Direct economic burden of patients with autoimmune encephalitis in western China

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Abstract

Objective
To analyze the cost of autoimmune encephalitis (AE) in China for the first time.

Methods
Patients who were newly diagnosed with antibody-positive AE (anti-NMDA receptor [NMDAR], anti-γ aminobutyric acid type B receptor [GABA_B], antileucine-rich glioma-inactivated 1 [LGI1], and anticontactin-associated protein-2 [CASPR2]) at West China Medical Center between June 2012 and December 2018 were enrolled, and a cost-of-illness study was performed retrospectively. Data on clinical characteristics, costs, and utilization of sources were collected from questionnaires and the hospital information system.

Results
Of the 208 patients reviewed, the mean direct cost per patient was renminbi (RMB) 94,129 (United States dollars [USD] 14,219), with an average direct medical cost of RMB 88,373 (USD 13,349). The average inpatient cost per patients with AE was RMB 86,810 (USD 13,113). The direct nonmedical cost was much lower than the direct medical cost, averaging RMB 5,756 (USD 869). The direct cost of anti-LGI1/CASPR2 encephalitis was significantly lower than that of anti-NMDAR encephalitis and anti-GABA_B encephalitis. The length of stay in the hospital was significantly associated with the direct cost.

Conclusions
The financial burden of AE is heavy for Chinese patients, and there are significant differences between different types of AE.
Autoimmune encephalitis (AE) is an immune-mediated neurologic disorder associated with autoantibodies against intracellular neuronal antigens (e.g., Hu and Ma2) and autoantibodies to the neuronal surface or synaptic antigens (e.g., anti-NMDA receptor [NMDAR], antileucine-rich glioma-inactivated 1 [LGI1], anti-γ-aminobutyric acid type B receptor [GABA_{B_{R}}], and anticontactin-associated protein-2 [CASPR2]). An epidemiologic study in the United States indicated that the incidence rate of AE from 1995 to 2015 was 0.8 of 100,000. A study in China showed that the relative frequencies of NMDAR, LGI1, GABA_{B_{R}}, and CASPR2 antibodies in patients with AE were 79.7%, 12.8%, 5.6%, and 1.3%, respectively.

Previous studies, including ours, showed that 16.7%–38.0% of patients with anti-NMDAR encephalitis had underlying neoplasms, such as ovarian teratomas, and 32.0%–50.0% of patients with anti-GABA_{B_{R}} encephalitis had coexisting small cell lung cancer and other types of tumors. Most patients with AE respond to immunotherapy; however, some require long-term hospitalization and intensive care resources. The medical severity and long-term disabilities associated with patients with AE that would inevitably burden society and families have also been reported. Therefore, it is important to assess the economic burden of AE for the rational allocation of medical resources. However, few studies on such an issue have been conducted. One study in the United States reported the hospitalization cost of definite AE and probable AE. However, this finding does not represent the status of China. To provide baseline data for evaluating the economic impact of AE in western China, we studied the direct medical and direct nonmedical cost of the main types of AE (anti-NMDAR, anti-LGI1/CASPR2, and anti-GABA_{B_{R}} encephalitis) among Chinese patients for the first time. Notably, the costs assessed did not include indirect costs because of failure to work, sick leave for family members, and so on. The cost presented did not exclude medical insurance reimbursement. Medical insurance coverage is high in China (96.3% in 2018). However, only some patients use medical insurance mainly because of the complicated refund procedure (some patients do not know how to obtain a refund). Medical insurance in China can reimburse only a part of the hospitalization costs (from 30.0% to 70.0%, depending on different medical insurance systems) and not outpatient and nonmedical costs, which would impose a heavy burden on patients.

### Methods

#### Subjects and interviews

Patients with a discharge diagnosis of AE between June 2012 and December 2018 (financial year 2012–2018) at the inpatient department of neurology, West China Medical Center, were identified from the hospital information system by searching the following terms: “autoimmune,” “autoimmunity,” “autoimmune encephalitis,” “antibodies,” “NMDAR,” “GABA_{B_{R}},” “CASPR2,” or “LGI1.” We included patients who satisfied the criteria for definite (antibody-positive) AE according to definitions of AE from a recent consensus statement. These patients met the following diagnostic criteria for AE: (1) rapid onset (<3 months) of 1 or more of the following symptoms—abnormal (psychiatric) behavior or cognitive dysfunction, speech dysfunction, seizures, movement disorder, decreased level of consciousness, and autonomic dysfunction or central hypoventilation and (2) positive results for one of the antibodies (anti-NMDAR, GABA_{B_{R}}, and LGI1/CASPR2 antibodies) in the CSF. The exclusion criteria were as follows: (1) patients with laboratory evidence of infectious encephalitis, for example, viral (TORCH immunoglobulin M), bacterial (CSF smear and culture), mycobacterium tuberculosis (acid-fast stain), parasitic (antibody detection), or fungal and cryptococcus (CSF smear, culture and ink stain); (2) patients diagnosed with toxic-metabolic encephalopathy, brain tumor or metastasis, vitamin deficiency or alcohol-related encephalopathy, epilepsy, and/or another nervous system disease before the onset of AE; (3) patients with positive antibodies for other AEs, such as a-amino-3-hydroxy-5-methyl-4-isoxazol-propionic acid receptors, dipeptidylpeptidase-like protein, or IgLON5, or with neurologic paraneoplastic antibodies (anti-Hu, anti-Ri, anti-Yo, anti-CV2, anti-Ma, anti-amphiphysin, anti-Tr, Purkinje cell cytoplasmic antibody type 2, and anti-glutamic acid decarboxylase); (4) patients with encephalitis of unknown cause; (5) patients diagnosed with AE who received treatment previously in another hospital; and (6) patients who did not agree to participate in the survey.

Resource utilization of the direct medical costs included the number of diagnostic and therapeutic services, length of stay (LOS) in the hospital, and duration of immunotherapy (IV methylprednisolone [IVMP], IV immunoglobulin [IVIG], rituximab, and cyclophosphamide). To determine contributors to a prolonged LOS, 2 neurologists (Z.H. and D.Z.) independently reviewed the charts of all prolonged (≥20.0 days) hospitalizations, with any discrepancies resolved by further review and discussion. The following categories were defined: (1) delay in diagnosis of ≥7.0 days from admission, defined as lack of a secure diagnosis resulting in a delay in the initiation of immune treatment for AE; (2) duration of inpatient immunotherapy ≥7.0 days; (3) lack of a response, defined as neurologic deterioration or a lack of neurologic...
improvement after the completion of immunotherapy and resulting in ≥7-day additional stay in the hospital; (4) complications (i.e., pneumonia, sepsis, and gastrointestinal bleeding) resulting in ≥7-day stay in hospital; (5) modified Rankin Scale (mRS) on admission; and (6) tumor condition.

Resource utilization of direct medical costs, direct medical costs, and clinical characteristics were extracted from the hospital information system. Direct nonmedical costs and resource utilization of direct nonmedical costs were assessed by a questionnaire designed for this study. The questionnaire included 2 parts. Part A requested basic information about the patient, such as sociodemographic details and distance to our clinic. Part B assessed the means of transportation to the clinic and AE-related clinic travel expenses, costs of professional care, and diet during hospitalization. “Professional care” indicated private nurse care out of the hospital. Most of the patients in this study had visited our center outside of their hometown. The travel expenses included transportation and accommodation.

**Standard protocol approvals, registrations, and patient consents**

Written informed consent was obtained from the individuals or their caregivers before enrollment in the study. This study was approved by the Research Ethics Committee of West China Medical Center of Sichuan University.

**Estimation of costs**

In our study, the total expenditures for each patient were calculated as the sum of the direct medical costs and direct nonmedical costs due to AE-related clinic visits (whether inpatient or outpatient visits) in our center. There are 3 kinds of medical security systems, namely, urban basic medical insurance, basic medical insurance for urban residents, and new rural cooperative medical care. Because reimbursement by the different systems is highly variable in China, as stated in the Introduction section, costs as listed by the hospital before reimbursement were counted.

Direct medical costs included all inpatient and outpatient costs. Inpatient costs were grouped as treatment (immunotherapies [IVMP, IVIG, rituximab, and cyclophosphamide], antiepileptic drugs, antipsychotic drugs, anti-infective drugs, other treatment, etc.) cost, tests (MRI of the brain, EEG, antibody examination, lumbar puncture, biomedical assays, etc.), and other costs (room cost, nursing-related cost, etc.). The cost of tumor treatment was not included in these calculations. Direct nonmedical costs involved professional care, diet during hospitalization and travel expenses to the clinic, which were accessed by face-to-face questionnaire investigations.

Notably, only AE-related resource use was recorded. The initial valuation of cost items was in the Chinese currency renminbi (RMB), and the exchange rate was converted into United States dollars (USD) for reference, with an average exchange rate equaling USD 1 = RMB 6.62 for 2018. The demographic and clinical characteristics, LOS, and inpatient costs of our cohort were compared to those of the United States cohort.12

**Statistical analysis**

SPSS 20.0 (SPSS Inc., Chicago, IL), as well as GraphPad Prism 8.0 (GraphPad Software Inc., San Diego, CA), was used for the statistical analyses. The χ² test was used for categorical variables. The Kruskal-Wallis test was used for continuous variables. Linear regression analysis was conducted to compare direct inpatient cost and time after applying logarithmic transformation. For univariate regression analyses, 6 variables were preselected by 2 experienced neurologists (Z.H. and D.Z.) to examine their associations with direct costs (age, sex, tumor condition, mRS, LOS, and AE-related neurologic care visit), and 11 variables were preselected to examine associations with LOS (age, sex, antibody type, MRI abnormality, EEG abnormality, tumor condition, mRS at admission, complications, delay in diagnosis, lack of a response, and prolonged immune treatment). The ordinary least squares method was used.

**Data availability**

The authors confirm that the data supporting the findings of this study are available within the article and from the corresponding author upon reasonable request.

**Results**

**Demographic and clinical characteristics of patients**

A total of 217 patients who met the study criteria were retrospectively reviewed. Nine patients with NMDAR encephalitis declined to participate in the survey. Ultimately, 208 patients were enrolled (table 1). There were 155 patients in the anti-NMDAR encephalitis group, 26 in the GABA₉R group and 27 in the LGI1/CASPR2 group. The details of anti-LGI1/CASPR2 patients are shown in table e-3 (links.lww.com/NX1/A315). Overall, the median age at admission was 29 years (102 [49.0%] males and 106 [51.0%] females). Some of the patients (40.9%) chose to use medical insurance. Thirty-eight of 208 patients (18.3%) had neoplasms. Of these 38 patients, only 1 patient with anti-GABA₉R encephalitis knew about the neoplasm before inpatient admission for AE. A total of 134 of the 208 patients (64.4%) had other complications, and detailed information on the complications is shown in table e-2. Twenty-two of the 208 patients (11.0%) were admitted to the intensive care unit (ICU) during their hospitalization, all of whom had ICU stays >48 hours. The mRS of admitted patients in the LGI1/CASPR2 group was better than that in the NMDAR and GABA₉R groups. Only 1 patient died during hospitalization due to multiple organ failure, while 18 died during follow-up investigations. There was no significant difference in sex, complications, MRI, EEG, ICU rate or discharge disposition between the different subgroups.
Resource utilization

Neurologic care
There were 295 hospitalizations for the 208 patients, with an average number of 1.4 per patient (range 1–7). The annual number for each patient was 0.6 (range 0.14–2). There were 516 outpatient visits for the 208 patients after their first hospitalization, with an average number of 2.5 (range 0–27) and 0.9 outpatient visits per year per patient (range 0–10). The median LOS was 24.0 days. The total number of diagnostic and therapeutic activities (outpatient and hospitalization) for each AE category is depicted in table 2. The highest mean number (5.3 per patient) of medical visits was incurred by patients with anti-LGI1/CASPR2 encephalitis, while patients with anti-NMDAR encephalitis had the lowest mean number (3.5 per patient) of diagnostic and therapeutic interventions. Regarding diagnostic tests, a total of 277 EEG tracings, 293 MRI scans, 312 lumbar punctures, and 257 antibody examinations were performed during hospitalizations.

Immuno therapy during hospitalization
In total, 119 of the 208 (57.2%) patients were receiving IVMP, 170 (81.7%) were receiving IVIG, and 85 (40.9%) were receiving first-line immunotherapy containing IVMP and IVIG. Only 6 of the 208 (2.9%) patients received second-line immunotherapy (rituximab or cyclophosphamide). The proportion of patients receiving IVIG was significantly higher in the NMDAR group than in the GABABR (87.7% vs 65.4% p < 0.05) and LGI1/CASPR2 (87.7% vs 63.0% p < 0.05) groups. The average days of IVIG use was highest in the NMDAR group (5.8 days), followed by the GABABR group (5.4 days) and the LGI1/CASPR2 group (3.7 days). The mean number of days of IVMP use was highest in the GABABR group (3.6 days), followed by the NMDAR group (3.5 days) and the LGI1/CASPR2 group (2.3 days).

Transportation and nonneurologic care
The mean distance from the location of residence to our hospital was 250.1 ± 402.4 km, and all patients used transportation tools (taxi or bus) to travel to our neurology clinic. Sixty of the 208 (29.0%) patients claimed to ask for professional care services during hospitalization. Thirty-four of the 208 (16.3%) patients claimed to choose accommodations in Chengdu at the time of their outpatient visits.

Economic burden of AE
The financial burden of AE patients is shown in table 3. The total direct cost contained direct medical costs (inpatient costs and outpatient costs) and direct nonmedical costs. The average direct medical cost was RMB 88,373 (SD ±87,909),

| Table 1 Demographic and clinical characteristics of patients |
|-------------------------------------------------------------|
| **Variable** | **Anti-NMDAR (N = 155 [74.5%])** | **Anti-GABABR (N = 26 [12.5%])** | **Anti-LGI1/CASPR2 (N = 27 [13%])** | **Total (N = 208 [100%])** | **p Value** |
| **Sex, male** | 75/155 (48.4%) | 14/26 (53.8%) | 13/27 (48.1%) | 102 (49.0%) | 0.87 |
| **Age, median (IQR), y** | 25 (19–37) | 55 (41–62) | 44 (32–58) | 29 (20–44) | <0.001 |
| **Insurance, yes** | 60/155 (38.7%) | 10/26 (38.5%) | 15/27 (55.6%) | 85/208 (40.9%) | 0.25 |
| **Tumor** | 28/155 (18.1%) | 9/26 (34.6%) | 1/27 (3.7%) | 38/208 (18.3%) | 0.014 |
| **Complication** | 103/155 (66.5%) | 17/26 (65.4%) | 14/27 (51.9%) | 134/208 (64.4%) | 0.34 |
| **MRI, abnormality** | 63/155 (40.6%) | 9/26 (34.6%) | 9/27 (33.3%) | 81/208 (38.9%) | 0.7 |
| **EEG, abnormality** | 108/155 (69.7%) | 15/26 (57.7%) | 17/27 (63%) | 140/208 (67.3%) | 0.4 |
| **ICU admission** | 19/155 (12.3%) | 2/26 (7.7%) | 1/27 (3.7%) | 22/208 (10.6%) | 0.27 |
| **mRS on admission, median (IQR)** | 4 (4–5) | 4 (3–4) | 3 (2–4) | 4 (3–5) | <0.001 |
| **mRS at discharge, median (IQR)** | 2 (2–3) | 2 (1–3) | 1 (1–2) | 2 (2–3) | <0.001 |
| **Discharge disposition** | 0.12 |
| **Home** | 101/155 (65.2%) | 21/26 (81.8%) | 23/27 (85.2%) | 145/208 (69.7%) |
| **Other hospital** | 53/155 (34.2%) | 5/26 (19.2%) | 4/27 (14.8%) | 62/208 (29.8%) |
| **Inpatient death** | 1/155 (0.6%) | 0/29 (0) | 0/33 (0) | 1/208 (0.5%) |

Abbreviations: GABA_B = γ-aminobutyric acid receptor type B; ICU = intensive care unit; IQR = interquartile range; mRS = modified Rankin Scale; NMDAR = NMDA receptor.
Tumors included teratoma (18), lung cancer (7), adrenal adenoma (2), choriocarcinoma (1), pituitary tumor (1), renal cancer (1), diffuse glioma (1), thyroid tumor (1), mucinous cystadenoma (1), bladder cancer (1), hysterosarcoma (1), pancreatic cancer (1), rectal cancer (1), and ovarian cancer (1).
Anti-LGI1/CASPR2 represents antileucine-rich glioma-inactivated 1 (n = 19), contactin-associated protein-2-positive (n = 3), and dual antibody (n = 5)-positive encephalitis.
which accounted for a major (93.9%) proportion of the total direct cost (RMB 94,129 [SD ±93,427]) (figure 1). The mean hospitalization cost was RMB 86,810, and the average outpatient cost was RMB 1,563. The cost of immunotherapy (81.6%) accounted for a major proportion of the treatment cost, and the mean treatment for each patient cost more than RMB 45,000. The average direct nonmedical cost was RMB 5,756. The average travel expense (RMB 571), diet (RMB 2,286), and professional care (RMB 2,899) accounted for only 9.9%, 39.7%, and 50.4% of the direct nonmedical costs, respectively (figure 1). It can be seen in table 3 that the pattern of resource use in the different categories is almost uniform. Except for the test and other costs, the main expenditure was immunotherapy, followed by anti-infective drugs and professional care.

The costs associated with outpatients differed only slightly across AE categories, in contrast with the costs associated with inpatients. The total direct cost was highest in the NMDAR group (RMB 101,863 or USD 15,387), followed by the GABABR group (RMB 91,455 or USD 13,815) and the LGI1/CASPR2 group (RMB 52,301 or USD 7,900).

| Table 2 | Diagnostic and therapeutic services per patient by type |
|---------|-------------------------------------------------------|
|         | Anti-NMDAR (N = 155) | Anti-GABABR (N = 26) | Anti-LGI1/CASPR2 (N = 27) | Total (N = 208) | p Value |
| Hospitalizations, mean ± SD, number | 1.3 ± 0.7 | 1.7 ± 1.2 | 1.6 ± 0.8 | 1.4 ± 0.8 | 0.08 |
| Annual hospitalizations, mean ± SD, number | 0.5 ± 0.5 | 0.8 ± 0.5 | 0.7 ± 0.4 | 0.6 ± 0.5 | 0.002 |
| LOS in the hospital, median (IQR), d | 24.0 (17.0–34.0) | 26.0 (13.0–36.0) | 17.0 (15.0–24.0) | 24.0 (16.0–33.0) | 0.43 |
| IVMP, mean ± SD, d | 3.5 ± 3.4 | 3.6 ± 4.2 | 2.3 ± 2.5 | 3.3 ± 3.4 | 0.31 |
| IVIG, mean ± SD, d | 5.8 ± 3.7 | 5.4 ± 5.3 | 3.7 ± 3.3 | 5.5 ± 3.9 | 0.02 |
| Rituximab, mean ± SD, d | 0.4 ± 3.2 | 1.1 ± 5.5 | 0 | 0.4 ± 3.3 | 0.4 |
| Cyclophosphamide, mean ± SD, d | 0.1 ± 0.7 | 0 | 0 | 0.07 ± 0.6 | 1 |
| Outpatient visits, mean ± SD, number | 2.1 ± 4.1 | 3.5 ± 5.1 | 3.7 ± 4.5 | 2.5 ± 4.3 | 0.01 |
| Annual outpatient visits, mean ± SD, number | 0.7 ± 1.2 | 1.6 ± 2.3 | 1.8 ± 2.7 | 0.9 ± 1.7 | 0.003 |
| MRI, mean ± SD, number | 1.3 ± 0.5 | 1.7 ± 0.9 | 1.6 ± 0.7 | 1.4 ± 0.6 | 0.04 |
| 1–2 checks, proportion of patients | 97.4% | 76.9% | 92.6% | 94.2% | 0.001 |
| 3–4 checks, proportion of patients | 2.6% | 23.1% | 7.4% | 5.8% | 0.2 |
| EEG, mean ± SD, number | 1.3 ± 0.5 | 1.5 ± 0.8 | 1.3 ± 0.4 | 1.3 ± 0.5 | 0.27 |
| 1–2 checks, proportion of patients | 99.4% | 92.3% | 100% | 98.6% | 0.2 |
| 3–4 checks, proportion of patients | 0.6% | 7.7% | 0 | 1.4% | 0.2 |
| Lumbar, mean ± SD, number | 1.5 ± 0.8 | 1.4 ± 0.8 | 1.6 ± 0.6 | 1.5 ± 0.8 | 0.41 |
| 1–2 checks, proportion of patients | 91.6% | 92.3% | 96.3% | 92.3% | 0.9 |
| 3–4 checks, proportion of patients | 7.7% | 7.7% | 3.7% | 7.2% | 0.5 |
| 5–6 checks, proportion of patients | 0.7% | 0 | 0 | 0 | 0.5% |
| Antibody examination, mean ± SD, number | 1.2 ± 0.5 | 1.3 ± 0.5 | 1.4 ± 0.5 | 1.2 ± 0.5 | 0.01 |
| 1–2 checks, proportion of patients | 98.1% | 96.2% | 100% | 98.1% | 0.5 |
| 3–4 checks, proportion of patients | 1.4% | 3.8% | 0 | 1.4% | 0.5 |
| 5–6 checks, proportion of patients | 0.5% | 0 | 0 | 0.5% | 0.5 |
| Outpatient death, proportion of patients | 5.8% | 34.6% | 0 | 9.1% | <0.001 |

Abbreviations: GABABR = γ-aminobutyric acid receptor type B; IVIG = IV immunoglobulin; IVMP = IV methylprednisolone; LOS = length of stay; NMDAR = NMDA receptor. Anti-LGI1/CASPR2 represents antileucine-rich glioma-inactivated 1 (n = 19), contactin-associated protein-2-positive (n = 3), and dual antibody (n = 5)-positive encephalitis.
Table 3 Economic costs per patient by type

| Variable          | Anti-NMDAR (N = 155) | Anti-GABA<sub>b</sub>R (N = 26) | Anti-LGI1/CASPR2 (N = 27) | Total (N = 208) | p Value |
|-------------------|----------------------|---------------------------------|---------------------------|-----------------|---------|
| Total             | 101,864 ± 101,834    | 91,455 ± 74,568                 | 52,301 ± 23,296           | 94,129 ± 93,427 | 0.002   |
| (10,452–722,859)  | (10,963–323,652)     | (10,872–108,382)                | (10,452–722,859)          |                 |         |
| Direct nonmedical | 6,316 ± 7,220 (804–40,250) | 4,711 ± 3,504 (896–13,970)    | 3,549 ± 2,366 (1,104–10,300) | 5,756 ± 6,479 (804–40,250) | 0.27    |
| Professional care | 3,564 ± 6,200 (0–32,200) | 1,262 ± 2,937 (0–10,800)    | 659 ± 1,646 (0–5,800)      | 2,899 ± 5,595 (0–32,200) | 0.01    |
| Diet              | 2,298 ± 1,274 (600–8,050) | 2,539 ± 2,103 (550–11,300)    | 1,976 ± 1,214 (850–6,700)  | 2,286 ± 1,395 (550–11,300) | 0.32    |
| Travel            | 455 ± 1,019 (0–7,495) | 911 ± 1,827 (0–8,000)           | 913 ± 1,856 (0–8,100)      | 571 ± 1,284 (0–8,100)   | 0.4     |
| Direct medical    | 95,548 ± 95,527 (9,452–690,609) | 86,744 ± 72,295 (10,067–309,682) | 48,753 ± 22,599 (9,768–100,710) | 88,373 ± 87,909 (9,452–690,609) | 0.001   |
| Outpatient        | 1,254 ± 3,451 (0–29,030) | 3,156 ± 8,645 (0–43,395)   | 1,798 ± 2,437 (0–10,135)   | 1,563 ± 4,362 (0–43,395) | 0.01    |
| Inpatient         | 94,293 ± 95,012 (9,452–690,609) | 85,588 ± 72,379 (9,162–309,679) | 46,955 ± 21,964 (9,768–100,710) | 86,810 ± 87,520 (9,162–690,609) | 0.001   |
| Treatment         | 50,090 ± 34,667 (3,490–231,653) | 48,334 ± 47,029 (304–179,319) | 26,722 ± 19,416 (65–71,332) | 46,837 ± 35,631 (65–231,653) | 0.001   |
| Immunotherapy     | 39,954 ± 25,495 (1,700–173,750) | 42,051 ± 44,135 (0–177,000) | 24,572 ± 19,467 (0–69,000) | 38,219 ± 28,193 (0–177,000) | 0.04    |
| AEDs              | 2,362 ± 4,853 (0–37,178) | 1,098 ± 1,262 (54–4,860)       | 202 ± 212 (0–765)          | 1,924 ± 4,282 (0–37,178) | 0.002   |
| Antipsychotic drugs | 573 ± 802 (0–5,666) | 355 ± 467 (0–1,944)           | 205 ± 442 (0–2,095)        | 498 ± 740 (0–5,666) | 0.003   |
| Anti-infective drugs | 3,981 ± 6,808 (0–33,489) | 2,922 ± 4,228 (0–16,530)   | 690 ± 2,022 (0–9,945)      | 3,422 ± 6,196 (0–33,489) | <0.001  |
| Other treatment   | 3,221 ± 6,111 (0–58,028) | 1,909 ± 3,234 (0–12,046)   | 1,052 ± 1,562 (0–5,560)    | 2,775 ± 5,476 (0–58,028) | 0.019   |
| Test and other    | 44,203 ± 69,739 (5,498–531,082) | 35,254 ± 37,287 (8,858–191,114) | 20,233 ± 9,353 (9,555–41,386) | 39,973 ± 62,163 (5,498–531,082) | 0.15    |

Abbreviations: AED = antiepileptic drug; GABA<sub>b</sub>R = γ-aminobutyric acid receptor type B; NMDAR = NMDA receptor.

Numbers represent the mean ± SD and ranges are shown in parentheses. Costs are shown in renminbi.

Anti-LGI1/CASPR2 represents antieleucine-rich glioma-inactivated 1 (n = 19), contactin-associated protein-2-positive (n = 3), and dual antibody (n = 5)-positive encephalitis.

Immunotherapy included IV methylprednisolone, IV immunoglobulin, rituximab, and cyclophosphamide.

Test and other included MRI of the brain, EEG, an antibody examination, lumbar puncture, biomedical assays, room cost, and nursing-related cost.

Age, sex, tumor condition, mRS, and AE-related neurologic care visit were preselected as variables for the univariate regression analyses. LOS was strongly associated with the log10 total direct cost (LOS $r^2 = 0.54$, p < 0.001) (figure e-1, links. lww.com/NXI/A315). Age, sex, tumor condition, mRS, and AE-related neurologic care visit did not improve the proportion of variance explained. The average cumulative direct medical expenses per patient increased significantly from first admission to 3 months in patients with all types of encephalitis, while the cumulative direct medical expenses increased slightly from 3 months to 36 months (figure 2A). Moreover, the direct medical cost of anti-LGI1/CASPR2 encephalitis was significantly lower than that of anti-NMDAR and anti-GABA<sub>b</sub>R encephalitis.

The average inpatient cost per patient in China showed a downward trend over time (figure 2B). The mRS for patients did not significantly change over time (data not shown). The cost for each examination, treatment and stay item did not significantly change over time (data not shown). The number of targeted tests also did not change over time. LOS exhibited a linear relationship with the financial year ($r^2 = 0.84$, figure 2C), which might explain why the inpatient cost per patient in China decreased over time.

Contributors to prolonged LOS in the hospital

Of the 136 patients with an LOS ≥200 days, 102 were in the NMDAR group, 18 were in the GABA<sub>b</sub>R group, and 16 were in the LGI1/CASPR2 group. The factors contributing to the prolonged LOS included mRS on admission ≥4 (n = 113, p = 0.02), complications (n = 101, p = 0.03), delay in diagnosis (≥7 days, n = 89, p = 0.04), lack of a response (n = 48, p = 0.04), prolonged immune treatment that required inpatient immunotherapy lasting ≥7 days (n = 46, p = 0.03), and tumor condition (n = 31, p = 0.04).

Of the 89 hospitalizations with a delay in establishing the diagnosis of AE, 68 patients were in the NMDAR group, 10
were in the GABA\(_{\beta}\)R group, and 11 were in the LGI1/CASPR2 group. Among the 46 patients with prolonged immune treatment, 36 had anti-NMDAR encephalitis, 9 had anti-GABA\(_{\beta}\)R encephalitis, and 1 had anti-LGI1/CASPR2 encephalitis.

**Discussion**

To the best of our knowledge, this is the first study to provide data on the cost of AE in China. A modest estimate of the mean direct cost of AE in China based on this study was RMB 94,129 (USD 14,219) per person. The direct cost varied widely, with an SD of USD 14,113. The mean annual income per person in Sichuan Province was RMB 20,580 (USD 3,109),\(^\text{14}\) while the mean annual income per person in China was RMB 25,974 (USD 3,924).\(^\text{15}\) Thus, AE is a cost-intensive disorder, and its economic burden on both patients and the healthcare system is heavy in China.

In the present study, the nonmedical direct costs were much lower than the direct medical costs, consistent with a recent economic survey on encephalitis in Canada\(^\text{16}\) and our previous study on epilepsy.\(^\text{17}\) However, different conditions have been reported by a previous study on MS patients with spasticity in Sweden,\(^\text{18}\) indicating that the largest share of total costs was direct nonmedical costs (accounting for 60.0% of the total costs). The high proportion of direct nonmedical costs (accounting for 58.0% of total costs) has also been represented in a cost-of-illness study on stroke in Italy.\(^\text{19}\) These discrepancies could be explained by differences among the diseases in nature and progression. Composition proportions of AE costs (figure 1) were analyzed in the present study but not yet by any other study of AE to our knowledge. Inpatient costs accounted for a major proportion (92.0%) of the total direct costs, consistent with the findings of 2 surveys on West Nile encephalitis.\(^\text{16,20}\) Notably, immunotherapy, which is not normally covered by insurance and imposes a heavy economic burden on patients, accounted for 40.6% of the total direct cost and 44.0% of the inpatient cost in our study. Our study also compared the cost of different kinds of AE. The direct cost was lower in anti-LGI1/CASPR2 encephalitis than in the other 2 kinds of AE. The reason for this difference may be as follows: patients in the LGI1/CASPR2 group had the shortest LOS in the hospital (median of 17.0 days, interquartile range [IQR] of 15.0–24.0), in agreement with a previous study indicating that LOS was significantly related to cost.\(^\text{12}\)

Previous studies in the United States\(^\text{21–24}\) reported a shorter LOS in the hospital but more inpatient costs for patients with encephalitis of all causes than patients with AE in China in the present study. The average LOS in the hospital was 10.6–15.1 days.\(^\text{21–24}\) The median inpatient cost was $48,852 (IQR $23,831–$104,835) during 1998–2010,\(^\text{21}\) and the mean inpatient expenditure was $60,181 (SD $130,276) during 2010–2014.\(^\text{22}\) Specific comparisons of the disease burden of AE in American\(^\text{12}\) and Chinese hospitals were performed (table e-1, links.lww.com/NXI/A315). The total LOS was 1.6 times greater for patients in China than for patients in the United States\(^\text{12}\) (median of 24.0 days vs median of 15.0 days per patient). However, the inpatient cost for patients with AE in the United States\(^\text{12}\) was 7.7 times greater than that for patients with AE in China (median of 74,319 USD.
vs mean of 13,113 USD or median of 9,636 USD (6,707–13,625), which may mostly be due to the different price levels. However, the fact that the average annual income per person in China is only 6.6% of that in the United States should not be ignored. The lower proportion of females and lower tumor rate in anti-NMDAR encephalitis and anti-GABA<sub>R</sub> encephalitis compared with those in the United States are consistent with previous studies from our center and other centers in China6,8,25–30 and may be due to the different genetic backgrounds. In addition, the lower ICU rate in anti-GABA<sub>R</sub> encephalitis is consistent with previous studies from our center8 and other centers30 in China. This study focused on antibody-positive AE, while the United States study did include antibody-negative patients.12 According to the United States study,12 antibody-negative patients may incur a prolonged LOS in the hospital and increased medical costs given that they typically undergo consideration of other diagnoses and therefore more work-up and empiric therapy. Only 11.0% of patients were admitted to the ICU (compared to other cohorts, 43.0%–77.0%), which may be related to the different medical environments and economic burdens of patients, since the severity of patients in the admission stage was similar between our cohort and the American cohort5,12,31 based on the mRS evaluation. In addition, only 2.9% of patients in our cohort received a second-line immunotherapy agent, which is very different from that in United States studies (17.0%–27.0% of patients).5,32 This phenomenon observed in our cohort may be due to the economic reasons of patients, off-label use of second-line immunotherapy for AE in China, and concerns about side effects by doctors and patients.33 In addition, the inpatient cost of each AE patient in America12 has remained roughly constant over time. The average inpatient cost per patient in China has shown a downward trend over time (figure 2B). However, the change in the average inpatient cost per patient over time for specific kinds AE (such as GABA<sub>R</sub> and LGI1/CASPR2) needs further study due to the limited number of patients. The health care costs and per capita disposable income of residents has increased over time in China (figure e-2, links.lww.com/NXI/A315). The shortened LOS, which may be due to earlier diagnosis and treatment, could partly explain the reduced costs in China. However, given the low number of patients per year and the difference in patient types over time, this phenomenon needs further verification. The difference between the above 2 countries may be explained by the different observation periods (financial years 2006–2015 in America12 vs financial years 2012–2018 in the present study).

Notably, although a general practitioner was normally available within 5 km from their residence, most patients chose to

Figure 2 Trend in autoimmune encephalitis cost and length of stay over time
travel more than 200 km for medical consultations with specialists at our tertiary center. These long trips contributed to the direct nonmedical costs of AE. This phenomenon may result from the lack of identification of AE by general practitioners in primary hospitals in developing countries and the lack of confidence among patients in doctors in primary hospitals, since similar results were also reported in our epilepsy economic burden study in China and in a previous study in India but not in developed countries.

The limitations of this study should be noted. First, the present study was a single-center study. However, our tertiary center is one of the largest local hospitals. Patients came from Sichuan Province and the surrounding provinces of western China, which are characterized by average socioeconomic levels. Hence, the results from our study should, in general, represent the situation of the target population. Second, the cost presented here did not exclude medical insurance reimbursement. Notably, in Sichuan Province, China, some examinations, such as PET CT, and some treatments, such as IVIG, must be fully paid for by patients themselves (even inpatients), imposing a heavy burden on patients. Third, a total of 217 patients met the study criteria, and 208 patients were enrolled. The limited number of patients with no response may have led to significant bias. Finally, due to the small numbers of patients with anti-LGI1 and anti-CASPR2 encephalitis, we merged the 2 types of encephalitis for analysis, although the literature suggests that they are separate entities. A larger sample size study on the economic burden of anti-LGI1 encephalitis, anti-CASPR2 encephalitis and dual antibody-positive encephalitis is necessary for further details on these entities.

Moreover, it is possible that the actual cost for AE patients was underestimated. First, assistance provided by family members was not included due to the difficulty in valuing such efforts. Only a small proportion of families (29.0%) turned to professional care during hospitalization or after discharge, even though the patients needed personal assistance, which may be based on economic and cultural factors. Second, the cost of tumor treatment was not included in these calculations. Third, our investigation did not involve indirect costs, which included sick leave, early retirement, unemployment and loss of income, for patients and individuals who accompanied the patient to the clinic because of the difficulty of accessing or evaluating such factors. Fourth, patients who received care at multiple centers and were therefore excluded from our study may have even higher costs. Finally, we did not look at how many had outpatient treatment only nor knew about costs of outpatient-only treatment or rehab costs.

In summary, this study is the first to provide information on the economic burden of AE patients in China. This research is critical for the rational allocation of medical resources to patients and healthcare payers. Future research on the strategies of the early application of targeted immune-based treatment and how to decrease LOS in the hospital is needed. It is likely that improvements in more effective and targeted immune-based treatment strategies will improve patient outcomes and decrease the economic burden of AE accordingly.

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Appendix Authors

| Name            | Location                                      | Contribution                                                                 |
|-----------------|-----------------------------------------------|------------------------------------------------------------------------------|
| Aiqing Li, MD   | Department of Neurology, West China Medical Center, Sichuan University | Major role in the acquisition of data, analyzed the data, and drafted the manuscript for intellectual content |
| Xue Gong, MD    | Department of Neurology, West China Medical Center, Sichuan University | Contributed to data collection                                                |
| Kundian Guo, MD | Department of Neurology, West China Medical Center, Sichuan University | Contributed to data collection                                                |
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| Dong Zhou, MD, PhD | Department of Neurology, West China Medical Center, Sichuan University | Interpreted the data and revised the manuscript for intellectual content     |
| Zhen Hong, MD, PhD | Department of Neurology, West China Medical Center, Sichuan University | Designed and conceptualized the study and revised the manuscript for intellectual content |

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