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One-year direct and indirect costs of ischaemic stroke in China

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ABSTRACT

Background This is the first real-world study to estimate the direct costs and indirect costs of first-ever ischaemic stroke with 1-year follow-up in China, based on a nationally representative sample.

Methods Patients were chosen from 20 geographically diverse sites from the nationally representative database China National Stroke Registry-III (CNSR-III). The inclusion criteria were surviving patients who were hospitalised with first-ever ischaemic stroke from February 2017 to February 2018 (the index event); aged 18–80 during the index event; no history of other stroke types. The primary endpoints were direct medical costs, direct non-medical costs, indirect costs and total cost (ie, the sum of all cost components). Patient characteristics and clinical data were extracted from CNSR-III. Stroke-related in-hospital direct medical costs were collected from hospital electronic medical records. The patient survey collected data related to out-of-hospital direct medical costs, direct non-medical costs and indirect costs. The secondary objective was to explore clinical factors associated with cost outcomes through univariate analysis and multiple regression.

Results The study enrolled 520 patients. The total cost was 57 567.48 CNY, with 26 612.67 CNY direct medical costs, 2 787.56 CNY direct non-medical costs and 28 167.25 CNY indirect costs. Univariate analysis showed that longer lengths of stay during the index event, higher National Institutes of Health Stroke Scale (NIHSS) and modified Rankin Scale scores were associated with higher costs in all categories. Conversely, EuroQol 5 Dimension utility scores were associated with decreased costs except direct non-medical costs. Multiple regressions showed that higher admission NIHSS scores were independently associated with higher direct medical costs, indirect costs and total cost. Higher 3-month utilities were associated with lower total cost.

Conclusion This real-world study showed substantial 1-year economic burden following first-ever ischaemic stroke in China, and that indirect costs are a non-negligible driver of costs.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Several regional studies in China have estimated index hospitalisation costs of ischaemic stroke ranging from 12 000 to 18 000 CNY. Follow-up costs and other types of cost (direct non-medical costs and indirect costs) have rarely been studied.

WHAT THIS STUDY ADDS

⇒ This retrospective real-world observational study is the first in China with a nationally representative sample to investigate follow-up costs as well as direct non-medical costs and indirect costs, showing that indirect costs are a significant driver of total cost. The index event accounts for the majority of direct medical costs, but only a minor portion of direct non-medical costs and indirect costs.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Economic evaluations are often part of public healthcare policy assessments. These evaluations should account for follow-up costs and other types of cost (direct non-medical costs and indirect costs) in order to reflect the long-lasting impact of ischaemic stroke on patients' lives, while considering only the acute treatment costs would underestimate the value of functional recovery from stroke.

INTRODUCTION

Stroke is one of the leading causes of mortality and disability worldwide,[1] and the burden of stroke in China is growing due to the ageing population, urbanisation and lifestyle changes.[2] A national study showed that the age-standardised prevalence of stroke in China was more than 1000 per 100 000 in 2013.[3] More than 1.5 million deaths in China were attributable to stroke in 2018,[4] and stroke was also the largest contributor to disability-adjusted life years (DALYs) in 2017.[3] Among all strokes in China, ischaemic stroke and transient ischaemic attacks account for approximately 70%.[5]

In addition to death and disability, the onset of stroke poses significant economic burden to society. Previous studies have shown that the treatment cost of ischaemic stroke in China is substantial.[6–12] Stroke-related disability also affects patients' lives in the form of absenteeism or early retirement and the need for living assistance and nursing care,[13] however, such costs are rarely reported.[10 14] In addition, no studies included patient quality of life as a potential factor in their analysis. To our knowledge, these published works on stroke burden in China are either based on regional

data with limited national representativeness or limited to short-term direct medical costs.

A comprehensive analysis of economic burden should account for different types of costs, including direct medical costs, direct non-medical costs and indirect costs. According to Jo, direct medical costs refer to medical care expenditures for services and resources, including diagnosis, treatment, rehabilitation, etc, and direct non-medical costs measure costs due to non-healthcare resources, such as transportation, food and accommodations.[15] Indirect costs are disease-related productivity losses of the patient as well as the cost of time spent by family members to care for the patient (informal care).[15 16] A systematic review of the global economic burden of stroke reported that less than half of cost-of-illness studies accounted for indirect costs, and less than 20% included direct non-medical costs.[17]

This retrospective real-world observational study is the first in China with a nationally representative sample to comprehensively investigate the economic burden of first-ever ischaemic stroke in the following 12 months.

Table 1 Geographic distribution of the chosen sites

Regions	Sites from provincial capitals	Sites from other cities
East (Shanghai, Shandong Province, Zhejiang Province, Jiangsu Province)	4	1
West (Shaanxi Province, Sichuan Province, Chongqing Province, Yunnan Province)	2	1
South (Guangdong Province, Fujian Province, Guangxi Province)	2	1
North (Beijing, Tianjin, Liaoning Province, Jilin Province, Heilongjiang Province, Hebei Province)	4	1
Middle (Hubei Province, Hunan Province, Anhui Province, Henan Province, Jiangxi Province)	3	1
Total	**15**	**5**

METHODS

Study design and subjects

This study consisted of two parts. The first part extracted real-world data from databases, specifically clinical data from the Third China National Stroke Registry (CNSR-III) and in-hospital cost data from hospital electronic medical records (EMRs). The second conducted a patient survey (online supplemental file 2) to collect data on other costs (out-of-hospital direct medical costs, direct nonmedical costs, indirect costs).

The CNSR-III database enrolled 15 166 consecutive ischaemic stroke and TIA patients between August 2015 and March 2018.[18] The registry covers 201 hospitals from 22 provinces and four municipalities in China. Patients were followed for up to 5 years. The quality and completeness of the data were improved from previous registries due to the use of an electronic data capture system.[18]

Patients for this study were selected from 20 geographically diverse sites, the distribution of which is shown in table 1. The study enrolled patients who met the following criteria: hospitalised with first-ever ischaemic stroke from February 2017 to February 2018 (the index event), identified by a final diagnosis of ischaemic stroke in the CNSR-III database; aged 18–80 during the index event; no history of any stroke type (including ischaemic stroke and haemorrhagic stroke); CNSR-III data record missing rate of less than 15%; EMR cost data available and willing to complete the follow-up survey.

Cost definitions

The primary endpoints were direct medical costs, direct non-medical costs, indirect costs and total cost. Direct medical costs comprise stroke-related in-hospital direct medical costs (outpatient, emergency and hospitalisation costs) and stroke-related out-of-hospital direct medical costs (poststroke rehabilitation and supportive care). Non-medical costs include transportation during the index event, accommodation and food costs for family members during the index event and homecare worker costs during the index event and poststroke period. Indirect costs include the costs of patient early retirement or absenteeism due to stroke and days of informal poststroke care provided by the informal caregiver. Finally, the total cost was the sum of all cost components.

To calculate the indirect costs, the total days of patient productivity loss and informal care during the index event and poststroke period were aggregated. The human capital approach was used to estimate the cost of patient productivity loss and the replacement approach for the cost of informal care.[16] The human capital approach measures productivity loss by foregone earnings due to disease, which can be assessed by wages.[16 19] The replacement approach estimates the value of informal care as the cost of paying a caregiver to provide the same types of services provided by the informal caregiver.[16] Following the previous literature,[10] the daily cost of productivity loss and informal care was estimated by taking the annual wage of workers of non-private institutions in cities and towns from the 2020 Wage and Payroll statistics published by the National Bureau of Statistics (97,379 CNY) divided by the number of working days (250 days).

Data collection

Data were collected from three sources. Patient characteristics and clinical data from the index event and from

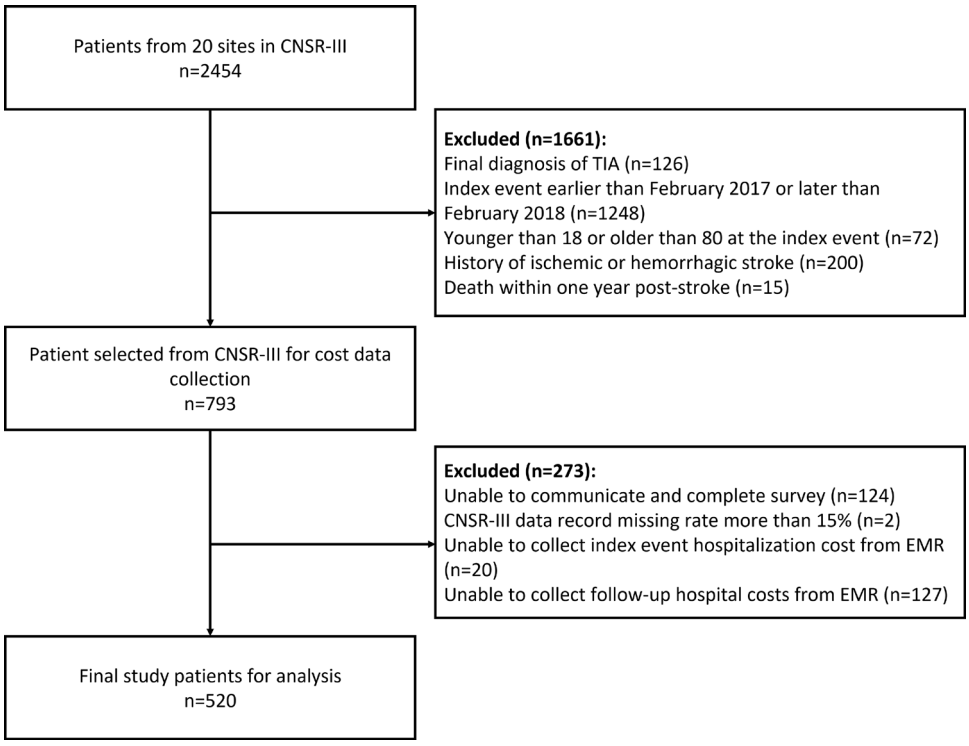

Figure 1 Study population flowchart. CNSR, China National Stroke Registry; EMR, electronic medical record; TIA, transient ischaemic attack.

the 3-month and 12-month follow-ups were collected from the CNSR-III database. These data included demographics (age, gender, insurance, etc), baseline characteristics (admission National Institutes of Health Stroke Scale (NIHSS) score and modified Rankin Scale (mRS) score, comorbidities), treatment (types of surgical and medical treatment used), discharge conditions (length of stay, discharge to home or other institutions, discharge medication, discharge NIHSS score and mRS score), follow-up conditions (living alone or with family, medication compliance, 3-month and 12-month mRS score and utility calculated from the EuroQol 5 Dimension (EQ-5D) questionnaire).

Stroke-related in-hospital direct medical costs were collected from hospital EMRs. The costs of the index event were collected from the 20 sites enrolled in the study. Poststroke in-hospital costs were collected from sites of follow-ups.

The patient survey was conducted by telephone. We collected data related to out-of-hospital direct medical costs, direct non-medical costs and indirect costs (days of patient productivity loss and family member informal care).

Statistical analyses

For descriptive statistics, means and SD are reported for continuous variables, and category proportions are reported for categorical variables.

Univariate analysis was conducted using Spearman's ρ to assess the correlation between cost outcomes and continuous variables and one-way analysis of variance (ANOVA) to test for associations between outcomes and categorical variables. No corrections for multiple comparisons were performed.

Three multiple regression models were established with direct medical costs, indirect costs and total cost as outcomes. Generalised linear models with gamma distribution and log link were chosen to model direct medical costs and total cost due to their right-skewed distribution. Indirect costs had a bimodal distribution; therefore, this outcome was dichotomised to represent whether the patient's indirect cost was higher or lower than the median, the likelihood of which was estimated using logistic regression.

Independent variables for the regressions were screened first by whether they were included as potential covariates of cost in previous literature, and for each model, variables were further screened by whether they were significantly associated with the corresponding cost outcome in the univariate analysis. For variables with repeated measurements at different time points, only one set was selected. Admission NIHSS score was selected to represent the initial disease severity. For follow-up data, the 3-month follow-up had the least missing data; therefore, the 3-month mRS score and EQ-5D utility were chosen to represent the patient's condition after treatment.

Starting from models that included all of the remaining variables, backward stepwise regression was conducted to improve the model parsimony using the Akaike Information Criterion as the selection criterion.

Table 2 Patient characteristics and univariate analysis results

Variable	Total (N=520)	Univariate analysis p values			
		Direct medical cost	Direct nonmedical cost	Indirect cost	Total cost
Basic information					
Gender: male	362 (69.6%)	0.051	0.114	0.353	0.031
Age (years old)	61.64 (9.74)	0.046	0.822	p<0.001	0.068
Work status before stroke		0.178	0.387	p<0.001	p<0.001
Working (full-time, part-time, farm work)	170 (32.7%)				
Not working (retired, unemployed, stopped farm work)	350 (67.3%)				
Insurance: urban employee basic medical insurance	243 (46.7%)	0.73	0.231	p<0.001	0.003
Insurance: urban resident basic medical insurance	125 (24.0%)	0.766	0.746	0.014	0.069
Insurance: rural cooperation medical insurance	117 (22.5%)	0.038	0.239	p<0.001	p<0.001
Family monthly income per capita		0.002	0.037	p<0.001	p<0.001
<3000 CNY	77 (14.8%)				
3000–8000 CNY	243 (46.7%)				
8001–20 000 CNY	157 (30.2%)				
> 20 000 CNY	43 (8.3%)				
Education level		0.814	0.519	p<0.001	0.033
College or above	51 (9.8%)				
High school	131 (25.2%)				
Junior school	180 (34.6%)				
Primary school	118 (22.7%)				
None	40 (7.7%)				
Hypertension	410 (78.8%)	0.486	0.857	0.053	0.287
Pathoglycemia		0.507	0.368	0.227	0.716
Pre-diabetes	14 (2.7%)				
Diabetes and classification	158 (30.4%)				
Lipid metabolism disorder	176 (33.8%)	0.7	0.22	0.858	0.812
Coronary heart disease	52 (10.0%)	0.195	0.669	0.166	0.499
Atrial fibrillation	31 (6.0%)	0.967	0.24	0.28	0.784
Treatment					
Time from onset to arrival (hours)	25.29 (30.96)	0.018	0.961	0.012	0.933
N-Miss	86				
Admission NIHSS total score	3.92 (3.77)	p<0.001	p<0.001	p<0.001	p<0.001
Intravenous thrombolysis: rt-PA intravenous thrombolytic	51 (9.8%)	0.011	0.774	0.01	0.459
Endovascular therapy: stent therapy	3 (0.6%)	0.012	0.864	0.614	0.189
Inpatient therapy: medicine	514 (98.8%)	0.449	0.934	0.979	0.771
Antiplatelet therapy	504 (96.9%)	0.26	0.852	0.84	0.43
Lipid-lowering drugs	509 (97.9%)	0.361	0.967	0.54	0.465
Antioxidant treatment	108 (20.8%)	0.743	0.524	p<0.001	0.002
Antihypertensive treatment	300 (57.7%)	0.417	0.835	0.757	0.442
Inpatient therapy: carotid artery stenting	3 (0.6%)	0.002	0.864	0.744	0.15
Inpatient therapy: decompressive craniectomy	0 (0.0%)	/	/	/	/
Length of stay of index event (days)	13.80 (5.77)	p<0.001	0.025	p<0.001	p<0.001

Continued

Table 2 Continued

Variable	Total (N=520)	Univariate analysis p values			
		Direct medical cost	Direct nonmedical cost	Indirect cost	Total cost
Discharge					
Discharge NIHSS total score	2.60 (2.90)	p<0.001	0.026	p<0.001	p<0.001
Whereabouts after discharge		0.041	0.922	0.003	0.082
N-Miss	15				
Home	482 (95.4%)				
Transferred to other hospitals (grade II)	5 (1.0%)				
Transferred to community hospital	2 (0.4%)				
Transferred to rehabilitation centre	12 (2.4%)				
Other	4 (0.8%)				
Discharge medication: antiplatelet agents	489 (94.0%)	0.009	0.359	0.559	0.061
Discharge medication: lipid-lowering drugs	493 (94.8%)	0.02	0.986	0.135	0.042
Discharge medication: antihypertensive therapy	317 (61.0%)	0.494	0.886	0.465	0.380
Discharge medication: antioxidant against lipid peroxidation	6 (1.2%)	0.674	0.831	0.174	0.207
Follow-up					
Living conditions during follow-up period		0.426	0.621	0.414	0.255
N-Miss	2				
Living alone	25 (4.8%)				
Living with others	493 (95.2%)				
3-month mRS score		p<0.001	0.004	p<0.001	p<0.001
N-Miss	3				
0–2 points	450 (87.0%)				
3–5 points	67 (13.0%)				
3-month EQ-5D utility	0.88 (0.17)	p<0.001	0.055	p<0.001	p<0.001
N-Miss	2				
12-month mRS score		p<0.001	0.003	p<0.001	p<0.001
N-Miss	7				
0–2 points	448 (87.3%)				
3–5 points	65 (12.7%)				
12-month EQ-5D utility	0.89 (0.18)	p<0.001	0.341	0.041	p<0.001
N-Miss	6				

EQ-5D, EuroQol 5 Dimension; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale.

All hypothesis tests were two sided with a significance level of 0.05. All statistical analyses were performed using R V.4.1.2.

RESULTS

Patient characteristics

A total of 520 patients were enrolled out of 2454 patients screened. Patient attrition at each step is shown in figure 1.

Descriptive statistics of the patient characteristics are presented in table 2. The enrolled patients were 69.6% male, aged 61.64 years on average. Almost half (46.7%) of the patients had urban employee basic medical insurance (UEBMI). Urban resident basic medical insurance (URBMI) and rural cooperation medical insurance each accounted for approximately 20% of patients. Almost half (46.7%) of the patients had a monthly family income between 3001 and 8000 CNY. Approximately one-third (32.7%) of the patients worked before stroke. Comorbidities were common among the patients, with hypertension affecting 78.8% and atrial fibrillation (AF) affecting 6.0%.

Patients arrived at the hospital 25.29 hours after symptom onset on average. Less than 1% of patients received preadmission emergency endovascular therapy

Table 3 Cost breakdowns

Cost type (N=520)	Costs Mean (SD), CNY	SE	95% CI
Total cost	57 567.48 (60036.44)	2632.77	52395.28, 62 739.68
Direct medical costs	26 612.67 (24373.40)	1068.84	24512.87, 28 712.46
Index event cost (hospitalisation cost)	18 143.79 (13381.40)	586.81	16990.97, 19 296.61
Follow-up cost	8468.88 (18667.60)	818.63	6860.64, 10 077.11
Rehabilitation	3942.55 (8594.02)	376.87	3202.16, 4682.93
Supportive care	1078.02 (3301.69)	144.79	793.58, 1362.46
Hospital care	3448.31 (15600.20)	684.11	2104.34, 4792.28
Direct nonmedical costs	2787.56 (25775.26)	1130.32	566.99, 5008.12
Index event cost	472.94 (1921.72)	84.27	307.38, 638.50
Food and accommodation (family members)*	32.89 (482.54)	21.16	0, 74.46
Homecare worker	428.10 (1859.68)	81.55	267.88, 588.31
Transportation	11.96 (24.19)	1.06	9.88, 14.05
Follow-up cost (homecare worker)	2314.62 (25381.53)	1113.05	127.97, 4501.26
Indirect costs	28 167.25 (44209.80)	1938.73	24358.53, 31 975.97
Index event cost	6741.62 (4359.28)	191.17	6366.07, 7117.18
Patient productivity loss	1767.05 (2887.73)	126.64	1518.27, 2015.84
Informal care	4974.57 (2648.44)	116.14	4746.40, 5202.74
Follow-up cost	21 425.63 (41653.21)	1826.61	17837.16, 25 014.09
Patient productivity loss	14 669.77 (32888.99)	1442.28	11836.35, 17 503.19
Informal care	6755.86 (20820.42)	913.04	4962.15, 8549.56

*Lower bound of 95% CI truncated to 0 due to costs being non-negative.

or inpatient surgical therapy. Most patients (98.8%) received inpatient medical therapy, the most common being antiplatelet therapy (97.9%) and lipid-lowering drugs (96.9%). The average length of stay was 13.80 days.

The mean NIHSS score on admittance was 3.92, which decreased to 2.60 at discharge. During follow-up, the patients' mRS score and EQ-5D utility stayed stable from 3 months to 12 months, with a slight numerical but non-significant improvement.

Cost outcomes

The total cost was 57 567.48 (95% CI 52 395.28 to 62 739.68) CNY on average, with a breakdown of costs shown in table 3, consisting of 26 612.67 (46% of total costs; 95% CI 24,512.87 to 28 712.46) CNY direct medical costs, 2787.56 (5% of total costs; 95% CI 566.99 to 5008.12) CNY direct non-medical costs and 28 167.25 (49% of total costs; 24 358.53 to 31 975.97) CNY indirect costs. A major proportion of the direct medical costs (68%) were incurred during the index event. Conversely, the follow-up period accounted for 83% of direct non-medical costs and 76% of indirect costs. As AF patients are often a subgroup of interest in the stroke research literature, we have also included the results of the AF patients in our sample in online supplemental table 1.

Univariate analysis

Associations between costs and other variables are shown in table 2. In addition, statistical test values and costs by characteristic (categorical variables) are provided in online supplemental tables 2 and 3, respectively. Age was a significant factor that impacted direct medical costs (p=0.046) and indirect costs (p<0.001). Having work before stroke was associated with significantly increased indirect and total cost (p<0.001). Rural cooperation medical insurance was significantly associated with decreased direct medical costs (p=0.038) but increased indirect costs and total cost (p<0.001 for both). UEBMI was significantly associated with decreased indirect costs (p<0.001) and total cost (p=0.003).

Higher NIHSS scores (admission and discharge) were associated with significant increases in total cost and the three cost categories, similar to mRS scores at months and 12 months. Higher EQ-5D utility values at 3 months and 12 months were significantly associated with decreases in direct medical costs, indirect costs, and total cost.

Regression analysis

The variables selected for initial inclusion in the regression analysis are shown in online supplemental table 4. The results of the multiple regressions are shown in table 4. The regression model for direct medical costs showed

Table 4 Multiple regression results

Variable	exp(Beta)	95% CI	P value
Direct medical cost model			
Insurance: Rural cooperation medical insurance			
No	/	/	/
Yes	0.78	0.68, 0.90	<0.001
Insurance: Self-payment			
No	/	/	/
Yes	1.28	1.03, 1.60	0.029
Family monthly income per capita			
< 3000 CNY	/	/	/
3000–8000 CNY	1.11	0.93, 1.31	0.3
8001–20 000 CNY	1.24	1.04, 1.49	0.017
> 20 000 CNY	1.38	1.09, 1.77	0.009
Length of stay for index event	1.04	1.03, 1.05	<0.001
Admission NIHSS total score	1.04	1.02, 1.06	<0.001
Intravenous thrombolysis: rt-PA intravenous thrombolytic			
No	/	/	/
Yes	1.40	1.16, 1.70	<0.001
Inpatient therapy: carotid artery stenting			
No	/	/	/
Yes	3.07	1.60, 6.96	0.003
Whereabouts after discharge			
Home	/	/	/
Transferred to other hospitals (Grade II)	0.94	0.55, 1.75	0.8
Transferred to community hospital	0.69	0.32, 1.96	0.4
Transferred to rehabilitation centre	1.73	1.22, 2.55	0.004
Other	1.10	0.62, 2.20	0.8
Discharge medication: antiplatelet agents			
No	/	/	/
Yes	0.76	0.59, 0.96	0.027
3-month EQ-5D utility	0.64	0.39, 1.01	0.054
3-month mRS score			
0–2 points	/	/	/
3–5 points	0.81	0.63, 1.03	0.076
Indirect cost model			
Age (years old)	1.04	1.01, 1.08	0.021
Insurance: urban employee basic medical insurance			
No	/	/	/
Yes	0.45	0.23, 0.85	0.015
Insurance: urban resident basic medical insurance			
No	/	/	/
Yes	0.4	0.19, 0.84	0.017
Work status before stroke			
Working (full-time, part-time, farm work)	/	/	/
Not working (retired, unemployed, stopped farm work)	0.01	0.00, 0.02	<0.001
Admission NIHSS total score	1.1	1.01, 1.20	0.032
Length of stay for the index event	1.38	1.27, 1.53	<0.001

Continued

Table 4 Continued

Variable	exp(Beta)	95% CI	P value
Intravenous thrombolysis: rt-PA intravenous thrombolytic			
No	/	/	/
Yes	0.41	0.15, 1.03	0.068
3-month EQ-5D utility	0.21	0.03, 1.79	0.2
3-month mRS score			
0–2 points	/	/	/
3–5 points	0.39	0.13, 1.17	0.1
Total cost model			
Education level			
College or above	/	/	/
High school	0.91	0.72, 1.16	0.5
Junior school	1.03	0.82, 1.29	0.8
Primary school	1.08	0.84, 1.37	0.5
None	1.33	0.97, 1.83	0.081
Work status before stroke			
Working (full-time, part-time, farm work)	/	/	/
Not working (retired, unemployed, stopped farm work)	0.46	0.40, 0.53	<0.001
Admission NIHSS total score	1.06	1.04, 1.09	<0.001
Length of stay for the index event	1.04	1.03, 1.05	<0.001
Inpatient therapy: antioxidant treatment			
Did not receive medicines	/	/	/
No	0.84	0.41, 1.52	0.6
Yes	0.74	0.35, 1.35	0.4
3-month EQ-5D utility	0.33	0.19, 0.57	<0.001
3-month mRS score			
0–2 points	/	/	/
3–5 points	0.81	0.62, 1.08	0.13

EQ-5D, EuroQol 5 Dimension; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale.

that rural cooperation medical insurance was significantly associated with decreased direct medical costs, while self-payment and higher family income were significantly associated with increased direct medical costs. Utilisation of healthcare resources, including longer length of stay during the index event, treatment with rt-PA intravenous thrombolysis or carotid artery stenting and discharge to a rehabilitation centre, was significantly associated with increased direct medical costs. Higher admission NIHSS scores were also associated with increased direct medical costs. Discharge with antiplatelet medication was associated with decreased direct medical costs.

The logistic regression results for indirect costs showed that having work before stroke was significantly associated with increased indirect costs as well as older age. A longer length of stay during the index event and higher admission NIHSS scores were also associated with increased indirect costs. On the other hand, UEBMI and URBMI were associated with decreased indirect costs.

Regression results for total cost primarily included variables from the direct medical and indirect cost regression results. Work status before stroke, which strongly influence indirect costs, also show the same trend in the total cost. A longer length of stay and higher admission of NIHSS score increased total cost, similar to their effects on direct medical and indirect costs. Higher 3-month EQ-5D utility was associated with decreased total cost.

DISCUSSION

This study is the first to investigate the comprehensive first-year cost of first-ever stroke using real-world patient data from 20 geographically diverse sites. In addition to quantifying the direct medical costs, our results also show that indirect costs contribute significantly to the economic burden of ischaemic stroke patients in China.

Our findings indicate that indirect costs play a significant role in driving the overall economic burden of

ischaemic stroke, and it is crucial to include them in cost-of-illness studies. This suggests that a wider range of costs should be taken into account when evaluating the economic value of stroke treatment or prevention measures. Adopting a societal perspective would offer a more complete understanding of the interventions' value and improve patients' access to them. While indirect costs are often considered irrelevant by payers, it is important for those in a single-payer healthcare system to consider the potential societal benefits of incorporating indirect costs in economic evaluations. These include reducing work productivity loss and informal care costs, which can have a positive impact on the economy and healthcare funding. Moreover, the societal perspective is relevant in many other medical conditions, such as rheumatoid arthritis and Alzheimer's disease, where effective interventions may be deemed cost-ineffective if only direct medical costs are taken into account.[20] Thus, adopting the societal perspective could lead to more efficient use of resources, promote innovation, and ultimately benefit patients and society as a whole.[20 21]

The majority of previous studies on the cost of ischaemic stroke in China have focused on the cost of acute treatment. These studies agree that the economic burden of stroke is substantial, although it is difficult to directly compare the specific costs due to a multitude of influencing factors, including time period, geographical region, patient characteristics, etc. Several studies reported index event hospitalisation costs of 12 000–18 000 CNY,[6–8 10] which are close to our finding of 19 111 CNY. In regards to follow-up costs, one study reported 3-month hospital and medication costs of 16 000 CNY among nationwide patients from 2006 of all stroke subtypes,[12] which is difficult to compare to our results due to different stroke types and length of follow-up.

The indirect cost of stroke has not been investigated as much as treatment cost. One study reported 12 000 CNY in indirect costs based on lifetime DALYs and the gross national product.[14] Another study reported 16 000 CNY in first-year indirect costs among seven IS patients with AF who were not retired at the time of the stroke, based on 2010 wage statistics.[10] Due to the difference in methodology and patient sample, these results are not directly comparable to ours.

Results from our univariate analysis showed that a 3-month mRS score of 3–5, which is considered a disabling stroke, was associated with significantly increased costs, consistent with previous literature.[13 22–25] Previous studies have noted that this finding is meaningful because medical interventions can directly act on the extent of disability,[25–27] unlike factors such as patient characteristics and initial disease severity. Evaluations of acute stroke treatments with a high initial cost should take into account the potential cost offsets due to improvements in 3-month mRS scores.[24 25]

Based on regression results, we may summarise that direct medical cost is influenced by three aspects, namely, patient purchasing power, healthcare utilisation and disease-related factors (eg, severity and recurrence). Patients with rural cooperation medical insurance are usually less wealthy, while self-paying patients and patients with higher family income would be able to afford more treatment, which explains the negative influence of the former factor and the positive influence of the latter two factors.

Indirect costs were strongly influenced by the patient's work status before stroke, as patients who did not work would not have any productivity loss. UEMBI and URBMI, which signify an urban patient, were associated with lower indirect costs. This may be due to more convenient access to follow-up healthcare in urban areas, demanding less of the patients' and caretakers' time.

It was interesting to find that higher 3-month EQ-5D utility was a significant predictor of decreased total cost. Dohl *et al* also found that as a generic measure of health-related quality of life, EQ-5D performed as well as more detailed clinical outcome measures (such as mRS, Barthel index, gait speed, etc) in predicting healthcare costs.[28] Previous work showed that publicly funded care (home care, nursing home and physiotherapists) could be substituted by care provided by cohabitants.[29] Under the cost framework utilised in our study, this means that patients with low EQ-5D utility may choose interchangeably between using more rehabilitation services (direct medical cost), home care services (direct nonmedical cost) or informal care (indirect cost). This may explain why EQ-5D utility was an independently significant predictor of total cost but not direct medical or indirect costs.

This study has several limitations. First, several cost components were based on patient recall of events from several years prior, which may lead to inaccuracy. In addition, the exclusion of patients who were unable to communicate—likely those more severely affected—may lead to an underestimation of actual costs. Another potential contributor to the underestimation of costs is the exclusion of patients who underwent follow-up hospital consultations or hospitalisations but were missing cost data for these visits. These patients had higher admission NIHSS scores, likely implying higher direct medical costs. Furthermore, by definition, these excluded patients all incurred in-hospital follow-up costs, while some patients in the final sample had no such costs because they did not have any follow-up hospital visits. Therefore, these excluded patients would have higher costs.

CONCLUSION

This study showed that the economic burden of ischaemic stroke is significant, consistent with previous studies. Notably, indirect costs are a non-negligible driver of the total cost. Compared with previous studies, this study has broader geographic coverage, a longer timescale and a more holistic consideration of cost types.

Contributors X M had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. XM formulated the study concept and designed the studies; WL, AW and QW wrote and edited the manuscript; RW, SW, YH, JL and JJ contributed to the acquisition of data; QX and YJ interpreted data, reviewed; HL and YW conducted research supervision and organisation for the project.

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