs in this study will be higher due to the increasing number of AEDs especially new AEDs. Haroon had approved that direct cost increased dramatically with the increasing number of AEDs[35]. New AEDs have many advantages both in pharmacokinetics and curative effects, although the price of new AEDs is generally higher than that of traditional AEDs[36]. The drug combination rate is high in this study, which might be caused by the differences in patient structure based on a convenient sampling in hospitals.

Compared with patients whose disease courses were more than 5 years, the direct medical cost of patients who have experienced epilepsy for less than 5 years was higher. After the primary one or several seizures, patients and their families are inclined to

go to various medical institutions for diagnosis and treatments. Meanwhile, conditions of new patients are not stable in the short-term, and seizure control is usually unsatisfactory. All of these reasons lead new patients to bear a greater medical expenditure and energy. Approximately 50.0% to 60.0% of children with epilepsy eventually have complete seizure remission. With longer follow-up, the remission rate improves[37]. To obtain a satisfactory prognosis, patients are encouraged to get treatment as soon as possible even if it presently costs more.

In this study, patients with a severe seizure index seemed to suffer the heaviest economic burden, but this number was not significant. The limited sample size of patients with a severe seizure index could be the most reasonable explanation. Research carried out by Cramer has attested that medical costs would increase if the seizures of epilepsy patients are not well-controlled[38]. Tetto also maintained that the direct costs of epilepsy vary significantly depending on the severity of the disease and the response to treatment[39]. Guekht also found that costs predominated in patients with uncontrolled seizures requiring treatment changes and more frequent use of newer antiepileptic drugs[40]. Seizure severity is an index integrating seizure frequency, seizure type, and side effects of treatment[22]. Patients with more serious and complex seizures had to accept more frequent doctor visits, treatment, and drug adjustment or dose increasing, which all increase their economic burden.

Our study showed that epilepsy-specific economic burden and direct economic burden were considerably higher for drug-resistant active epilepsy than for controlled or treatment-responsive epilepsy. An investigation carried out by de Zélicourt in France also indicated that the mean annual direct costs were 2.3 times higher in drug-resistant patients than in drug-responsive patients. The costs of drugs, additional tests, and hospital admissions were, respectively, two, four, and thirteen times higher in the former compared with the latter category[41]. The International League Against Epilepsy defines drug-resistant epilepsy as 'failure of adequate trials of two tolerated, appropriately chosen and used antiepileptic drug schedules (whether as mono-therapies or in combination) to achieve sustained seizure freedom'[42]. As a consequence of poor control over their epileptic seizures, they present an increased risk of early death, trauma and psychosocial alterations, while their quality of life is diminished[43]. In China, patients with poor response to therapy are very likely to visit more advanced hospitals in metropolises, such as Shanghai and Beijing. More detailed evaluation and treatments as well as possible expenditure on surgery or hospitalization all lead to their higher economic burden[44].

Though epilepsy caused economic burden for patients with epilepsy and those in severe seizures and complex treatments have to bear more, most patients with epilepsy could not get reimbursement in outpatient service under the current health insurance policy of China.

Epilepsy is a chronic condition that is best treated in the outpatient clinic setting[45]. While in most areas of China, patients with epilepsy are insured only when inpatient services happen which need proper adjustments.

In conclusion, patients with epilepsy in China are young and suffer from long-term illness in outpatient service. These patients require regular hospital visits for a satisfactory prognosis, which cause economic burden and other negative influences[46]. Patients who are newly diagnosed, those experiencing severe seizures, or those receiving multiple drug treatments bear a greater economic burden, especially for direct medical costs. For a better prognosis and less economic burden, epilepsy patients require more attention and support by an effectively running health system.

Based on a convenience sampling method and an investigation in hospitals, representativeness in this study is not satisfactory. However, the characteristics of epilepsy are reflected by the study to some extent. Further, recall bias is unavoidable when patients and their families are answering the same questions about illness and expenditures. Considering these main two limitations, we attempted to collect information from hospital information systems so that indicators would be reliable and accurate.

Conflict of interest statement

We declare that there is no conflict of interest.

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