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Incidence and cost of hemolytic uremic syndrome in urban China: a national population-based analysis

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Abstract

Background: HUS is a severe syndrome that imposes a substantial burden on patients and their families, furthermore, it's the leading cause of acute kidney failure in children. However, data on the epidemiology and disease burden of HUS are limited in Asia, including in China. We aimed to estimate the incidence and cost of HUS in China.

Methods: Data on HUS from 2012 to 2016 were extracted from the databases of the Urban Employee Basic Medical Insurance (UEBMI) and the Urban Resident Basic Medical Insurance (URBMI). All cases were identified by the ICD code and Chinese diagnostic terms. The national incidence rates in 2016 were estimated and stratified by sex, age and season; the associated medical costs were also calculated.

Results: The crude incidence was 0.66 per 100,000 person-years (95% CI: 0.57 to 1.06), and the standardized incidence was 0.57 (0.19 to 1.18). The highest incidence was observed in patients younger than 1 year old (5.08,95% CI: 0.23 to24.87). Meanwhile, the incidence was 0.38 per 100,000 person-years (95% CI: 0.13 to 0.75) in patients younger than 5 years old, and 0.29 per 100,000 person-years (95% CI: 0.09 to 0.57) in patients younger than 18 years old. The season with the highest incidence was autumn, followed by winter. The average cost was 1.75 thousand US dollars per patient, which was higher than the national average cost for all inpatients in the same period.

Conclusions: The incidence of HUS in our study was lower than those in the most developed countries, and with different age and season distribution in incidence, which may suggest that the cause of HUS in China may be different from that elsewhere. Due to insufficient knowledge of physicians and lacking laboratory facilities required for an accurate diagnosis, the incidence rate of HUS may be underestimated. In view of the healthcare economic burden of HUS, further analyses and supports are needed in the future.

Introduction

Hemolytic uremic syndrome (HUS), which was first described in the 1950s,(1) is a severe disease. Most HUS cases are caused by Shiga toxin-producing E. coli (STEC) infections; these cases are called typical HUS, accounting for 70 to 90% of all cases,(2-4) and typical HUS mainly affects children. (5) The remaining HUS cases are referred to as atypical HUS (aHUS), which is more common in adults. The mechanism underlying aHUS includes susceptibility due to genetic background and etiologic triggers, such as non-STEC infections, drugs, pregnancy, malignant hypertension, and other medical conditions.(6) HUS is the leading cause of acute kidney failure in children. 50% of patients require dialysis, and 25% have neurologic involvement, including seizures and coma.(7, 8) Although the HUS-related mortality rate in children in industrialized countries has decreased, 3 to 5% of patients still die during the acute phase of STEC-HUS, and approximately 12% of them progress to end-stage renal disease (ESRD). Most patients with aHUS have a poor outcome; up to 50%~60% of these patients progress to ESRD or develop irreversible brain damage, and 25% die during the acute phase of the disease.(9) In addition, patients with

HUS incur high medical expenses, and the total direct cost was reported to be 17,553.39 US dollars t in 2005 for each patient in Argentina.(10)

The annual incidence of STEC-HUS varies in different countries. The overall incidence of STEC-HUS is estimated to be 2.1 cases per 100,000 person-years in the United Kingdom and 2.7 cases per 100,000 person-years in the United States,(11) and 0.07 cases per 100,000 person-years in Australia.(12) The incidence of aHUS in children is approximately 5%-10% that of STEC-HUS.(13) For all ages, incidence of aHUS was ranging from 0.23 to 1.9 cases per 100,000 person-years in Europe and Oceania.(14)

In China, the only relevant reports have been some single-center case series in children with HUS.(15, 16) Relevant data are also limited across Asia.(17) Because the epidemiology of HUS in China is unknown, we conducted a retrospective analysis to analyze the epidemiological and medical costs by reviewing the medical insurance database records of patients with HUS in China.

Methods

Data source

There are two main health insurance programs in the urban areas of China: The Urban Employee Basic Medical Insurance (UEBMI) for urban working and retired employees and the Urban Residence Basic Medical Insurance (URBMI) for urban residents without formal employment. The data regarding HUS were obtained from the claims information in these two databases. Briefly, the insured individuals' sociodemographic characteristics (age, sex), the International Classification of Diseases (ICD) code, the names of the major and secondary disease, and the total medical expenses were extracted for analysis. The study protocol was approved by the ethics review committee of the Peking University Health Science Center, and the need to obtain informed consent was waived. (IRB00001052-18012)

Study population

A retrospective national population-based study in 16 provinces of mainland China was performed from January 1st, 2012, to December 31th, 2016 (**Additional file 2**). Provinces excluded in this study were due to the following reasons: missing information on ICD codes or diagnostic terms; reporting policy exemptions; only one insurance type available; missing information or abnormal data reporting for crucial information, e.g., the primary diagnosis; short history of electronic records (< five years). The claims data used in this study were all anonymous.

HUS case identification

We identified potential HUS patients using ICD-9 codes (283.11, World Health Organization 10th, 1999), ICD-10 codes (D59.3, World Health Organization version 2010, 2010) and medical terms in Chinese. Natural language processing was utilized to standardize the text or codes. Diagnostic terms for each potential patient were independently reviewed by two clinical experts to confirm the diagnosis. If the diagnostic terms contained words like “undetermined”, “uncertainty”, “?”, “possible”, and “suspicious”, the patients were excluded; we only included patients with both ICD codes and Chinese terms.

Statistical analysis

All patients with STEC-HUS should undergo 2 to 5 years of follow-up to detect late-emerging sequelae,(18) and many patients with aHUS appear to have a life-long risk of recurrence.(6) We estimated the national incidence in only 2016 by setting up a four-year wash-out period (the longest period in our database) to reduce the impacts of prevalent HUS cases. The incidence estimate was also stratified by sex and age.

Incidences were calculated using a two-stage approach. First, we calculated the incidence in each province. The method was as follows: the denominator (N) used to calculate the annual incidence of HUS was the total number of patients in both the UEBMI and URBMI in each province during a given year. The numerator (M) was the estimated number of patients with HUS in the population used in the denominator in each province, with consideration of the issue of missing diagnostic values. In detail, the total enrolled population in each province was separated into three groups: subjects with no records of medical claims (N_1), subjects with complete diagnostic information in the claims records (N_2), and subjects with claim records but with missing diagnostic information (N_3). The patients with incident HUS (M_1) belonged to N_2. However, N_3 actually contained a certain number of patients with incident HUS (M_2). Thus, we adopted a method based on Poisson regression to estimate M_2. The detailed description of the method is presented in the Additional file 1. Then, a random-effects meta-analysis was used to pool the province-specific estimates to calculate the national average estimates. At this stage, the variance in the province-specific estimates was stabilized with the Freeman-Tukey double arcsine transformation.(19)

The incidence was expressed per 100,000 person-years at risk. In addition, 95% confidence intervals (CIs) were also calculated assuming a Poisson distribution. Age-standardized rates were estimated using the Chinese 2010 census data as the standard population. Sensitivity analyses were conducted to assess the robustness of the results: (1) including only observed cases to assess the lower bounds of the rates and (2) excluding the top 10% of provinces with missing diagnostic information. We also calculated HUS-associated costs and hospitalization costs including the total costs per year and the costs per patient per year. Costs were discounted by consumer price index (CPI) in each year to 2016 and converted into US dollars based on the 2016 RMB to US dollar exchange rate (period average). The CPI and exchange rate were from 2017 China statistical yearbook. Student’s t-test for continuous variables and the chi-square test for categorical variables were used for comparisons between male and female patients. All statistical analyses were conducted with Stata version 15.0, and 2-sided tests with $P < 0.05$ were considered statistically significant.

Results

A total of 0.37 billion residents in 16 provinces were included in this study (**Additional file 3)**. In addition, 1,060 patients received a confirmed diagnosis of HUS from 2012 to 2016, with a male to female ratio of 1.36:1. Most of the patients were Han Chinese (1001, 94.43%), with a disease onset in autumn and winter (606, 57.17%). In addition, the mean age (SD) of the male and female patients with HUS were 49.98 (15.66) and 49.21 (16.03) years, respectively (**Table 1**).

HUS incidence

The national incidence of HUS was 0.66 cases per 100,000 person-years (95% CI:0.37-1.06) in 2016. Standardized to the Chinese 2010 census population, the total adjusted incidence rate for HUS was 0.57 cases per 100,000 person-years (95% CI: 0.19-1.18). The incidence rate for males was 0.68 cases per 100,000 person-years (95% CI: 0.36 to 1.11), which was slightly higher than that of females (0.58 cases per 100,000 person-years, 95% CI: 0.29 to 0.99). The highest incidence occurred in patients younger than 1 year old (5.08 cases per 100,000 person-years, 95% CI, 0.23-24.87) and the lowest incidence was approximately 0.10 cases per 100,000 person-years (95% CI: 0.03-0.20), which was observed in the 12 to 17-year-old group. Meanwhile, the incidences in patients younger than 5 years old, 15 years old and 18 years old were 0.38 cases per 100,000 person-years (95% CI: 0.13 to 0.75), 0.35 cases per 100,000 person-years (95% CI: 0.13 to 0.66) and 0.29 cases per 100,000 person-years (95% CI: 0.09 to 0.51), respectively. The incidence was the highest in autumn (0.87 cases per 100,000 person-years, 95% CI: 0.48 to 1.37), followed by winter (0.74 cases per 100,000 person-years, 95% CI: 0.33 to 1.32) (**Table 2**)

Costs of HUS

The total costs associated with HUS over the study period were 2.28 million US dollars, with an average of 2.15 thousand US dollars per patient. The total costs increased approximately 2.64-fold from 318.65 thousand US dollars in 2012 to 840.70 thousand US dollars in 2016. The total hospitalization costs for HUS patients over the 5 years were 1,105.41 thousand US dollars and 1.75 thousand US dollars per patient. The total hospital cost first decreased in 2013 and 2014, and then increased. By 2016, it was twice as much as in 2012 (from 191.86 to 456.48 thousand US dollars). The cost per patient showed a similar trend. (**Figure 1)**.

Sensitivity analysis

Considering only observed cases, the lower bound of the national incidence was 0.30 cases per 100,000 person-years (95% CI 0.19–0.43). The results calculated by excluding the top 10% of provinces (Shandong and Jiangxi) with missing diagnostic information was 0.50 cases per 100,000 person-years (95% CI 0.27–0.81), which was similar to the main results reported above.

Discussion

In this large population-based study, we used a nationally representative database and calculated the incidence of HUS in China for the first time. The incidence rate of HUS was 0.66 cases per 100,000 person-years, with a peak incidence in children younger than 1 year old (5.08 cases per 100,000 person-years). The season with the highest incidence of HUS was autumn (0.9 cases per 100,000 person-years). The total cost associated with HUS was 456.86 thousand US dollars per year, with an average of 2.15 thousand US dollars per patient per year.

The incidence of HUS is likely to be related to the incidence of STEC infections, as these infections are the most common cause of HUS and are usually epidemic. The epidemiologic features of HUS have been thoroughly studied in many countries. A wide range of incidences of HUS have been reported, depending on the diagnostic criteria and populations studied. The incidence of HUS was 0.66 cases per 100,000 person-years in China, which is lower than the 2.1 cases per 100,000 person-years reported in in the United Kingdom and 2.7 cases per 100,000 person-years in the United States.(11) However, the annual incidence of HUS has been reported to be 0.07 cases per 100,000 person-years in Australia and 0.28 cases per 100,000 person-years in Iran,(20) which are lower than our results. These differences may be caused by the following factors. First, our estimation of the incidence of HUS was extrapolated from the Urban Medical Insurance databases. Some studies have shown that urban residents may have a lower prevalence of STEC-HUS than rural residents. Cows, which are a reservoir of STEC, are much rarer in urban areas. In addition, because of better sanitary conditions in urban areas, the risk of gastroenteric infections with STEC is also reduced.(5) North American seroepidemiological surveys have shown higher frequencies of antibodies against the O157 lipopolysaccharide among residents of rural areas than among those of urban areas.(21) Second, HUS is a rare disease. Many physicians may have difficulty diagnosing of HUS. Some hospitals in developing countries may lack the laboratories and facilities required for an accurate diagnosis.(22) These factors may have caused the incidence of HUS in China to be underestimated. Third, the influence of ethnic factors is still unclear. In different study populations, there may also be differences in the genetic propensity to develop HUS.(5, 23)

In our study, the incidence was slightly higher in males than in females, but the difference was not significant. aHUS can be triggered by cancer and hypertension.(24, 25) Both the crude incidence rate of cancer and the prevalence of hypertension in China are higher among men than women(26, 27), which may be the reason the incidence of HUS is higher in men than in women. However, many previous studies reported a higher incidence of HUS in women. The reasons for the higher incidence in female patients are unknown, but it may be partially attributable to the increased risk of HUS after E. coli O157:H7 gastroenteritis in females(28-30)and some cases of aHUS have been found to be associated with pregnancy.(31) However, the proportions of HUS cases that were STEC-HUS and pregnancy-associated aHUS in our study were unknown. More research in the future is needed on specific triggers in female and male Chinese patients.

The incidence rate was highest in children <1 year of age, with an annual incidence rate of 5.08 cases per 100,000 person-years. However, many previous reports from Europe and North America showed the age group younger than 5 years was the most frequently affected, and the age-specific incidence of HUS is similar to that of STEC.(32-34)The incidence rate of HUS in Chinese children younger than 5 years old (0.38 cases per 100,000 person-years) was lower than those in the United States and Western Europe

(1.57 to 3 cases per 100,000 person-years),(9, 32)but similar to the incidence of 0.49 cases per 100,000 person-years in Australia. This may be due to the low proportion of patients with STEC-HUS in our study. First, there are some different habits and customs in exposure to STEC; for example, Chinese people prefer fully cooked meat and boiled water. Second, the STEC infection rate is lower in urban areas than in rural areas.(5) At last, the peak season of HUS in our study was not summer, which is usually the season during which there is a high incidence of STEC infection. Therefore, we speculate that STEC may not be the main cause of HUS in China's urban population.

The peak incidence of HUS in our study was in autumn (0.9 cases per 100,000 person-years) and winter (0.7 cases per 100,000 person-years), which is different from other reports(35-37). In previous studies, HUS was most commonly triggered by STEC. The peak incidence of HUS was in summer, which is the peak incidence of STEC infections occurred. This significant seasonal difference suggests that STEC may not be the main cause of HUS in China, at least in the urban population. There are many risk factors for developing STEC-HUS that differ between China and Europe or the Americas, including eating habits, the local environment, meteorological conditions, and the population genetic background.(38) In China, we prefer fully cooked meat. Moreover, aHUS cases are relatively more common in adults. Most of the patients in our study were over the age of 18 years, accounting for approximately 98.1% of the total number, which was much higher than the proportion of adults with HUS reported elsewhere.(39) Furthermore, the lower pneumonia and influenza vaccination rates(40, 41) and high population density in China may lead to a relatively higher incidence of HUS associated with respiratory infections in autumn and winter. However, these speculations need investigation in the future.

The total cost incurred by HUS patients over our study period in the 16 provinces was 456.86 thousand US dollars per year, and the total expenses associated with the first hospitalization was 1,105.41 thousand US dollars. The average hospitalization cost for each HUS patient was 1.75 thousand US dollars, which is significantly higher than the national average hospitalization cost of 1.30 thousand US dollars per patient during the same period.(42) The total cost for each patient per year was 2.15 thousand US dollars per patient per year, which was also apparently higher than the national average medical care cost of urban residents (250 US dollars per patient).(42)The treatment of HUS includes supportive treatment, antibiotics, plasma infusion, plasma exchange, renal replacement therapy (CRRT or dialysis), and treatment for neurologic involvement. Most of these patients have to pay these high medical expenses. For example, the expense of single plasma exchange or CRRT session is approximately 1.50 thousand US dollars in China, and some patients may need to receive multiple treatments before recovery. In addition, eculizumab has been successfully used in patients with HUS in many countries but is still not available in China. This drug is expensive (for example the treatment of a child with a body weight of 30 kg would cost 350,000 US dollars per year), which imposes a significant economic burden.(32) Medical costs due to HUS may increase significantly after the introduction of eculizumab to the Chinese market in the near future. Finally, it is worth noting that some reports have highlighted that there has been an increase in morbidity due to HUS.(11) In this new situation, the prevalence of HUS becomes an important indicator for healthcare planning.

China's basic medical insurance system can cover approximately 95% of the population, and the combined basic population structure was close to the distribution in the Chinese 2010 census population data. However, the use of a medical insurance database still results in certain limitations. First, our data were extracted from urban populations. However, as STEC infection is more common in rural areas, we may have underestimated the annual incidence of STEC-HUS in China. Second, HUS is a rare disease, and many physicians in developing countries may not have enough clinical experience with this disease. The incidence rates of HUS in hospitals lacking diagnostic capabilities are probably underestimated. Third, newborns may not be insured for various reasons, but the insurance policy in China allows newborns to be covered by medical insurance for the first 90 days after birth. Moreover, the triggers for HUS in our patients were also not available. The current recommended diagnostic tests for HUS (such as Shiga toxin assay, Complement Factor H level, membrane cofactor protein expression, ect.) are not feasible for many hospitals of China. To develop better preventive measures and treatment,

Conclusion

In conclusion, our study provides the first population-based study of the incidence of HUS in China. Given the burden of HUS on patients and the medical insurance system, our investigation is of considerable importance for health care providers in China. In addition, our research also suggests that the cause of HUS in China may be different from that elsewhere, and physicians in China may underestimate the incidence due to insufficient understanding of HUS. On viewing from these perspectives, further etiological studies, government supports, and continuous education in healthcare are needed in the future.

Abbreviations

HUS: hemolytic uremic syndrome

UEBMI: urban employee basic medical insurance

URBMI: urban resident basic medical insurance

ICD: International Classification of Diseases

CI: confidence interval

SD: Standard deviation

CPI: consumer price index

STEC: Shiga toxin-producing E. coli

ESRD: end-stage renal disease

CRRT: continuous renal replacement therapy

COL1A1: collagen Type Iα1 gene

PAR: pseudoautosomal region

Declarations

Ethics approval and consent to participate

The study protocol was approved by the ethics review committee of the Peking University Health Science Center, and the need to obtain informed consent was waived. (IRB00001052-18012)

Consent for publication

Not applicable.

Availability of data and materials

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Competing interests

The authors declare that they have no competing interests.

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Author contributions

Zhan had full access to all the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Zhan, Ding, Shengfeng Wang, Gao.

Drafting of the manuscript: Feng, Ke Xu.

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Data interpretation: Shengfeng Wang, Ding, Ke Xu, Feng, Gao, Zhan.

Obtained funding: Zhan, Ding, Shengfeng Wang.

Administrative, technical, or material support: Ding, Ke Xu, Fang Wang, Zhong.

Supervision: Zhan, Ding, Shengfeng Wang, Gao.

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Tables

Table 1. Selected characteristic of HUS patients grouped by sex

		Total	Male	Female	Comparison between sex	
					Statistics	P value
Number		1060	610	450		
Age, y					-0.782	0.217
	Median age (Q_{25}, Q_{75})	50(39, 61)	50 (40, 61)	49 (39, 61)		
	Mean (SD)	49.65(15.82)	49.98 (15.66)	49.21 (16.03)		
Age group, n (%)					9.926	0.45
	<1	5 (0.47)	2 (0.33)	3 (0.67)		
	1~5	5 (0.47)	4 (0.66)	1 (0.22)		
	6~11	7 (0.66)	4 (0.66)	3 (0.67)		
	12~17	3 (0.28)	2 (0.33)	1 (0.67)		
	18~29	94 (8.87)	49 (8.03)	45 (10.00)		
	30~39	162 (15.28)	89 (14.59)	73 (16.22)		
	40~49	250 (23.58)	143 (23.44)	107 (23.78)		
	50~59	242 (23.83)	149 (24.43)	93 (20.67)		
	60~69	178 (16.79)	99 (16.23)	79 (17.56)		
	70~79	94 (8.87)	61 (10.00)	33 (7.33)		
	>=80	20 (1.89)	8 (1.31)	12 (2.67)		
Ethnicity, n (%)					6.040	0.05
	Han	1001 (94.43)	585 (95.90)	416 (92.44)		
	Other	59 (5.57)	25 (4.10)	34 (7.56)		
Season, n (%)					2.189	0.53
	Spring	189 (17.83)	102 (16.72)	87 (19.33)		

	Summer	265 (25.00)	159 (26.07)	106 (23.56)
	Autumn	277 (26.13)	164 (26.89)	113 (25.11)
	Winter	329 (31.04)	185 (30.33)	144 (32.00)

Table 2. Crude incidence of HUS grouped by sex, age-group and season (units: cases/100,000 person-years)

Groups		Incidence
Total		0.66 (0.35,1.06)
Sex	Male	0.68 (0.36,1.11)
	Female	0.58 (0.29,0.99)
Age group	<1	5.08 (0.23,24.87)
	1~5	0.47 (0.15,0.97)
	6~11	0.23 (0.07,0.48)
	12~17	0.10 (0.03,0.20)
	18~29	0.60 (0.29,1.02)
	30~39	0.63 (0.29,1.09)
	40~49	0.47 (0.01,0.80)
	50~59	0.51 (0.21,0.93)
	60~69	0.65 (0.25,1.22)
	70~79	0.81 (0.30,1.56)
	>=80	1.05 (0.42,1.95)
	<5	0.38 (0.13,0.75)
	<15	0.35 (0.13,0.66)
	<18	0.29 (0.09,0.57)
Season	Spring	0.58 (0.26,1.02)
	Summer	0.58 (0.29,0.96)
	Autumn	0.87 (0.48,1.37)
	Winter	0.74 (0.33,1.32)

Figures

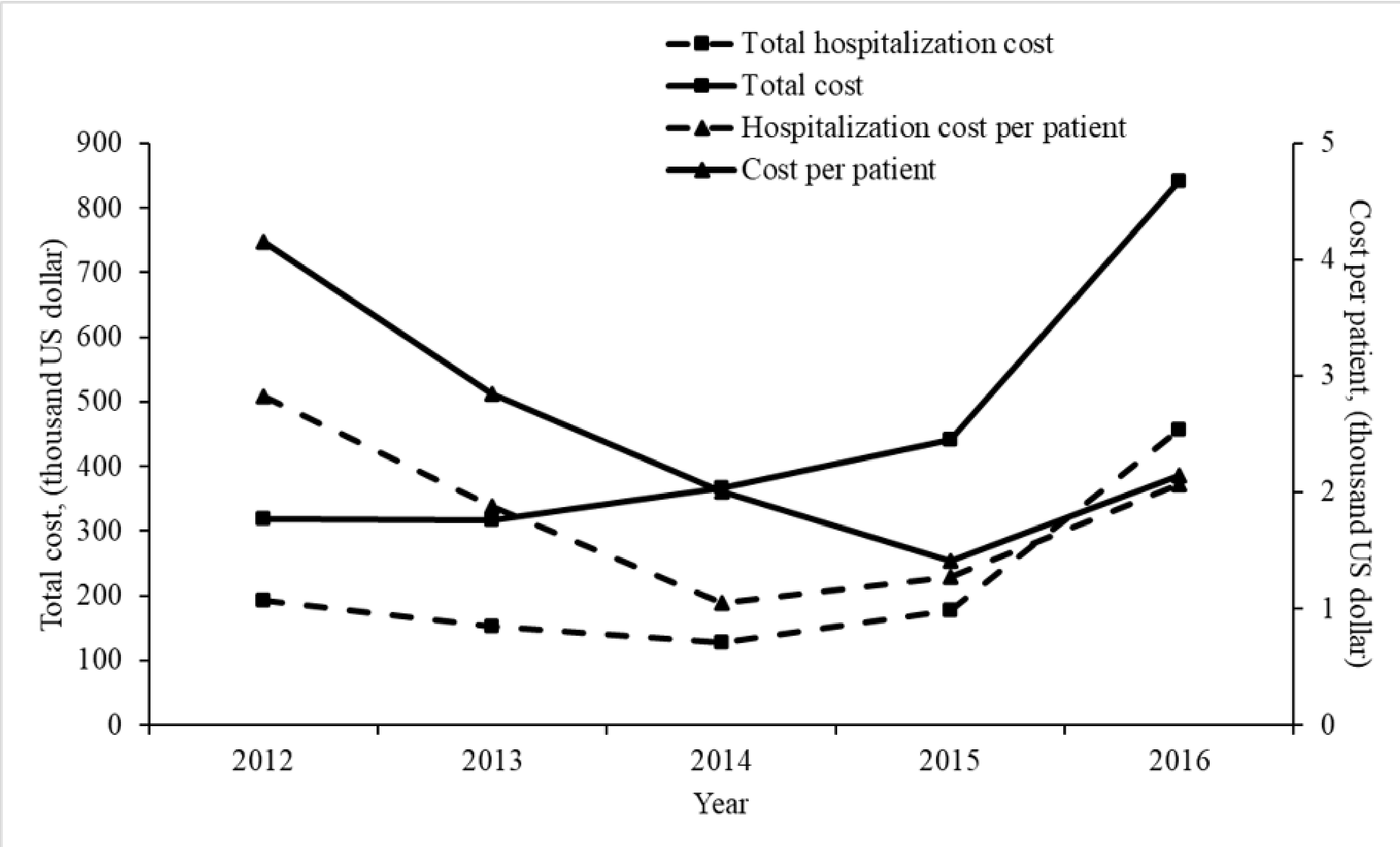

Figure 1

Medical expenses incurred by HUS patients in China from 2012 to 2016

Supplementary Files

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