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ORIGINAL RESEARCH

Disease Burden and Associated Factors in Chinese Patients with Tuberous Sclerosis Complex: Results of a Patient and Caregiver Survey

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Objective: Tuberous Sclerosis Complex (TSC) is a rare autosomal dominant genetic disorder primarily characterized by neurological symptoms. This study aimed to evaluate the current disease burden in Chinese patients with TSC and to identify the potential influencing factors.

Methods: A cross-sectional study design was employed using an online questionnaire survey. The questionnaire covered demographics, diagnosis and treatment status, medication use, and disease burden. Descriptive statistics were used to summarize the data, and multivariate logistic regression analysis was performed to examine factors influencing the disease burden in pediatric and adult patients with TSC.

Results: The survey involved a total of 840 patients or their caregivers, comprising 691 pediatric and 149 adult patients, with an average age at diagnosis of 1.77 years for pediatric patients and 15.28 years for adult patients. The most prevalent clinical manifestations were seizures (75.1% in pediatric, 43.6% in adult), brain calcification spots/nodules (87.8% pediatric, 82.5% adult), and hypomelanotic macules (89.5% pediatric, 72.4% adult). Intellectual disability (ID) was reported in 29.6% of pediatric patients and 19.4% of adult patients. Catastrophic health expenditure (CHE) was reported by 29.6% of patients. Factors influencing the disease burden included ID, misdiagnosis, and use of anti-seizure medications (ASMs) and mammalian target of rapamycin (mTOR) inhibitors for pediatric patients or educational attainment, medication use (such as ASMs and mTOR inhibitors), and ID for adult patients.

Conclusion: The study demonstrated that Chinese patients with TSC are confronted with a considerable disease burden. Comprehensive care strategies, tailored educational support for pediatric patients, and multidisciplinary approaches for early diagnosis are crucial for managing TSC.

Keywords: tuberous sclerosis complex, disease burden, cost of illness, medical expenses, economic burden, intellectual disability, quality of life, China

Background

TSC is a rare genetic disorder caused by mutations in the TSC1 or TSC2, contributing to progression of benign tumors in multiple organs, including the brain, skin, heart, and kidneys.[1] The global incidence of TSC ranges from 1/10,000 to 1/6000, with significant variability in clinical manifestations and disease severity.[2,3] The most common neurological features include epilepsy, intellectual disability (ID), and autism spectrum disorders (ASD), which profoundly impact patients' quality of life.[4] Epilepsy, reported in approximately 70–80% of TSC patients, is often refractory to treatment

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and increases cognitive and behavioral challenges.[4] Findings by Islam MP[2] underscored the disproportionate disease burden faced by TSC patients in resource-limited settings, where delays in diagnosis and treatment are prevalent. Such delays significantly amplify the neurological and psychiatric manifestations of the disease (most notably epilepsy, cognitive impairment, and autism spectrum disorders) exacting a profound toll on both patients and their families. Some manifestations, such as subependymal giant cell astrocytomas (SEGAs), renal angiomyolipomas (AMLs), and lymphangioleiomyomatosis (LAM), further complicate the clinical management of TSC.[5] The phenotypic diversity and dynamic progression of TSC pose significant challenges for understanding its disease burden and developing effective management strategies.[6]

The burden of TSC extends beyond clinical manifestations to significant economic costs.[7] Studies indicate that the total medical expenses for a pediatric patient with TSC over a three-month period are approximately 4949 euros, comprising medication, hospitalization, and adjunctive therapy costs.[8] On the other hand, indirect costs, largely attributed to caregivers taking leave, resigning, or reducing work hours to care for affected children, serve to exacerbate the economic strain on families.[9] Research by Chu et al revealed that pediatric patients with TSC incur considerable annual expenses in surgical procedures (HKD 10,989.1), emergency department visits (HKD 903.1), and intensive care unit admissions (HKD 2737.0).[10] Epilepsy-related costs for TSC patients in the United States are significantly higher than those for epilepsy patients without TSC, with prescription drug costs increasing by $14,639 per person and medical service expenses rising by $16,838 per person.[8] TSC treatment costs affect not only family economic stability but also the psychological well-being of caregivers, potentially leading to anxiety and depression.[9] These challenges ultimately compromise the quality of life for affected families.

An overall assessment of the disease burden in TSC treatment is essential for developing optimal management strategies for patients.[11] However, the extensive phenotypic diversity and dynamic clinical progression of TSC present significant challenges in investigating the disease burden due to the heterogeneity of the condition. Currently, research on the disease burden of Chinese TSC patients remains relatively limited. Gaining an in-depth understanding of the disease burden and related factors among Chinese TSC patients holds significant practical and theoretical value for developing precise diagnostic and therapeutic strategies and improving patient care. The uniqueness of this study lies in a large, representative sample of Chinese patients, with an in-depth analysis of the socioeconomic and clinical factors influencing the disease burden in this population. It aims that the findings can provide evidence-based support for optimizing TSC diagnostic and treatment standards and alleviating the burden on patients and their families.

Methods and Materials

A cross-sectional, non-interventional online survey was conducted to collect data from Chinese patients with TSC from July to September 2023. The survey protocol and recruitment strategy used in this study were developed by the research team. Participants were instructed to independently complete the online questionnaire, with results recorded in real-time. The questionnaire, developed based on expert consultation and a comprehensive literature review, was tested with 20 participants to ensure clarity. Feedback was utilized to enhance its design. The incorporation of validation tools, precise instructions, and guaranteed anonymity facilitated the collection of accurate and truthful responses. The study strictly adhered to the guidelines of the *Declaration of Helsinki*, was approved by the Institutional Ethics Committee of Shenzhen Children's Hospital (approval number: 201900507), and complied with international ethical standards. The survey was conducted anonymously, and all participants provided informed consent online before completing the questionnaire. The average time to complete the survey was approximately 20 to 30 minutes.

Study Participants

The study participants included patients with TSC or their primary caregivers who voluntarily joined the TSC disease burden survey from July to September 2023. All participants were registered members of the TSC Alliance China, the largest national organization supporting patients with TSC in China. Participants were recruited through the center's Email and social media channels.

Inclusion criteria were: (1) patients with a confirmed diagnosis of TSC, with no age restrictions; (2) patients under 18 years old with a primary caregiver (aged ≥18 years) who was willing to complete the online survey on their behalf; (3)

patients and caregivers who could read Chinese and complete online surveys; (4) those who agreed to provide online informed consent. Exclusion criteria were: individuals with cognitive impairments or other health conditions that prevented them from completing the TSC-related online surveys, or those who refused to provide online informed consent. Eligible participants were directed to a consent page where they could indicate their agreement to participate by selecting the option "I agree to participate" rather than providing written informed consent. The survey was completed by patients with TSC over 18 years old or by caregivers of patients of any age.

Survey Components

The survey questionnaire was specially designed for this study and comprised three primary sections: (1) Demographic Information: Age, gender, medical expenditure ratio (MER) for both pediatric and adult patients, marital status (for adults), educational attainment (for adults), educational status (for children), and employment status (for adults); (2) Disease-related Information: Intellectual disability (ID), diagnostic odyssey, age at diagnosis, history of misdiagnosis, genotype, brain surgery, ketogenic diet, types of ASMs used, and information on the use of inhibitors; (3) Manifestations: Seizures, brain calcification spots/nodules, hypomelanotic macules, shagreen patch, angiofibromas, multiple renal cysts, renal angiomyolipomas (RAMLs), and lymphangioleiomyomatosis (LAM). The questionnaire was meticulously structured to capture both the sociodemographic characteristics of the patients and the specific aspects of their TSC conditions. This design facilitated a thorough assessment of the complex and multifaceted burden associated with TSC.

Disease Burden Assessment Indicators

Based on a systematic literature review and expert consultation, this study identified several core indicators across multiple dimensions to assess the disease burden. It aim to comprehensively reflect the impact of TSC on patients and their families comprehensively. These indicators are as follows.

MER for Children and Adults

In this study, out-of-pocket expenditure (OOP) refers to the amount paid by households for medical services or the net expenditure after deducting any insurance reimbursements. It typically includes consultation fees, medical costs, and hospitalization expenses.[12] MER refers to the proportion of household income spent on medical expenses, calculated as MER = (OOP / Annual Household Income) × 100%. According to the World Health Organization (WHO), CHE is a situation where a household's OOP equals or exceeds 40% of its capacity to pay, which may result in severe economic hardship and compromise the family's ability to satisfy other essential demands.[13] Three categories were established: ① Non-CHE 1: MER < 20%; ② Non-CHE 2: MER 20–40%; ③ CHE: MER ≥ 40%.

Educational Status (Pediatric)

Broadly, the educational status of pediatric patients can be categorized into two distinct groups delineated by their current educational engagement and circumstances. ① Formal Education Enrollment: Encompasses children and adolescents who are actively participating in structured educational settings, spanning primary, secondary, and potentially tertiary education levels. ② Education Disruption Due to Illness (EDDI): A pivotal group including pediatric patients whose educational trajectory has been significantly impacted, interrupted, or ceased due to health-related complications.

Marital Status (Adults)

The marital status of adult patients in this study was categorized into two distinct groups based on their current matrimonial situation: Single and Married. The Single group includes patients who do not currently have a spouse. It covers individuals who have never married and those who are divorced or widowed. The Married group refers to patients with a legally recognized spouse. It includes individuals who are formally registered as married, as well as those in de facto unions.

Employment Status (Adults)

Based on current occupational engagement and economic activity, adult patients can be employed and unemployed. The Employed group includes individuals actively engaged in paid work, whether on a full-time or part-time basis, including those who are self-employed. The Unemployed group refers to individuals not currently engaged in paid work. It

includes those actively seeking employment and those outside the labor force due to reasons such as disability, retirement, or personal choice.

Determinants Influencing Disease Burden Indicators

This section analyzes the determinants that influence key disease burden indicators, such as MER for both pediatric and adult patients, educational status for pediatric patients, as well as marital status and employment status for adults. These indicators are subject to the influences of the following independent variables.

Educational Attainment

① Primary Education or Below: Patients with no formal education or those who have completed only primary school. ② Junior High School Education: Patients who have completed junior high school or an equivalent level of education. ③ Senior High School: Patients who have completed senior high school or an equivalent qualification. ④ Undergraduate and Higher Education: Participants who have obtained an undergraduate degree or higher academic qualifications.

Intellectual Disability

It refers to an intelligence quotient (IQ) below two standard deviations from the mean IQ or an IQ score of less than 70. The level of intellectual functioning is evaluated using standardized IQ tests and comprehensive assessments of adaptive behaviors.[14]

Misdiagnosis

① Misdiagnosis: Patients who received an incorrect or inaccurate initial diagnosis, which was later corrected after further evaluation. ② Accurate diagnosis: Patients who received a correct initial diagnosis, which remained consistent throughout their medical evaluation and treatment.

Genotype

① TSC1 Positive: Patients with a definitive diagnosis of a mutation in the TSC1. ② TSC2 Positive: Patients with a definitive diagnosis of a mutation in the TSC2. ③ Genetic Testing Negative: Patients with no identified mutations in the TSC1 or TSC2.

① 0 ASMs: Patients who were not prescribed with any anti-seizure medications. ② 1–3 ASMs: Patients who were prescribed with one to three concurrent anti-seizure medications. ③ 4–6 ASMs: Those who were prescribed with four to six concurrent anti-seizure medications. ④ ≥ 7 ASMs: Patients who were prescribed with seven or more concurrent anti-seizure medications.

mTOR Inhibitors

① Active Use: Patients with ongoing administration of mTOR inhibitors. ② Non-Use: Patients with no administration of mTOR inhibitors.

Statistical Analysis

Data were statistically analyzed using R software (version 4.2.2). For categorical variables, frequencies and percentages were calculated to describe data distribution. The Shapiro–Wilk test was used to assess the normality of continuous variables. Normally distributed data were expressed as mean ± standard deviation (SD), while non-normally distributed data were reported as median and interquartile range (IQR). For categorical dependent variables, binary logistic regression analyses and ordinal logistic regression were utilized to evaluate their relationships with the outcome variables. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to quantify the strength of associations. No imputation methods were applied for missing data. Statistical significance was determined using a threshold of $P < 0.05$, and the significance level for all statistical analyses was set at a two-sided $\alpha = 0.05$.

Results

Current Status of Disease Burden for TSC

There were 840 survey respondents, including 691 (82.3%) caregivers of pediatric patients, 46 (5.5%) caregivers of adult patients, and 103 (12.3%) adult patients providing self-cares. The final analytic data were from 691 pediatric patients and 149 adult patients. In term of geographical distribution, 840 patients included 104 from Guangdong Province, 92 from Shandong Province, and the remaining 644 from 21 other provinces. Figure 1 illustrates the geographical distribution of the study participants via a map representation.

Sociodemographic Characteristics

The median age of all patients with TSC was 7 years (IQR: 4–14 years), with a median age of 6 years (IQR: 4–9 years) for pediatric patients and 29 years (IQR: 25–34 years) for adult patients. Gender distribution analysis revealed a male predominance in the pediatric group (54.2%) compared to the adult group (32.2%). Conversely, females constituted the majority in the adult group (67.7%) compared to the pediatric group (45.7%). ID was reported in 29.6% of pediatric patients and 19.4% of adult patients. Regarding educational status, 45.9% of pediatric patients were of preschool age, 44.7% were enrolled in formal education, and 9.4% experienced EDDI. Among adult patients, 10.0% had primary school education or below, 28.8% had completed junior high school, 33.5% had attained senior high school education, and 27.5% had undergraduate or higher education. In the adult group, 46.3% were married, while 53.7% were single. The MER was ≤ 40% for 57.9% of all patients and > 40% for 42.1%, as indicated in Table 1.

Diagnostic and Therapeutic Profiles

In the pediatric group, 60% were diagnosed with TSC before the age of one year, with an average age at diagnosis of 1.77 years (1.77 ± 2.19 SD, range: 8 weeks gestation to 13 years). In the adult group, the average age at diagnosis was 15.28 years (15.28 ± 11.78 SD), with 61% being diagnosed before the age of 18. Misdiagnosis was reported in 39.3% of

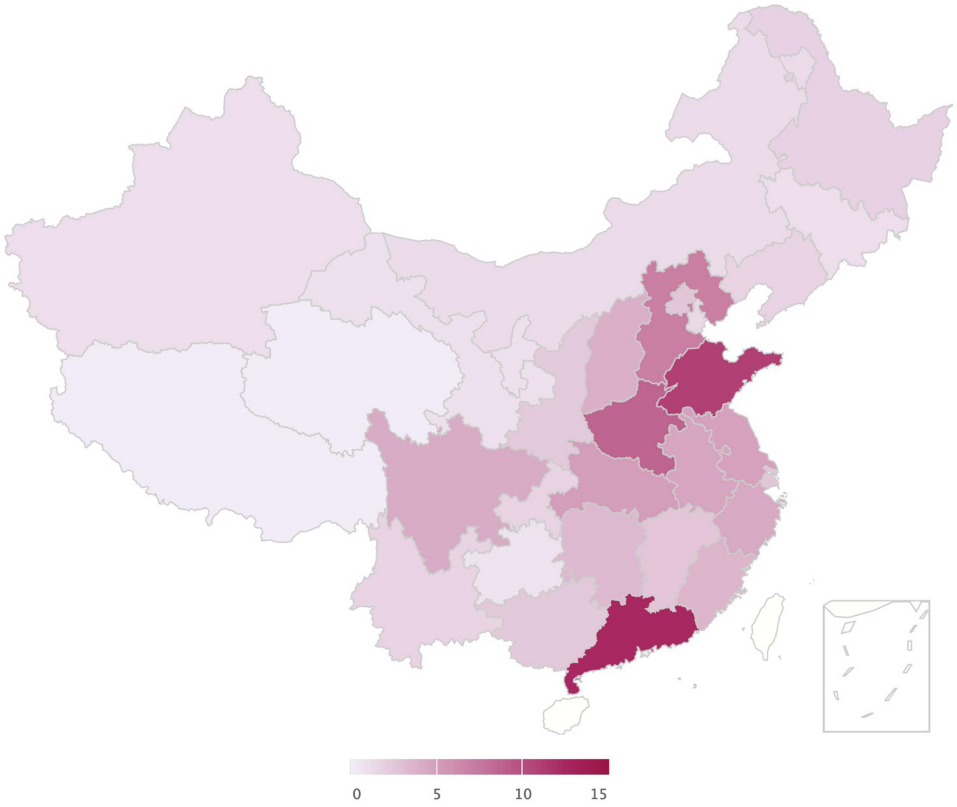

Figure 1 Geographical Distribution of TSC Patients in China.

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Table 1 SC Patient Sociodemographic Information

Items	Patient Age ≤ 18 Years (n = 691)	Patient Age > 18 Years (n = 149)	Total Patients (n = 840)
Age [y, M (P25, P75)]	6 (4, 9)	29 (25, 34)	7 (4, 14)
Gender, n (%)			
Mail	375 (54.2)	48 (32.2)	423 (50.3)
Femail	316 (45.7)	102 (67.7)	417 (49.6)
ID, **n (%)**	205 (29.6)	29 (19.4)	234 (27.8)
Educational Status (Age ≤ 18 Years), n (%)			
Pre-School Age	317 (45.9)		
Formal Education Enrollment	309 (44.7)		
EDDI	65 (9.4)		
Educational Attainment (Age > 18 Years), n (%)			
Primary School and Below		15 (10.0)	
Junior High School		43 (28.8)	
Senior High School		50 (33.5)	
Undergraduate and Higher Education		41 (27.5)	
Marital Status, n (%)			
Married		69 (46.3)	
Single		80 (53.7)	
Employment Status, n (%)			
Unemployed		16 (10.7)	
Employed		133 (89.3)	
MER, n (%)			
< 20%	110 (15.9)	37 (24.8)	147 (17.5)
20–40%	370 (53.5)	74 (49.6)	444 (52.8)
> 40%	211 (30.5)	38 (25.5)	249 (29.6)
Misdiagnosis, n (%)	272 (39.3)	95 (63.7)	367 (43.6)
Diagnostic odyssey, n (%)			
0–1 month	261 (37.7)	14 (9.3)	275 (32.7)
2–6 months	222 (32.1)	18 (12)	240 (28.5)
6–12 months	73 (10.5)	14 (9.3)	87 (10.3)
1–3 years	73 (10.5)	19 (12.7)	92 (10.9)
3–5 years	30 (4.3)	6 (4.0)	36 (4.2)
More than 5 years	32 (4.6)	78 (52.3)	110 (13)

(*Continued*)

Table 1 (Continued).

Items	Patient Age ≤ 18 Years (n = 691)	Patient Age > 18 Years (n = 149)	Total Patients (n = 840)
Genotype, n (%)			
Not Tested	109 (15.7)	40 (26.8)	149 (17.7)
TSC1 Positive	130 (18.8)	24 (16.1)	154 (18.3)
TSC2 Positive	384 (55.5)	69 (46.3)	453 (53.9)
Genetic Testing Negative	68 (9.8)	16 (10.7)	84 (10)
ASMs, n (%)			
0 ASMs	40 (5.7)	73 (48.9)	113 (13.4)
1–3 ASMs	429 (62.0)	49 (32.8)	478 (56.9)
4–6 ASMs	184 (26.6)	19 (12.7)	203 (24.1)
≥ 7 ASMs	38 (5.4)	8 (5.3)	46 (5.4)
Brain Surgery, n (%)	33 (4.7)	5 (3.3)	38 (4.5)
Ketogenic Diet, n (%)	4 (0.5)	0 (0)	4 (0.4)
mTOR Inhibitors, n (%)	527 (76.2)	94 (63)	621 (73.9)

Abbreviations: ID, Intellectual Disability; MER, Medical Expenditure Ratio; EDDI, Education Disruption Due to Illness; ASMs, Anti-seizure medications.

pediatric patients and 63.7% of adult patients. The diagnostic odyssey exhibited significant differences between the two groups, with 37.7% of pediatric patients and 9.3% of adult patients diagnosed within one month (0–1 month). Conversely, a diagnostic delay of over five years was reported in 52.3% of adult patients, compared to only 4.6% of pediatric patients. Genotypic analysis revealed *TSC2* positivity in 55.5% of pediatric patients and 46.3% of adult patients, while *TSC1* positivity was observed in 18.8% and 16.1% of pediatric and adult patients, respectively. 15.7% of pediatric patients and 26.8% of adult patients did not undergo genetic testing. With regard to ASM use, 62.0% of pediatric patients were prescribed 1–3 ASMs, in contrast to 32.8% of adults. Notably, 48.9% of adult patients did not receive any ASMs therapy, compared to only 5.7% of pediatric patients, as shown in Table 1.

Clinical Characteristics

Table 2 delineates the manifestations of TSC across pediatric (≤ 18 years) and adult (> 18 years) groups. In the pediatric group (n = 691), the most prevalent manifestations were hypomelanotic macules (89.5%), brain calcification spots/nodules (87.8%), and seizures (75.1%). Other notable manifestations included shagreen patches (39.9%), angiofibromas (39.7%), and cardiac rhabdomyomas (30.9%).

In the adult group (n = 149), the most frequently reported manifestations included angiofibromas (85.2%), brain calcification spots/nodules (82.5%), hypomelanotic macules (72.4%), and multiple renal cysts (72.4%). Additionally, shagreen patches were observed in 59.0% of adult patients. Notably, seizures had a higher prevalence in the pediatric group (75.1%) compared to the adult group (43.6%). Conversely, angiofibromas and multiple renal cysts exhibited substantially higher prevalence in adults (85.2% and 72.4%, respectively) than in pediatric patients (39.7% vs 19.2%). Additionally, LAM was predominantly observed in the adult group (32.8%) in contrast to the pediatric group (0.1%).

Factors Influencing the Current Disease Burden

Logistic regression models were employed to investigate the factors influencing the disease burden in both pediatric and adult patients. For pediatric patients, MER and educational status were designated as dependent variables,

Table 2 TSC Manifestations

Manifestations	Patient Age ≤ 18 Years (n= 691)	Patient Age > 18 Years (n = 149)	Total Patients (n = 840)
Seizures, n (%)	519 (75.1)	65 (43.6)	584 (69.5)
Brain Calcifications Spots/Nodules, n (%)	607 (87.8)	123 (82.5)	730 (86.9)
Hypomelanotic macules, n (%)	619 (89.5)	108 (72.4)	727 (86.5)
Shagree patch, n (%)	276 (39.9)	88 (59.0)	364 (43.3)
Angiofibromas, n (%)	275 (39.7)	127 (85.2)	402 (47.8)
RAMLs, n (%)	133 (19.2)	108 (72.4)	241 (28.6)
Mutiple renal cysts, n (%)	45 (6.5)	40 (26.8)	85 (10.1)
Cardiac Rhabdomyoma, n (%)	214 (30.9)	20 (13.4)	234 (27.8)
LAM, n(%)	1 (0.1)	49 (32.8)	50 (5.9)

Abbreviations: RAMLs, Renal Angiomyolipomas; LAM, Lymphangioleiomyomatosis.

whereas MER, marital status, and employment status were selected for adult patients. Independent variables were assigned based on their statistical significance ($P < 0.05$) in the baseline analysis. For pediatric patients, the significant variables were ID, misdiagnosis, and use of ASMs and mTOR inhibitors (Table 3). The independent variables in the adult group incorporated ID, educational attainment, use of ASMs and mTOR inhibitors (Table 4). Ordinal logistic regression was adopted for MER, while binary logistic regression was applied to educational status, marital status, and employment status. To account for potential confounding effects, age and gender were controlled for in all analyses.

Table 3 Baseline Characteristics of Child Patients Stratified by MER and Educational Status

Item	MER (n = 691)					Educational Status (n = 374)*			
	> 40%	< 20	20%-40%	*P*	Missing (%)	EDDI	Formal Education Enrollment	*P*	Missing (%)
Gender, n (%)									
F	91 (43.10)	62 (56.40)	163 (44.10)	0.05	0	27 (41.50)	147 (47.60)	0.453	0
M	120 (56.90)	48 (43.60)	207 (55.90)			38 (58.50)	162 (52.40)		
Age (mean (SD))	6.37 (3.78)	7.29 (4.30)	7.08 (4.26)	0.076	0.1	10.13 (3.68)	9.77 (3.25)	0.422	0
ID, n (%)									
Non-Disability	124 (58.80)	92 (83.60)	270 (73.00)	< 0.001	0	17 (26.20)	208 (67.30)	< 0.001	0
Disability	87 (41.20)	18 (16.40)	100 (27.00)			48 (73.80)	101 (32.70)		
Misdiagnosis, n (%)									
Accurate diagnosis	116 (55.00)	82 (74.50)	221 (59.70)	0.003	0	24 (36.90)	187 (60.50)	0.001	0
Misdiagnosis	95 (45.00)	28 (25.50)	149 (40.30)			41 (63.10)	122 (39.50)		
Genotype, n (%)									
Genetic Testing Negative	18 (10.20)	9 (9.20)	41 (13.40)	0.151	15.8	5 (11.10)	38 (14.70)	0.805	19
TSC1 Positive	32 (18.10)	29 (29.60)	69 (22.50)			11 (24.40)	63 (24.40)		
TSC2 Positive	127 (71.80)	60 (61.20)	197 (64.20)			29 (64.40)	157 (60.90)		
ASMs, n (%)									
≥7 ASMs	16 (7.60)	6 (5.50)	16 (4.30)	< 0.001	0	13 (20.00)	17 (5.50)	< 0.001	0
0 ASMs	5 (2.40)	14 (12.70)	21 (5.70)			1 (1.50)	24 (7.80)		
1–3 ASMs	114 (54.00)	73 (66.40)	242 (65.40)			24 (36.90)	190 (61.50)		
4–6 ASMs	76 (36.00)	17 (15.50)	91 (24.60)			27 (41.50)	78 (25.20)		
mTOR Inhibitors, n (%)									
Non-Use	39 (18.50)	41 (37.30)	84 (22.70)	0.001	0	19 (29.20)	58 (18.80)	0.084	0
Active Use	172 (81.50)	69 (62.70)	286 (77.30)			46 (70.80)	251 (81.20)		

Note: *The sample size for Educational Status (n = 374) is smaller than the total sample due to the exclusion of pre-school aged children.
Abbreviations: MER, Medical Expenditure Ratio; EDDI, Education Disruption Due to Illness; ID, Intellectual Disability; ASMs, Anti-seizure medications.

Table 4 Baseline Characteristics of Adult Patients Stratified by MER, Marital Status, and Employment Status

Item	MER (n = 149)					Marital Status (n = 149)				Employment Status (n = 149)			
	>40%	<20	20%-40%	p	Missing (%)	Married	Single	p	Missing (%)	Unemployed	Employed	p	Missing (%)
Gender, n (%)													
F	26 (68.40)	24 (64.90)	51 (68.90)	0.907	0	59 (85.50)	42 (52.50)	< 0.001	0	11 (68.80)	90 (67.70)	1	0
M	12 (31.60)	13 (35.10)	23 (31.10)			10 (14.50)	38 (47.50)			5 (31.20)	43 (32.30)		
Age (mean (SD))	31.05 (8.40)	30.41 (6.20)	29.88 (8.49)	0.759	0	35.62 (7.41)	24.82 (3.90)	< 0.001	0	31.31 (8.67)	30.19 (7.86)	0.593	0
ID, n (%)													
Non-Disability	28 (73.70)	35 (94.60)	57 (77.00)	0.041	0	60 (87.00)	60 (75.00)	0.119	0	16 (100.00)	104 (78.20)	0.081	0
Disability	10 (26.30)	2 (5.40)	17 (23.00)			9 (13.00)	20 (25.00)			0 (0.00)	29 (21.80)		
Education Attainment													
Undergraduate and Higher Education	6 (15.80)	17 (45.90)	18 (24.30)	0.001	0	19 (27.50)	22 (27.50)	0.924	0	9 (56.20)	32 (24.10)	0.005	0
Senior High School	9 (23.70)	13 (35.10)	28 (37.80)			21 (30.40)	29 (36.20)			7 (43.80)	43 (32.30)		
Junior High School	14 (36.80)	5 (13.50)	24 (32.40)			22 (31.90)	21 (26.30)			0 (0.00)	43 (32.30)		
Primary School and Below	9 (23.70)	2 (5.40)	4 (5.40)			7 (10.10)	8 (10.00)			0 (0.00)	15 (11.30)		
Misdiagnosis, n (%)													
Accurate diagnosis	13 (34.20)	14 (37.80)	27 (36.50)	0.946	0	22 (31.90)	32 (40.00)	0.223	0	7 (43.80)	47 (35.30)	0.699	0
Misdiagnosis	25 (65.80)	23 (62.20)	47 (63.50)			47 (68.10)	48 (60.00)			9 (56.20)	86 (64.70)		
Genotype, n (%)													
Genetic Testing Negative	2 (8.00)	4 (14.30)	10 (17.90)	0.671	26.8	10 (17.90)	6 (11.30)	0.759	26.8	3 (25.00)	13 (13.40)	0.252	26.8
TSC1 Positive	5 (20.00)	8 (28.60)	11 (19.60)			12 (21.40)	12 (22.60)			4 (33.30)	20 (20.60)		
TSC2 Positive	18 (72.00)	16 (57.10)	35 (62.50)			34 (60.70)	35 (66.10)			5 (41.70)	64 (66.00)		
ASMs, n (%)													
≥7 ASMs	3 (7.90)	0 (0.00)	5 (6.80)	0.018	0	1 (1.40)	7 (8.80)	< 0.001	0	0 (0.00)	8 (6.00)	0.163	0
0 ASMs	16 (42.10)	26 (70.30)	31 (41.90)			49 (71.00)	24 (30.00)			12 (75.00)	61 (45.90)		
1–3 ASMs	10 (26.30)	9 (24.30)	30 (40.50)			15 (21.70)	34 (42.50)			3 (18.80)	46 (34.60)		
4–6 ASMs	9 (23.70)	2 (5.40)	8 (10.80)			4 (5.80)	15 (18.70)			1 (6.20)	18 (13.50)		
mTOR Inhibitors, n (%)													
Non-Use	13 (34.20)	23 (62.20)	19 (25.70)	0.001	0	28 (40.60)	27 (33.70)	0.672	0	7 (43.80)	48 (36.10)	0.745	0
Active Use	25 (65.80)	14 (37.80)	55 (74.30)			41 (59.40)	53 (66.30)			9 (56.20)	85 (63.90)		

Abbreviations: MER, Medical Expenditure Ratio; ID, Intellectual Disability; ASMs, Anti-seizure medications.

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Table 5 Analysis of Factors Influencing Children's Educational Status and MER (n=691)

Independent Variable	Level	MER*		Educational Status: EDDI	
		OR_CI	P	OR_CI	P
ID	N	Reference	Reference	Reference	Reference
	Y	2.62 (1.88–3.67)	< 0.001	5.75 (3.2–10.79)	< 0.001
Misdiagnosis	N	Reference	Reference	Reference	Reference
	Y	1.64 (1.22–2.21)	0.001	2.58 (1.49–4.54)	0.001
ASMs	≥ 7 ASMs	Reference	Reference	Reference	Reference
	0 ASMs	0.21 (0.09–0.51)	< 0.001	0.05 (0–0.29)	0.006
	1–3 ASMs	0.54 (0.28–1.05)	0.0695	0.17 (0.07–0.39)	< 0.001
	4–6 ASMs	1.11 (0.55–2.21)	0.775	0.45 (0.19–1.06)	0.066
mTOR Inhibitors	N	Reference	Reference		
	Y	1.85 (1.31–2.62)	< 0.001		

Notes: *denotes a categorical variable representing MER, classified into three groups: Non-CHE 1 (MER < 20%), Non-CHE 2 (MER 20–40%), and CHE (MER ≥ 40%).

Abbreviations: Non-CHE, Non-Catastrophic Health Expenditure; CHE, Catastrophic Health Expenditure; MER, Medical Expenditure Ratio; EDDI, Education Disruption Due to Illness; ID, Intellectual Disability; ASMs, Anti-seizure medications.

Factors Influencing MER and Educational Status in Pediatric Patients

MER and educational status in pediatric patients were influenced by various factors. Non-use of ASMs emerged as a protective factor for both better educational outcomes (OR = 0.05, 95% CI: 0–0.29, $P = 0.006$) and reduced MER (OR = 0.21, 95% CI: 0.09–0.51, $P < 0.001$). ID negatively impacted the education of pediatric patients (OR = 5.75, 95% CI: 3.2–10.79, $P < 0.001$) and elevated the risk of MER (OR = 2.62, 95% CI: 1.88–3.67, $P<0.001$). Misdiagnosis contributed to adverse effects on both educational outcomes (OR=2.58, 95% CI: 1.49–4.54, $P=0.001$) and MER (OR = 1.64, 95% CI: 1.22–2.21, $P = 0.001$). The use of mTOR inhibitors was associated with elevated MER (OR = 41.85, 95% CI: 1.31–2.62, $P = 0.012$) (Table 5).

Factors Influencing MER, Marital Status and Employment Status in Adult Patients

In adult patients, non-use of ASMs was associated with higher likelihood of being married (OR = 0.07, 95% CI: 0–0.7, $P = 0.048$) and lower MER (OR = 0.23, 95% CI: 0.06–0.89, $P = 0.034$). ID (OR = 2.45, 95% CI: 1.14–5.34, $P = 0.022$), lower educational attainment, and use of mTOR inhibitor (OR = 2.37, 95% CI: 1.22–4.7, $P = 0.012$) were associated with elevated MER. Notably, compared to patients with undergraduate or higher education levels, those with junior high school education (OR = 4.21, 95% CI: 1.79–10.10, $P = 0.001$) and those with primary school education and below (OR = 10.54, 95% CI: 3.07–39.1, $P < 0.001$) presented higher risks. Employment status showed no significant relationship in the regression model (Table 6).

Discussion

This study makes a significant contribution to the current literature on TSC in China, being one of the few investigations focusing on the disease burden and its influencing factors in both pediatric and adult patients with TSC. It elucidated the concept of disease burden in TSC and reported the MER for pediatric and adult patients with TSC. Furthermore, it investigated the educational status of pediatric patients and the marital and employment status of adult patients. Additionally, it analyzed the factors influencing the disease burden in these patients.

Table 6 Analysis of Factors Influencing Adult Marital Status, MER and Employment Status (n=149)

Independent Variable	Level	MER*		Marital Status: Single		Employment Status: Unemployment	
		OR_CI	P	OR_CI	P	OR_CI	P
ID	N	Reference	Reference				
	Y	2.45 (1.14–5.34)	0.022				
Educational Attainment	Undergraduate and Higher Education	Reference	Reference			Reference	Reference
	Senior High School	1.98 (0.86–4.59)	0.108			0.6 (0.18–1.90)	0.384
	Junior High School	4.21 (1.79–10.16)	0.001			NA	0.991
	Primary School and Below	10.54 (3.07–39.10)	< 0.001			NA	0.995
ASMs	≥7 ASMs	Reference	Reference	Reference	Reference		
	0 ASMs	0.23 (0.06–0.89)	0.034	0.07 (0–0.70)	0.048		
	1–3 ASMs	0.42 (0.10–1.67)	0.221	0.22 (0.01–2.49)	0.282		
	4–6 ASMs	1.32 (0.27–6.34)	0.723	0.26 (0.01–4.94)	0.4		
mTOR Inhibitors	N	Reference	Reference				
	Y	2.37 (1.22–4.70)	0.012				

Notes: *denotes a categorical variable representing MER, classified into three groups: Non-CHE 1 (MER < 20%), Non-CHE 2 (MER 20–40%), and CHE (MER ≥ 40%); **: Full CI: 0 (0–118,084,528,680,365,872); ***: Full CI: 0 (NA-6.67603890317742e+70); NA Values in the unemployment group for Junior High School and Primary School and Below categories are due to zero observations in these educational levels among unemployed individuals.

Abbreviations: Non-CHE, Non-Catastrophic Health Expenditure; CHE, Catastrophic Health Expenditure; MER, Medical Expenditure Ratio; ID, Intellectual Disability; ASMs, Anti-seizure medications; NA, Not Applicable.

In this study, it was observed that patients with TSC experienced varying clinical manifestations and a wide range of ID resulting from these manifestations. The prevalence of ID was found to be 29.6% in pediatric and 19.4% in adult patients with TSC, which is generally consistent with previous research findings. Prior studies have indicated that approximately 40–60% of patients with TSC experience varying degrees of ID.[15] While this study did not sub-categorize the severity of ID, the Tuberous Sclerosis registry to increase disease Awareness (TOSCA) cohort study systematically analyzed the distribution of intellectual status. Specifically, the participants showed a range of intellectual abilities, with 44.4% exhibiting normal intelligence, 28.1% displaying mild disability, 15.1% demonstrating moderate disability, 9.3% exhibiting severe disability, and 3.1% showing profound disability.[16] These data further corroborate the complexity and diversity of ID in patients with TSC, thereby mutually validating the results of this study.

In terms of educational status, this study found that within the pediatric group, 45.9% were in the preschool stage, 44.7% were engaged in formal education, and 9.4% exhibited EDDI. Prior research has reported that learning difficulties are prevalent among patients with TSC, with an incidence of approximately 60%, regardless of intellectual attainment.[11] In light of these findings, early and continuous screening for learning difficulties in patients with TSC, along with prompt implementation of intervention measures, is advocated. Delays in early developmental stages may predict future learning challenges. Therefore, it is suggested to develop individualized education plans (IEPs) for all pediatric patients with TSC to address their specific learning needs. Moreover, providing appropriate educational environment is crucial, including high-quality teaching strategies, responsive intervention methods, and necessary accommodations. It is essential to continually monitor the TSC-associated neuropsychiatric disorders in pediatric patients with TSC for planning appropriate educational transitions.[14]

The present study identified hypomelanotic macules, brain calcification spots/nodules, and seizures as the most prevalent clinical manifestations in pediatric patients with TSC, aligning with those reported by Ding et al,[17] who observed epilepsy in 84.7% of 124 pediatric patients with TSC. Neuroimaging examinations revealed tubers or cortical dysplasia in 91.6% and subependymal nodules in 90.3% of pediatric patients. In contrast, adult patients with TSC

exhibited distinct clinical characteristics, with RAML as a primary manifestation, alongside hypomelanotic macules and brain calcification spots/nodules. Notably, RAMLs are the most common renal lesions in patients with TSC,[18] with a reported incidence rate of up to 85.4% in a retrospective study.[19]

TSC places a significant economic burden on patients and their families. This study unveiled that 70.3% of patients had a MER of ≤ 40% and a CHE of 29.6%. The comparison indicated that the overall incidence of CHE for other chronic diseases in China is 27.84%.[20] Since TSC is a chronic condition that affects multiple systems, patients face higher medical costs than the general population.[21] Therefore, it is essential to implement appropriate policies to guarantee the provision of health services and economic security for patients with TSC, thus reducing their risk of incurring CHE. We recommend expanding insurance coverage for costly treatments like mTOR inhibitors, and providing subsidies for low-income families. Compared to studies from high-income countries,[21] our findings highlight unique challenges faced by Chinese patients with TSC, such as higher rates of CHE and limited access to specialized care. These disparities underscore the importance of tailoring interventions to the specific needs of low- and middle-income countries.

The majority of adult patients with TSC had completed at least secondary education, with over 60% having attained a high school education or above. With regard to marital status, there was a slight predominance of single patients compared to those who were married. In terms of employment status, 89.3% of patients were employed. International consensus guidelines[14] acknowledge that TSC significantly impacts the employment and vocational life of patients and their families, calling for special attention in psychosocial support. The data reveal the duality of challenges and opportunities facing TSC patients in social life while demonstrating positive outcomes in education and employment.

This study illustrated that the disease burden of both adult and pediatric patients with TSC is influenced by multiple factors. The findings in this study indicated that the primary factors affecting the disease burden of adult patients with TSC include ID, medication use (ASMs and mTOR inhibitors), misdiagnosis, and educational attainment. It is evident that ID also greatly impacts the educational performance of pediatric patients with TSC, manifesting as EDDI. In areas requiring social and cognitive abilities, ID presents a significant obstacle to academic achievement and interpersonal competence on these patients.[22] Available evidence suggests that learning difficulties are common among patients with TSC who have ID, signifying that the majority of school-age patients with TSC could benefit from additional support and/or personalized educational approaches.[23] Moreover, ID is strongly correlated with a higher MER. A previous study observed that patients with TSC who experience cognitive impairment are at a significantly higher risk for hospitalization, intensive care unit treatment, and outpatient visits compared to the general population.[24] This leads to a considerable increase in medical expenses.[24] Concurrently, the use of mTOR inhibitors can substantially increase the economic burden of patients with TSC. A study by Crall et al[25] indicated that patients with TSC undergoing rapamycin treatment often encounter significant economic challenges, primarily due to difficulties in obtaining insurance coverage. Of the patients surveyed, 47.7% reported being affected, with 32.3% receiving no insurance reimbursement. The monthly medical expenses ranged from $1 to $1600, with 56.4% of patients paying over $100 OOP.

The use of ASMs has a pivotal effect on the disease burden of patients with TSC, with different impact patterns observed between pediatric and adult patients. This study revealed that non-use of ASMs is associated with a lower MER in both pediatric and adult patients with TSC. The use of ASMs typically necessitates periodic medical assessments, continuous monitoring, and regular follow-ups,[26] which not only consume more medical resources but also significantly increase the overall costs of treatment. Betts et al further corroborated the assertion that patients with TSC and epilepsy bear a higher burden in terms of healthcare resource utilization and expenses compared to those without epilepsy.[27]

In pediatric patients with TSC, those with non-use of ASMs or with use only one to three ASMs are have a lower likelihood of EDDI. It has been demonstrated that the most commonly used ASMs influence the cognitive functions, particularly affecting children's learning abilities.[28] Furthermore, some pediatric patients with TSC exhibit notable enhancements in behavioral performance and advances in communication and social skills following epilepsy surgery, which can be attributed to seizure control and less or no use of ASMs.[29] These findings emphasize the significance of medication management for cognitive development and behavioral intervention and demonstrate the potential beneficial impacts of surgery. This study suggested that, adult patients with TSC who do not use ASMs may have an advantage in establishing partner relationships, which is consistent with the findings of previous research. Wakamoto H[30] in Japan reported a 23% of marriage rate for young epilepsy patients (aged 20–30), which is significantly lower than that observed

in the general population of the same age group (51.9%). This suggests that epilepsy may influence the marital status of patients with TSC.

Furthermore, this study revealed that educational attainment significantly influences the disease burden of adult patients with TSC and shows a negative correlation with MER. This finding indicates that adult patients with TSC having lower educational attainment experience a greater disease-related economic burden. This aligns with other studies, which signify that individuals with lower educational attainment are disadvantaged in health management, leading to an increased economic burden.[31] Such a relationship between educational attainment and health-related economic burden warrants further investigation, and relevant policies can be formulated to address the health inequalities faced by less educated populations. Misdiagnosis also emerges as another crucial factor affecting the disease burden of pediatric patients with TSC. The results in this study indicated that 60% of pediatric patients with TSC were diagnosed prior to the age of one, with an average diagnostic age of 1.77 years, compared to 15.28 years for adult patients. A previous study reported an average diagnosis age of 7.5 years for TSC, with 81% of cases diagnosed before ten, although diagnoses in adolescence and adulthood were also common.[32] This suggests progress in diagnosing TSC in early childhood; however, considerable delays in diagnosis still persist. Moreover, this study revealed that misdiagnosis increases the disease-related economic burden on patients. Research has shown that misdiagnosis gives rise to medical and non-medical costs, thereby increasing the economic burden on patients and forcing them to seek medical services across regions. This exacerbates personal expenditure while negatively affecting the timeliness and efficacy of treatment.[33] Therefore, it is crucial to establish a multidisciplinary team comprising experts from different specialities, including neurology, nephrology, urology, pulmonology, ophthalmology, cardiology, dermatology, genetics and psychiatry/psychology,[34] to enhance the comprehensive diagnosis and treatment of TSC. Moreover, misdiagnosis adversely affects the education of pediatric patients with TSC, especially those with epilepsy. Delayed diagnosis during critical periods of brain function maturation may lead to developmental and cognitive impairments, which affect the educational and learning abilities.[35] This underscores the importance of early diagnosis and intervention to improve the long-term prognosis of pediatric patients children with TSC.

Conclusion

This comprehensive study elucidated the multifaceted disease burden and its contributing factors among Chinese pediatric and adult patients with TSC. The findings revealed that both groups experienced elevated MER, with pediatric patients encountering EDDI and adults struggling with establishing marital relationships. ID and misdiagnosis were identified as significant factors impacting the educational development of pediatric patients and contributing to their increased MER. For adult patients, lower educational attainment was strongly associated with higher MER. Furthermore, the use of ASMs and mTOR inhibitors significantly escalated the MER in both groups, impacting the educational outcomes of pediatric patients and the marital status of adult patients. These findings underscored the complex interaction among clinical, socioeconomic, and therapeutic factors in shaping the disease burden of TSC. Meanwhile, the results highlighted the critical importance of providing tailored educational support for pediatric patients and comprehensive care strategies in response to medical and psychosocial needs. Establishing multidisciplinary teams is crucial for early and accurate diagnosis. Subsequent research should focus on developing targeted interventions to reduce the economic burden and improve the overall quality of life for patients with TSC throughout their lifespans.

Ethics Approval and Consent to Participate

This study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki and was approved by Shenzhen Children's Hospital, Shenzhen, Guangdong Province, People's Republic of China.

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Author Contributions

All authors have made substantial contributions to the conception, study design, execution, data acquisition, analysis and interpretation, or all these areas, of the work. They actively participated in drafting, revising or critically reviewing the manuscript; gave final approval of the version to be published, and have agreed on the journal to which the article has been submitted. Furthermore, they are collectively accountable for all aspects of the work.

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