

Analysis of the Situation of Unmet Health Care Need Among Extremely Rare Disease of Gaucher

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Research

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Abstract

Background

The diagnosis and health care of patients with rare diseases present a tremendous challenge worldwide. This study estimated the health service utilization, cost of illness, and patients with Gaucher disease (GD)'s/caregivers' health-related quality of life in China.

Method

An online retrospective survey of patients with GD and their caregivers was conducted during May-June 2018. Socio-demographic, health service utilization, disease-related expenses, social support, sleep quality (Pittsburgh Sleep Quality Index [PSQI]), and the Short Form Health Survey (SF-36) were investigated. Using self-reported information, we estimated the annual cost of illness, including direct medical, direct non-medical, and indirect medical costs.

Results

Forty patients and their 49 caregivers were surveyed. The patients' onset age of GD was 9.3 ± 10.9 ; their disease course was 3.5 ± 3.1 years. 21 (42.9%) patients had ≥ 2 caregivers, but 35 (71.4%) caregivers reported have no experience as a caregiver. 79.6% caregivers have stopped working, and 87.8% changed weekly working schedule. Before final diagnosis, patients visited 3.9 ± 3.1 (max=20) hospitals and took 1.2 ± 1.7 (max=6.6) years for confirmed diagnosis. On average, 5.0 ± 9.6 misdiagnoses occurred, and the per-patient diagnoses cost was USD (\$) 7,576. After GD confirmation, 8 (16.3%) patients received no treatment, 40 (81.6%) received pharmacotherapy, 10 (20.4%) received surgery, 38 (77.6%) received outpatient service (8.8 ± 9.1 times/annually), and 37 (77.5%) received inpatient service (4.0 ± 3.5 times/annually). Annual per-patient cost was USD (\$) 49,925 (95% confidence interval: 29,178, 70,672). Average direct medical cost was \$41,816, including pharmaceutical (\$29,908), inpatient (\$7,451), and outpatient (\$1,838). Productivity loss per-caregiver was \$1,980, and their Zarit Burden Inventory score was moderate-severe (48.6 ± 19.6). Both patients/caregivers reported lower social support (32.4 ± 7.4 , 34.9 ± 7.6), two times higher PSQI (7.9 ± 2.9 , 8.7 ± 3.6), and half lower SF-36 (41.3 ± 18.6 , 46.5 ± 19.3) than those reported for healthy Chinese individuals.

Conclusion

This study finds out that fill the unmet need for extremely rare diseases is very challenging. The high misdiagnosis rate, together with delayed diagnosis, substantial costs, and deteriorated health-related quality of life of GD patients as well as their heavy care burden, calls for extreme attention from policymakers in China. Further efforts of government and society are urgently demanded, including pharmaceutical reimbursement, screening newborns, developing precise diagnostic tools, and training doctors.

Background

Gaucher disease (GD), an ultra-rare multi-organ involvement, inherited recessive enzyme deficiency[1, 2], is slowly progressing. Its standardized incidence and prevalence among the general population worldwide vary from 0.30 to 5.80 per 100,000 population, respectively; however, the initial estimate was 0.25 to 1.24 per 100,000 population[3, 4] with hundreds of patients diagnosed with GD in China. Accompanying symptoms of GD include anemia, thrombocytopenia, splenomegaly, hepatomegaly, and bone involvement[5], which often cause significant impairs to their health and the quality of life. And once diagnosed, it ought to be managed with enzyme replacement therapy[6, 7], but results in enormous expenses.

The World Health Organization has emphasized the need for urgent action to diagnose and treat people with rare diseases[8]. However, the diagnosis and treatment of rare diseases in China is still at a preliminary stage. Definitive GD diagnosis in China is difficult, especially with the high phenotypic heterogeneity of GD[9]. Several studies have explored the length of time required for diagnosing rare diseases[10, 11]. A long duration is often required before a correct diagnosis or treatment, which implies considerable discomfort for the patients with rare diseases, such as GD, and their families. To the best of our knowledge, few studies have focused on health service utilization of GD, including the diagnosis[12]. Therefore, it is essential to find out the real situation and unmet health needs of patients with GD.

Currently, the effective therapy for GD patients, such as enzyme replacement therapy and substrate reduction therapy, that must be administered continually, are extremely costly for patients and caregivers[13, 14]. Further, caregivers may experience workdays loss, absenteeism, and job changes while caring for their patients. Measuring the economic cost of illness can provide better information to policy makers to develop more targeted interventions to GD at various levels of health care system[15]. By measuring the economic and care burdens of diseases to the society will facilitate a prioritized healthcare policies and strategies[1]. However, evidence on the financial burden (e.g., direct medical costs, direct non-medical costs, and indirect costs) associated with GD in China is limited[16, 17]. Extensive health care needs and frequent medical care and expenses are associated with the economic burden of patients and caregivers[18]. Hence, it is essential to identify unmet gap of patients with GD in China[19].

This study aimed to assess the health service utilization, cost of illness, and health-related quality of life of patients with GD, as well as the quality of life of their caregivers.

Results

Socio-Demographic Characteristics

Characteristics of enrolled patients with GD, families, and caregivers are shown in Table 1, which shown GD often occur in child and adolescents. Nineteen (38.9%) of the patients were aged 0–4 years. And 77.5% of patients with GD were < 15 years old. GD treatment differs according to the disease classification, although in 40.8% of respondents, the exact type was unclear. The age of GD onset was

9.3 ± 10.9; disease course from symptom onset of GD ranged from 0.3 to 12.1 (3.5 ± 3.1) years. In total, 42.9% of patients had ≥ 2 caregiver.

Table 1
 Characteristics of enrolled patients with Gaucher disease, families, and caregivers.

Items	Sample (n)	Proportion (%)
Gaucher disease patients' characteristics		
Sex		
Male	25	51.0
Female	24	49.0
Age group (mean age at survey) in years		
0-4	19	38.9
5-7	5	10.2
8-12	12	24.5
13-14	2	4.1
≥15	11	22.5
Age at onset, years		
Mean ± SD	9.3 ± 10.69	
Max	44	
Min	1	
Disease course from symptom onset, days		
Mean ± SD	3.5 ± 3.1	
Max	12.1	
Min	0.3	
Median	2.0	
Types of Gaucher disease (GD)		
Type I	20	40.8
Type II	5	10.2
Type III	4	8.2
Not clear	20	40.8
Number of caregivers		
1	28	57.1
SD = standard deviation; ZBI = Zarit Burden Inventory-caregiver burden.		

Items	Sample (n)	Proportion (%)
≥2	21	42.9
Family characteristics		
Family history with GD		
No	40	81.6
Yes	9	18.4
Current residence		
Urban	19	38.8
Rural	30	61.2
Living on minimum subsistence allowance or relatives' relief		
No	32	65.3
Yes	17	34.7
Member with chronic disease		
No	30	61.2
Yes	19	38.3
Member > 60 years of age		
No	7	14.3
Yes	42	85.7
Member < 5 years of age		
No	26	53.1
Yes	23	46.9
GD caregiver's characteristics		
Sex		
Male	13	26.5
Female	36	73.5
Age	34.8 ± 10.4	
Education		
Primary School	4	8.2

SD = standard deviation; ZBI = Zarit Burden Inventory-caregiver burden.

Items	Sample (n)	Proportion (%)
Middle or high school	30	61.2
College	15	30.6
Daily care time		
<6 h	9	18.4
6–12 h	17	34.7
12–18 h	2	4.1
18–24 h	21	42.9
Experience being caregiver		
No	35	71.4
Yes	14	28.6
Main caregiver stopped working because of patients' GD		
No	10	20.4
Yes	39	79.6
Change of weekly working time because of patient's GD		
No	6	12.2
Yes	43	87.8
ZBI		
Maximum scores, 88 points		
No	30.6	
Yes	69.4	
Mean ± SD	48.57 ± 19.57	
SD = standard deviation; ZBI = Zarit Burden Inventory-caregiver burden.		

Among patients' families, 18.4% had a family history of GD and 85.7% had family members aged > 60 years. Among the 49 caregivers, 81.6% reported caring for the patients for > 6 h daily and 71.4% having no caregiving experience. Further, 79.6% and 87.8% of caregivers stopped working and absenteeism. 79.6% changed their weekly working schedule. The Zarit Burden Inventory (ZBI) score, indicating the burden of the caregivers, was from moderate to severe (48.57 ± 19.57).

Health Service Utilization

The profile of health service utilization of patients with GD are shown in Table 2. Patients' original reasons for visiting the doctors included enlarged liver and spleen (71.4%), normocytic anemia (36.7%), dyskinesia (12.2%), and osteopenia (8.2%). Among all surveyed patients, the two most frequent symptoms were hepatosplenomegaly (85.7%) and normocytic anemia (73.5%). Many patients (43.5%) reported that they had to travel to the tertiary hospitals in other provinces to get confirmed diagnosed. Among 49 patients, 77.6% received outpatient service and 77.5% received inpatient service.

Table 2

Descriptive analysis of the utilization of health service, including the diagnosis and treatment (n = 49).

Items	Sample (n)	Proportion (%)		
The original reason for visiting the doctors				
Osteopenia	4	8.2	2.3	19.6
Normocytic anemia	18	36.7	23.4	50.2
Dyskinesia	6	12.2	3.1	21.4
Obviously enlarged liver and spleen	35	71.4	56.7	83.4
Top current symptoms				
Hepatosplenomegaly	42	85.7	72.8	94.1
Normocytic anemia	36	73.5	58.9	85.1
Bone pain or other bone symptoms	17	34.7	21.7	49.7
Growth retardation	33	67.4	52.5	80.1
Nervous system involvement	10	20.4	10.2	34.3
Gastrointestinal symptoms	9	18.4	8.8	32.0
Types of medical institutions frequently visited				
Clinics/community health service centers	1	2.0	0.1	11.5
County-level medical institutions	4	8.2	2.3	19.6
Municipal medical institutions	11	22.4	11.8	36.6
Provincial medical institutions in the province	10	20.4	10.2	34.3
Provincial medical institutions in other provinces	20	40.8	27.0	55.8
None	3			
In the past year, outpatient visit for GD				
No	11	22.4	11.8	36.6
Yes	38	77.6	63.4	88.2
Mean ± SD	8.8 ± 9.1			
In the past year, inpatient visit for GD				
No	12	24.5	13.3	38.9
Yes	37	75.5	61.1	86.7
SD = standard deviation; GD = Gaucher disease.				

Items	Sample (n)	Proportion (%)		
Mean ± SD	4.0 ± 3.5			
Traffic time				
<5 h	24	49.0	34.4	63.7
≥5 h	25	51.0	36.3	65.6
Number of hospitals visited for GD to confirm GD diagnosis				
Median	3.0			
Mean ± SD	3.9 ± 3.1			
Max	20			
Total cost for GD diagnosis				
Median	7575.8			
Mean ± SD	15249.8 ± 22854.3	8685.3	21814.4	
Length of misdiagnosis (days)				
0–60	14	28.6	16.6	43.3
60–120	9	18.4	8.8	32.0
120–180	4	8.2	2.3	19.6
≥180	22	44.9	30.7	59.8
Mean ± SD, years	1.2 ± 1.7			
Duration of GD final confirmed diagnosed, years				
Mean ± SD	1.2 ± 1.7			
Median	0.4			
Max	6.6			
GD Misdiagnosis				
No	20	40.8	27.0	55.8
Yes	29	59.2	44.2	73.0
Number of GD misdiagnosis				
Median	2.0			

SD = standard deviation; GD = Gaucher disease.

Items	Sample (n)	Proportion (%)		
Mean ± SD	5.0 ± 9.6			
Before being correctly diagnosed with GD, (n = 29)				
Unexplained splenomegaly	19	65.5	48.2	82.8
Hypersplenism	13	44.8	26.5	64.3
Hemophilia	3	10.3	2.2	27.4
Therapy after diagnosis with GD				
No	8	16.3	7.3	29.7
Yes	41	83.7	70.3	92.7
Surgery, splenectomy				
No	39	79.6	65.7	89.8
Yes	10	20.4	10.2	34.3
Pharmacotherapy after diagnosis with GD				
No	9	18.4	8.8	32.0
Yes	40	81.6	68.0	91.2
Purchased medicine at medical institutions, (n = 40)				
No	4	10.0	2.8	23.7
Yes	36	90.0	76.3	97.2
Purchased medicine at social pharmacy or overseas, (n = 40)				
No	9	22.5	10.8	38.5
Yes	31	77.5	61.6	89.2
Taking medication as prescribed, (n = 40)				
No	14	35.0	20.6	51.7
Yes	26	65.0	48.3	79.4
SD = standard deviation; GD = Gaucher disease.				

Hardly recognized by many doctors, the patients visited 3.9 ± 3.1 hospitals, and it took 1.2 ± 1.7 (median = 0.4, max = 6.6) years for the diagnosis to be confirmed. The total cost for GD diagnosis was USD (\$) 7,575.8 (median); 59.2% of patients experienced ≥ 1 misdiagnosis, with a mean of 5.0 (SD = 9.6, median = 2.0). Before the correct diagnosis, most patients were misdiagnosed with unexplained splenomegaly

(65.5%), hypersplenism (44.8%), and hemophilia (10.2%). Eight (16.3%) patients received no health service following GD diagnosis. Ten patients underwent surgery (20.4%; splenectomy = 9; hematopoietic stem cell transplantation = 1). The remaining 40 (81.6%) received pharmacotherapy, among whom 14 (35.0%) had not used medications as prescribed, 27 (67.5%) reported using imported drugs, 9 took imiglucerase (the medicine used treatment of GD), and 5 were still using imiglucerase from the onset of GD diagnosis; all 49 (100%) agreed that the high price of medicine led to the failure of compliance with the doctor's prescription. Furthermore, 36 (90.0%) reported purchasing their medications at medical institutions or pharmacy, while 31 (71.5%) purchase from overseas.

Table 3 shows the caregivers' perception on GD treatment. Most (89.8%) caregivers perceived that the availability of therapeutic drugs was problematic. All (100%) caregivers reported their inability to afford therapeutic drugs. 48 (98.0%) Caregivers reported have no knowledge of GD. Most (96.0%) caregivers felt difficulty in obtaining diagnosis information. The top two problems confronting the caregivers during GD treatment were "high treatment cost" (95.8%), and "far away from hospitals" (75.0%). Up to 79.6% of 49 caregivers were extremely unconfident about future treatment.

Table 3
Caregiver' perception of Gaucher disease treatment (n = 49).

Variables	Samples (n)	Proportion(%)		
		Low limit	Upper limit	
Availability of therapeutic drugs				
Very insufficient	19	38.8	25.2	53.8
Insufficient	9	18.4	8.8	32.0
Medium	16	32.7	20.0	47.5
Sufficient	5	10.2	3.4	22.2
Affordability of therapeutic drugs				
Very unaffordable	7	14.3	5.9	27.2
Unaffordable	35	71.4	56.7	83.4
Medium	7	14.3	5.9	27.2
Knowledge of GD				
No	48	98.0		
Yes	1	2.0		
The difficulty to get diagnosis information				
Difficult	47	95.9		
Not difficult	2	4.1		
Feel of the difficult to treatment				
No	–	–		
Yes	49	100.0		
Difficulties during GD treatment				
Far away from hospital				
No	12	25.0	13.6	39.6
Yes	37	75.0	60.4	86.4
High treatment cost				
No	2	4.1	0.5	14.25
Yes	47	95.9	85.8	99.5
Extremely unconfident about future treatment				

Variables	Samples (n)	Proportion(%)		
No	10	20.4	10.2	34.3
Yes	39	79.6	65.7	89.8

Cost of Illness

The cost of illness of patients with GD is shown in Table 4 and Fig. 1. In total, the mean annual economic burden of GD was estimated at \$49,924. The mean direct medical costs of GD estimated at \$41,816.2 (83.8% of total costs) mainly comprised of taking medicine at home (59.9% of total costs), inpatient treatment (14.9%), outpatient treatment (3.7%), and medical tests (3.4%).

Table 4
Average annual cost of illness due to Gaucher disease (GD) in China (\$, n = 41)

	Mean annual costs	95% CI		Ratio of COI (%)
		Low limit	Upper limit	
Direct medical cost	41816.2 ± 65745.4	21064.4	62568.0	83.76
Outpatient medical treatment	1838.1 ± 3029.4	881.9	2794.4	3.68
Inpatient medical treatment	7451.2 ± 10392.2	4171.1	10731.4	14.92
Pharmaceutical treatment	29907.6 ± 63861.1	9750.6	50064.7	59.91
Medical tests	1675.9 ± 3207.2	663.6	2688.2	3.36
Formal care	580.6 ± 817.7	322.5	838.7	1.16
Other cost/expenditures	362.7 ± 654.3	156.2	569.3	0.73
Other cost/expenditures of outpatient	88.1 ± 159.7	37.7	138.5	0.18
Other cost/expenditures of inpatient	274.6 ± 633.0	74.8	474.5	0.55
Direct non-medical cost	4974.4 ± 4675.9	3498.5	6450.3	9.96
Accommodation	1245.0 ± 1711.2	704.9	1785.1	2.49
Accommodation of outpatient	440.3 ± 597.8	251.6	629.0	0.88
Accommodation of inpatient	804.7 ± 1562.6	311.5	1297.9	1.61
Transportation	819.9 ± 841.5	554.3	1085.5	1.64
Transportation of outpatient	581.8 ± 685.9	365.3	798.3	1.17
Transportation of inpatient	238.0 ± 376.3	119.3	356.8	0.48
Meals	749.8 ± 874.9	473.7	1026.0	1.50
Meals of outpatient	277.3 ± 356.2	164.8	389.7	0.56
Meals of inpatient	472.6 ± 740.1	239.0	706.2	0.95
Costs for artificial nutrition	1340.0 ± 2796.6	457.3	2222.7	2.68

Because of rounding, percentage might not add up to exactly 100%.

* The medical costs were converted to US Dollar using Purchasing Power Parities (PPP) in the study years (2018) (OECD National Accounts Statistics: PPP <https://data.oecd.org/conversion/purchasing-power-parities-ppp.htm#indicator-chart>).

COI = cost of illness.

	Mean annual costs	95% CI		Ratio of COI (%)
Other cost/expenditures	819.7 ± 929.0	526.4	1112.9	1.64
Direct cost	46790.6 ± 65714.2	26048.6	67532.5	93.72
Indirect cost	3134.2 ± 2556.4	2327.3	3941.1	6.28
Annual indirect cost of treatment	1153.7 ± 1046.9	823.3	1484.2	2.31
Productivity loss to caregiver due to caring	1980.4 ± 1962.8	1360.9	2600.0	3.97
Cost of illness (COI)	49924.7 ± 65729.9	29177.8	70671.6	100.00
Because of rounding, percentage might not add up to exactly 100%.				
* The medical costs were converted to US Dollar using Purchasing Power Parities (PPP) in the study years (2018) (OECD National Accounts Statistics: PPP https://data.oecd.org/conversion/purchasing-power-parities-ppp.htm#indicator-chart).				
COI = cost of illness.				

The average annual direct non-medical costs added up to \$4,974.4 (10.0% of total costs). With both direct medical and non-medical costs, the annual direct cost was estimated at \$46,790.6. The indirect costs for GD primarily originated from the productivity loss to the caregivers while caring for patients with GD (4.0% of total costs). Accordingly, the total annual indirect costs were estimated at \$3,134.2.

Social Support and Health-Related Quality of Life of Patients and Their Caregivers

The total Social Support Rating Scale (SSRS), Pittsburgh Sleep Quality Index (PSQI), and Short Form Health Survey (SF-36) scores for patients with GD, their caregivers, and norms of healthy Chinese people are shown in Table 5. Patients with GD and their caregivers reported mean SSRS scores of 25.3 ± 5.7 and 26.1 ± 5.6 , respectively. Both were remarkably lower than the SSRS score (40.5 ± 6.8) for healthy Chinese people (all p-value < 0.05). The mean PSQI scores for patients and caregivers scores were 7.9 ± 2.9 and 8.7 ± 3.6 , respectively. Patients with GD and their caregivers reported two times higher PSQI scores than the normal values for healthy Chinese people (3.9 ± 2.5) (all p-value < 0.05). Overall, 16 (32.7%) of caregivers rated sleep problems using PSQI dimensions. All the seven PSQI dimension scores for the caregivers were higher than the normal values for healthy Chinese people (all p-value < 0.05).

Table 5
Psychosocial burden of Gaucher disease on the caregivers.

	Patients (n = 30)	Caregivers (n = 49)	Norm of healthy Chinese people	p ^a	p ^b
SSRS^c					
Maximum score, 40 points					
Objective support	8.2 ± 2.5	8.2 ± 2.3	9.1 ± 2.9	0.059	0.009
Subjective support	17.6 ± 5.0	19.9 ± 4.9	23.5 ± 4.3	0.000	0.000
Utilization of support	6.6 ± 1.8	6.7 ± 1.9	7.8 ± 2.0	0.001	0.000
Mean ± SD	32.4 ± 7.4	34.9 ± 7.6	40.5 ± 6.8	0.000	0.000
PSQI^d					
Maximum score, 21 points					
Not good	6(20.0)	16(32.7)			
Good	24(80.0)	33(67.3)			
Mean ± SD	7.9 ± 2.9	8.7 ± 3.6	3.9 ± 2.5	0.000	0.000
Subjective sleep quality	1.57 ± 0.97	1.71 ± 0.89	0.63 ± 0.68	0.000	0.000
Sleep latency	1.77 ± 0.77	1.59 ± 0.91	0.70 ± 0.86	0.000	0.000
Sleep duration	0.87 ± 1.01	1.24 ± 0.97	0.70 ± 0.58	0.000	0.000
Habitual sleep efficiency	0.27 ± 0.69	0.63 ± 0.86	0.15 ± 0.47	0.000	0.000
Step disturbance	1.73 ± 0.52	1.61 ± 0.57	0.90 ± 0.44	0.000	0.000
Use of sleeping medication	0.00	0.08 ± 0.34	0.06 ± 0.24	–	0.000

^a Patients vs. normal values for healthy Chinese.

^b Caregivers vs. normal values for healthy Chinese.

^c N = 3342, [71]

^d N = 112, [72]

^e N = 17754, [73]

^f N of patients >= 15 is 11

SSRS = Social Support Rating Scale; PSQI = Pittsburgh Sleep Quality Index; SF-36 = Medical Outcomes Study 36-item Short Form; SD = standard deviation.

	Patients (n = 30)	Caregivers (n = 49)	Norm of healthy Chinese people	p ^a	p ^b
Daytime dysfunction	1.67 ± 1.03	1.82 ± 1.11	0.73 ± 0.83	0.000	0.000
SF-36^{e, f}					
Maximum score, 100 points for each item					
Total score	41.3 ± 18.6	46.5 ± 19.3			
Physical Component Summary (PCS)	39.4 ± 22.4	47.6 ± 23.0	77.5 ± 16.0	0.000	0.000
Mental Component Summary (MCS)	43.2 ± 16.1	45.4 ± 20.4	71.3 ± 17.9	0.000	0.000
Physical functioning (PF)	63.2 ± 20.2	63.8 ± 30.2	87.9 ± 17.0	0.000	0.000
Role physical (RP)	13.6 ± 32.3	27.6 ± 43.1	77.5 ± 34.9	0.000	0.000
Bodily pain (BP)	51.8 ± 23.3	60.3 ± 26.3	82.2 ± 17.0	0.000	0.000
General health (GH)	29.0 ± 25.9	38.9 ± 21.9	62.5 ± 17.9	0.000	0.000
Vitality (VT)	42.7 ± 16.5	45.3 ± 18.6	68.2 ± 17.6	0.000	0.000
Social functioning (SF)	71.6 ± 26.9	67.6 ± 30.0	80.7 ± 20.0	0.013	0.004
Role emotional (RE)	6.1 ± 20.1	20.4 ± 37.2	67.9 ± 39.4	0.000	0.000
Mental health (MH)	52.4 ± 17.1	48.3 ± 16.0	68.5 ± 16.9	0.000	0.000
^a Patients vs. normal values for healthy Chinese.					
^b Caregivers vs. normal values for healthy Chinese.					
^c N = 3342, [71]					
^d N = 112, [72]					
^e N = 17754, [73]					
^f N of patients > = 15 is 11					
SSRS = Social Support Rating Scale; PSQI = Pittsburgh Sleep Quality Index; SF-36 = Medical Outcomes Study 36-item Short Form; SD = standard deviation.					

Besides, the health-related quality of life of the patients with GD and caregivers was assessed. Patients (39.4 ± 22.4) and caregivers (47.6 ± 23.0) reported half lower Physical Component Summary than the normal values for healthy Chinese people (77.5 ± 16.0, all p-value < 0.05). Further, Mental Component

Summary in both patients (43.2 ± 16.1) and caregivers (45.4 ± 20.4) was significantly half lower than the normal values in healthy Chinese people (71.3 ± 17.9 , all p -value < 0.05).

Discussion

There is a dearth of evidence on the health service utilization and economic burden of rare disease patients with GD in China. In this study, we performed a comprehensive analysis and identified a wide range of unmet needs and problems of patients with GD in their health service utilization, cost of illness, and health-related quality of life associated with GD in China. Families of patients with GD often experienced delays in diagnosis and misdiagnosis, enormous economic cost, and caregiving burden. Lack of social support often resulted in deteriorated health related quality of life and other major health issues which deserve great attention of society.

Misdiagnosis or delayed diagnosis is especially detrimental to patients[20]. Although several publications have acknowledged that diagnostic delays or misdiagnosis often occurs in obtaining a definitive GD diagnosis [21], this study further quantified the exact time delay and difficulty in obtaining the correct diagnosis that occurred in 79.6% surveyed patients. 59.2% of them experienced misdiagnosis, of up to 5.0 ± 9.6 times. Besides, patients reported multiple referrals (3.9 ± 3.1) to different hospitals before their disease was accurately determined. Studies indicated the process of continually seeking diagnosis was a traumatic experience for patients with rare diseases[22]. Patients spent 1.2 ± 1.7 years to receive a definitive diagnosis since the onset of symptom, and 44.9% of 40 patients had lived with their rare condition for > 6 months before accurate diagnosis. Due to the frequent misdiagnosis and delayed diagnosis, patients ended up paying \$15,250 for the final GD diagnoses. Davari M et al. have shown a patient misdiagnosed with GD had taken medications for ten years at the cost of \$207,580[1]. Thus, a rapid precise diagnosis of patients is essential for reducing unnecessary tests or costs[21, 23, 24], and preventing psychological stress for the family[25].

The main reason for the prolonged diagnostic delay most likely is insufficient knowledge on GD[26–28] by the medical community due to its low prevalence, extreme variations in clinical manifestations[23, 29], and severity of symptoms (e.g., bone pain/bone crisis, thrombocytopenia, and splenomegaly) [12, 21, 23]. Nevertheless, a survey revealed that only one of five hematologist-oncologist considers GD in the differential diagnosis of patients with a history of anemia, thrombocytopenia, hepatomegaly, splenomegaly, and bone pain. In this study, 79.6% of patients had visited doctors with obvious symptoms (osteopenia, normocytic anemia, dyskinesia, and obviously enlarged liver) in whom GD was not diagnosed in a timely manner. Therefore, establishing an information center of rare disease symptoms[30] and providing training on diagnostic methods and appropriate clinical guidelines to medical doctors are essential to effectively support early diagnosis of rare diseases. Besides, because most rare diseases are caused by DNA mutations or are recessive genetic diseases[31], family history and genetic screening could facilitate earlier diagnosis, while genetic testing can be used to confirm disease diagnosis[32]. Nine families reported a family history of the same disorder in this study, indicating a need for awareness of genetic disorders to highlight the importance and burden of genetic diseases. Therefore,

newborn screening for disorders that meet the criteria for population screening[33], use of reliable diagnostic tools[1, 34–36], raising of awareness on the early signs/symptoms[37] or less severe manifestation [21], and initiation of therapy early for rare diseases[30], are essential.

In particular, long-term treatment with regular monitoring for GD can optimize outcomes[38], alleviate fewer exacerbations[1], and reduce the incidence of complications[39]. A Gaucher outcome survey involved 1209 patients with GD reported the overall treatment (1,209, 73.4%) and different treatment rates in countries [the UK (119, 93.3%), Israel (536, 63.6%), the US (380, 82.6%), rest of the world (174, 69.5%)] [40]. In this study, 8 of the 49 patients (16.3%) were never treated, while 83.7% get treated, and 10 (20.4%) of patients undergone splenectomy, which was higher than previous research (8.7%-13.3%) [2, 40]. Besides, other studies also shown a significant proportion of patients (e.g., asymptomatic or mildly affected) never accessed medical attention or required treatment[41, 42]. In this study, even 20 (40.8%) of patients did not clear the type of their GD. Maaswinkel Mooij et al.[43] found that no treatment for type 1 GD with enzyme replacement therapy can worsen the condition at any age in non-Jewish patients[44]. Besides, 4 of 9 patients who took imiglucerase interrupted their treatment in this study. However, Drelichman et al. emphasized the need to avoid interruption of medical treatment of patients with GD because of recurrent organomegaly, growth delays, and skeletal manifestations[45]. Furthermore, a previous study identified association of high immunoglobulin (Ig) A and IgG levels with long-term complications[46]. Therefore, long-term treatment and surveillance are required for improving the efficiency of GD management[47].

To estimate the annual cost of GD, we presented the core components of costs for health care services separately, from the payer' perspectives, excluding patients' out-of-pocket costs and informal care. The estimated annual per-patient cost of GD of \$49,925 (95% confidence interval [CI]: \$29,178, \$70,672, which is 5.3 times of GDP per capita of China in 2018(\$9,377)[48]. The additional time spent by caregivers for providing care reflects an annual productivity loss of \$1,980 per patient. In contrast, a recent analysis using the human capital approach showed high costs [e.g., Splenectomy (\$13,698), Bone complication (\$10,002), Multiple complications (\$10,615), and Malignancy (\$73,057)] that generated much higher indirect costs than ours[49], whereas we calculated indirect costs with the actual wage of the caregivers. Besides, direct non-medical costs (\$4,974), comprised those for accommodation, transportation, meals, and other expenditures, which accounted for 10.6% of direct costs; this indicated a high burden of access to medical services. Moreover, patients with GD required frequent healthcare utilization resulting in an annual direct cost (direct medical/non-medical costs) of \$46,791 per patient (95% CI: \$26,049, \$67,533); that is, 93.7% of total costs. In this study, the mean direct medical costs of \$41,816 per patient was about 66.5 times of the average health expenditure per patient (\$629) in China in 2018[50]. The direct medical costs included those for pharmaceutical (\$29,908, 59.9%), inpatient (14.9%), and outpatient treatments (3.7%). One study in Iran estimated the annual direct medical costs at \$20,758 in 2014 and identified drug costs as 95.2% (\$19,763) of direct medical costs[1]. These figures clearly show that the pharmaceutical cost encompasses most of the resources used by patients with GD. Recent research has also demonstrated that drug expenditures accounted for almost 90% of rare diseases' health expenditures[19].

Therefore, further efforts are needed to address the issue of pharmaceutical treatment costs holistically[51].

However, both the availability and affordability of orphan drugs[52] for the treatment of rare diseases in China are low[17]. Poor accessibility to drugs is the most problematic issue for patients with rare disease in China[53]. In this study, 89.8% of patients perceived the availability of therapeutic drugs to be problematic. Furthermore, 35.0% of patients who received pharmaceutical treatment could not take the medication as prescribed. These figures demonstrate poor availability of rare drugs. Several hindering factors contributing to the low availability of orphan drugs in China include the low market availability of orphan drugs in China[17, 54]. Compared with the earliest launch time globally, the average delay in the market authorization of orphan drugs for rare diseases in China was 7.7-9 years[17, 54]. Imiglucerase received China's marketing authorization in 2008[17]. On May 22, 2018, the Chinese Government officially included GD on the first list of rare diseases[55]. With a low availability of < 30% [17], many Chinese patients currently pay out-of-pocket for international treatments that are currently unapproved in China[56]. Second, lack of research and development and supply incentive policies for orphan drugs are possible reasons leading to low market availability[56]. Under a market-oriented economy, due to a small market share of orphan drugs, most pharmaceutical manufacturers are unwilling to invest in research and development on the production of orphan drugs without an incentive policy[17]. Third, low public hospital availability of orphan drugs is another major issue both for the patients[57] and the Chinese government. In this study, 31 (77.5%) of patients reported purchasing medicine at pharmacies or overseas. Due to the unique market attributes (e.g., low market volume, low profit, low turnover rate, and high price) of orphan drugs, and as the reform of public hospitals in China stipulated (control the share of drug sales in total hospital revenue), hospitals have little incentive to stock and prescribe expensive orphan drugs[58]. Lastly, there are no public national or provincial networks for rare diseases or orphan drugs to share useful information about these diseases, e.g., treatment or supply information. Therefore, it is urgent to improve the availability of rare drugs, e.g., simplify the approval procedure for imported orphan drugs, increase research and development investment, formulate incentive policies, and establish information-sharing platforms.

Furthermore, to recoup research and development costs and for profit, orphan drug manufacturers often adopt a strategy of charging high prices[59]. Miglustat and imiglucerase, which are effective medications for treating GD, had annual costs of \$116,800 and \$140,200, respectively in 2004[60], and the expenditure share was > 3% of per capita GDP[16]. A study focusing on seven selected rare diseases found that the affordability of treatment was relatively poor, with the health expenditure for GD equivalent to 69.34 years per urban resident's income in 2014[16]. In this study, 49 (100%) of patients reported the unaffordability of therapeutic drugs. A few cities/provinces are active in creating rare disease lists with a high reimbursement at 80%-95%[61]. However, due to the restrictive reimbursement caps, even with 5% out-of-pocket expenses, few drugs could be afforded by high-income urban residents[62]. The out-of-pocket costs are still unaffordable for many patients. Therefore, the low affordability of orphan drugs may be closely associated with many factors, e.g., high drug prices, lack of insurance coverage, low reimbursement rates, and low-income levels for Chinese residents[17]. Several measures should be taken

to improve the affordability of orphan drugs in China including: 1) formulating and implementing incentive policies[59, 63] to promote the development and supply of generic drugs, and to control the price of orphan drugs[64, 65]; 2) developing an orphan drug reimbursement system to increase insurance coverage; and 3) developing government-supported programs for patients with rare disease.

Due to the delayed diagnosis, unavailability, and unaffordability of costly drugs, 79.6% of 49 patients with GD felt poorly confident about future treatment. Moreover, the total social support, sleep quality, and quality of life scores for patients with GD/caregivers were significantly lower than those for normal healthy Chinese people. Thus, patients with GD experience limited access to health services, substantial costs, and low health-related quality of life [66].

Limitations

First, this study is limited primarily by the small sample size. Due to the rarity of GD, data collection was challenging. Second, families who voluntarily participate in the GD patient registry may represent a more compliant and motivated patient cohort in general. Thus, the findings may not be generalized to all. Thirdly, this study relied on responders' recall of health service utilization and the unit costs to capture a more inclusive set of cost components usually not included in billing data, such as traffic costs, formal care costs, and productivity loss to caregivers. To enhance the accuracy of the estimates reported, patients with GD and caregivers were asked to complete questions regarding the average consumption amount and costs per resource in the past year. However, recall bias may have led to errors. Lastly, utilization and corresponding costs from pharmaceutical use of prescription were not included in the survey. For pharmaceutical costs, we asked for the "annual purchase of imported/ domestic medicines," which could have resulted in an underestimation of this study's GD's financial burden. Hence, appraisal costs using data from health insurance is needed.

Conclusions

Patients with GD often encountered the frustrating experience of high misdiagnosis rate, long-delayed diagnosis, substantial costs, and deteriorated health-related quality of life in China. For patients with GD, a rapid, precise diagnostic tool for earlier and timely definitive diagnosis of GD is urgently needed. A more tailored medical insurance program that can effectively address the unmet health need of patients with GD should be designed. Measures targeting improving the availability and affordability of orphan drug needs to be developed holistically in China. Furthermore, newborn screening for disorders that meet the criteria for population screening with reliable diagnostic tools should be explored. Besides, enhancing doctors' ability in GD diagnosis and differential diagnosis, raising awareness of the early signs/symptoms or less severe manifestation to achieve earlier diagnosis and timely therapy of rare diseases, relieve caregivers' burden, and provide much needed social support are essential. This research can facilitate greater societal awareness of rare diseases, help policymakers develop appropriate intervention programs, and inform healthcare-focused support schemes and policies for patients and their families.

Methods

Development of the Survey

An online retrospective survey of patients with GD and their caregivers was conducted for data collection. The inclusion criteria for patients were as follows: (i) a diagnosis of GD by a physician before the study; (ii) with a caregiver who was familiar with the whole treatment process of them; (iii) if the patient was under 15, with a voluntary caregiver to help answer all the real information of them. The inclusion criteria for the caregivers included that he/she was: (i) the primary caregiver; (ii) was thoroughly familiar with the patient's disease; (iii) accompany patients every visit to the treatment; and (vi) was able to understand the content of the questionnaire.

The questionnaire, including the patient part and the caregiver part, is distributed simultaneously to eligible patients with GD and their caregivers. In the case of patients < 15 years or patients who are dependent partly or on full-time care, patient part asked whether the patient can answer independently, and questions were set up in two ways (et al., "Birthdate of you" or "Birthdate of the patient"). The patient part was answered by themselves or with their caregivers' help if they can understand questions; if not, patient' information will be answered only by their caregivers.

The patient part

- Social-demographic characteristics
- Medical service utilization
- Cost of illness
- Social support (surveyed patients ≥ 5 years)
- Sleep quality (surveyed patients ≥ 5 years)
- The Short Form Health Survey (surveyed patients ≥ 5 years)

The caregiver part

- Social-demographic characteristics
- Caregivers' perception of GD treatment
- Care burden
- Social support
- Sleep quality
- The Short Form Health Survey (SF-36)

The China Gaucher disease family exchange group (C-GDFEG) is currently the largest GD information exchange platform in China. From May to June 2018, we contacted a total of 98 families of patients with GD in C-GDFEG before conducting this survey. A total of eligible 51 (52.04%) patients enrolled in this

study. Both the patient part and the caregiver part completely answered was considered as a valid questionnaire. Of them, 49 (validity rate 96.08%) patients with GD and their caregivers (n = 49) completed the questionnaire were included in this study. The contact details of the researchers were also sent to the participants for information and further communication.

Questionnaire Design and Data Collection

From the literature review, we identified key areas that were both important for the patients and families, and essential for the health authorities and service provision planning. The online self-administered questionnaire for the patients with GD, their caregivers, and their households comprised the following sections: (i) socio-demographics characteristics; (i) medical service utilization; (ii) cost of illness; (iii) social support; (iv) sleep quality; (v) care burden; and (vi) self-reported health (using SF-36).

Definition and Measurements

Socio-demographic characteristics

The patients' socio-demographic characteristics included age, sex, current residence, mean age at onset, disease duration, type of GD, family history of GD, and caregivers' number. Socio-demographic characteristics of the caregivers included the daily care time, experience of being a caregiver, stopped working because of patients' GD, change of weekly working scheme because of patient's GD, and members with chronic disease > 60/<5 years of age. Besides, whether living on minimum subsistence allowance or relatives' relief or not was also reported.

Medical service utilization and caregivers' perception of GD treatment

The medical service utilization data were collected in this study to assess patients' diagnosis and treatment status. Health service utilization covering the 12 months health service utilization of patients with GD surveyed by self-designed questions, including the following: (i) the original reason to see the doctors; (ii) symptom; (iii) types of medical institutions frequently visited; (iv) number of hospitals visited for GD diagnosis; (v) total cost of GD diagnosis; (vi) length before the final GD diagnosis was confirmed; (vii) misdiagnoses; (viii) the number of misdiagnoses; (ix) therapy after GD diagnosis; (x) outpatient/inpatient visit for GD; (xi) traffic time; and (xii) surgery/pharmacologic therapy after GD diagnosis.

Additionally, caregivers' perceptions et al., "the availability and affordability of therapeutic drugs," "difficulties during GD treatment," "knowledge of GD," and "difficulties to get diagnosis information" were also investigated.

Cost of illness

We retrospectively evaluated the total cost of GD, comprising direct medical, direct non-medical, and indirect costs for individual patients and their families. Costs comprised the following components: *Direct*

medical costs: (i) daily outpatient/inpatient treatment cost; (ii) laboratory and diagnostic costs; (iii) imported/domestic drugs' costs; (iv) formal care cost; (v) other direct outpatient/inpatient medical costs; *Direct non-medical costs*: (vi) outpatient/inpatient costs for accommodation/transportation/meals; (vii) artificial nutrition costs; (viii) other direct non-medical costs; and *Indirect costs*: (ix) daily lost wages of caregivers; (x) annual indirect cost.

Respondents were also asked to recall the use of resources: (i) outpatient/inpatient visit frequencies (consultations) annually; (ii) the average days for each outpatient/inpatient visit; and (iii) total days of lost wages annually. The resources used were multiplied by the corresponding unit cost to estimate the annual cost per patient, and the monetary values of the unit prices were reported in USD (\$).

Zarit Burden Inventory

The subjective burden of the caregivers was measured by ZBI (22-item version), with item scores ranging from 0 (never) to 4 (nearly always). The total score ranges from 0 to 88, and scores < 21 correspond to little or no burden while scores > 61 correspond to severe burden[67].

Social Support Rating Scale

SSRS comprise 10 items and includes three subscales: subjective support (4 items), objective support (3 items), and utilization of support (3 items). The total SSRS score ranges from 12 to 66 points, and higher scores indicate higher level of social support[68].

Pittsburgh Sleep Quality Index

Sleep quality of individuals in 1 month was measured using the PSQI (comprises 19 items and 7 dimensions), which includes subjective sleep quality, sleep onset latency, total sleep duration, sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction. The sub-total of the scores of each dimension ranges from 0 to 3, and the maximum score is 21. The cut-off score for PSQI-defined cases of poor sleep quality is ≥ 6 . A Chinese PSQI version has been validated with adequate reliability[69].

The medical outcomes study 36-item Short Form

Quality of life was measured by the SF-36 comprising 36 items including the physical and mental component scores[70]. Subscale scores are then transformed from the normal scale to a 0-100 standardized score scale, with higher scores indicating more positive health status and a better health-related quality of life.

Statistical Analyses

Descriptive analysis was conducted to evaluate the social demographic characteristics, the status of medical service utilization, cost of illness, and health-related quality of life. Continuous variables were presented as means \pm SDs, and categorical variables were presented as absolute and relative frequencies.

The 2.5 and 97.5% quantiles of the bootstrap distribution were used as the limits of the 95% CI. All statistical analyses were conducted using SAS software, version 9.4 (SAS Institute, North Carolina, US).

Abbreviations

C-GDFEG

China Gaucher disease family exchange group

CI

Confidence interval

DMC

Direct medical costs

DNMC

Direct non-medical costs

DMC outpatient

Direct medical costs of outpatient medical treatment

DMC inpatient

Direct medical costs of inpatient medical treatment

DMC pharmaceutical

Direct medical costs of pharmaceutical treatment

DMC medical tests

Direct medical costs of medical tests

DMC formal care

Direct medical costs of formal care

DMC other costs

Direct medical costs of other costs

GD

Gaucher disease.

GDP

gross domestic product

MCS

Mental Component Summary

PCS

Physical Component Summary

PSQI

Pittsburgh Sleep Quality Index

SD

standard deviation

SF-36

Medical Outcomes Study 36-item Short Form

SSRS

Social Support Rating Scale
WHO
World Health Organization
ZBI
Zarit Burden Inventory

Declarations

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of Harbin Medical University (No.HMUIRB20200001).

Consent for Publication

Yes

Availability of Data and Materials

Not applicable

Competing Interests

The authors declare that they have no competing interests.

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Authors' Contributions

Writing – original draft by Xinye Qi; Conceptualization & Methodology by Xinye Qi and Jiao Xu; Resource by Jiao Xu and Qunhong Wu; Writing – Review & editing by Linghan Shan and Ye Li; Software by Yu Cui and Huan Liu; Formal analysis by Huan Liu and Kexin Wang; Project administration and Supervision by Lijun Gao and Zheng Kang; Funding acquisition & Supervision by Qunhong Wu.

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Figures

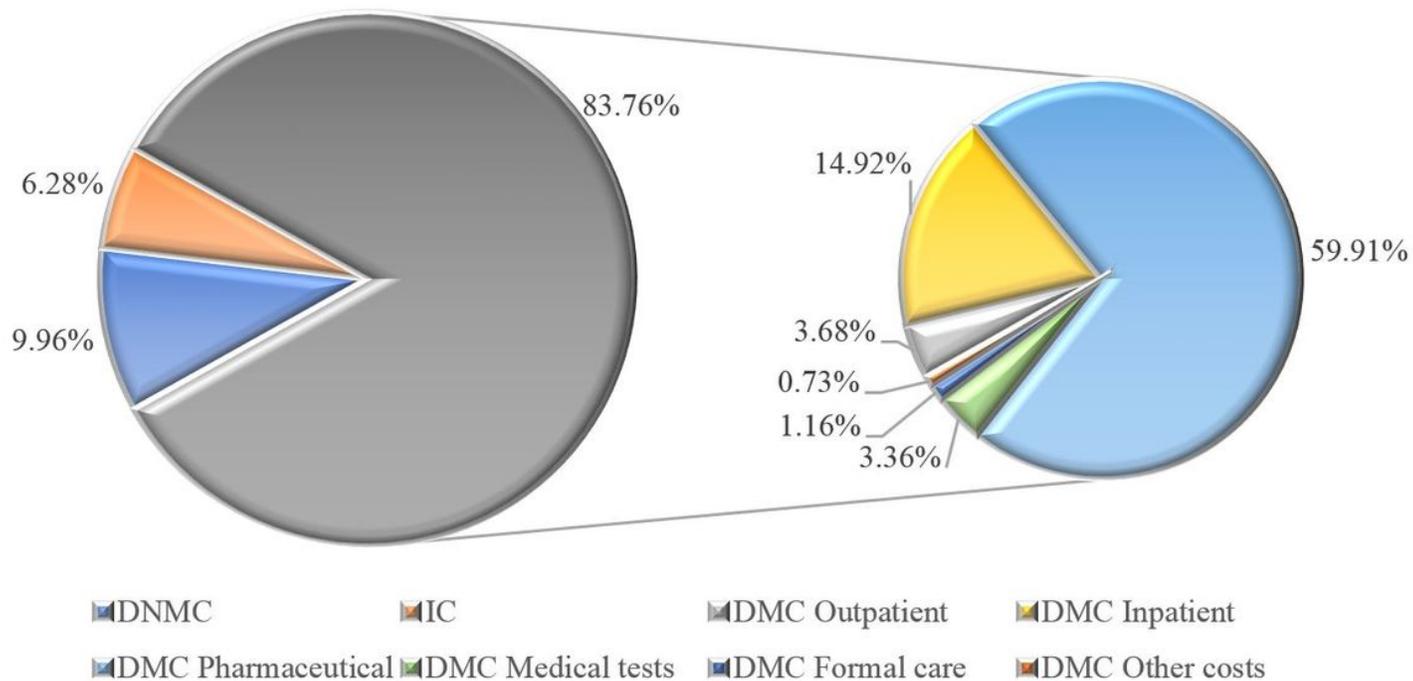


Figure 1

The annual cost of illness proportion of Gaucher Disease (GD) in China. Notes: DNMC= Direct non-medical costs; DMC = Direct medical costs; DMC outpatient = Direct medical costs of outpatient medical treatment; DMC Inpatient = Direct medical costs of inpatient medical treatment; DMC pharmaceutical = Direct medical costs of pharmaceutical treatment; DMC medical tests = Direct medical costs of medical tests; DMC formal care = Direct medical costs of formal care; DMC other costs = Direct medical costs of other costs.

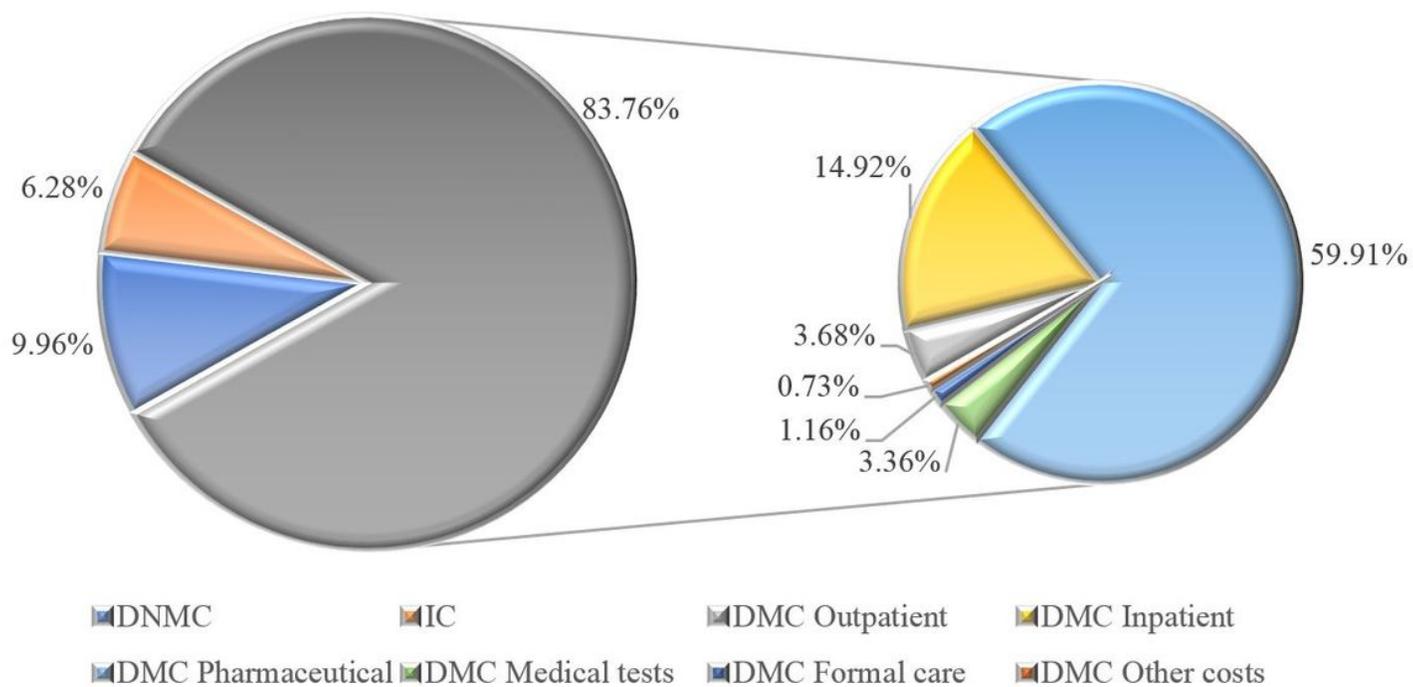


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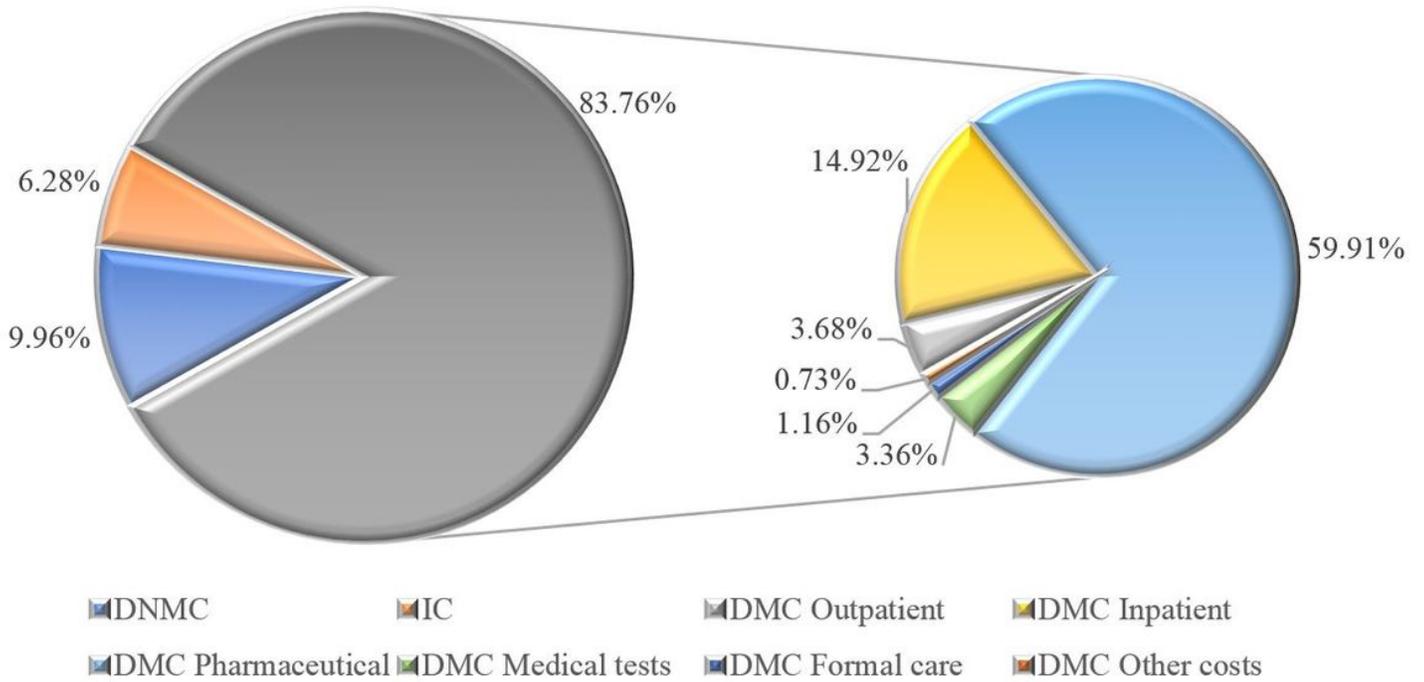


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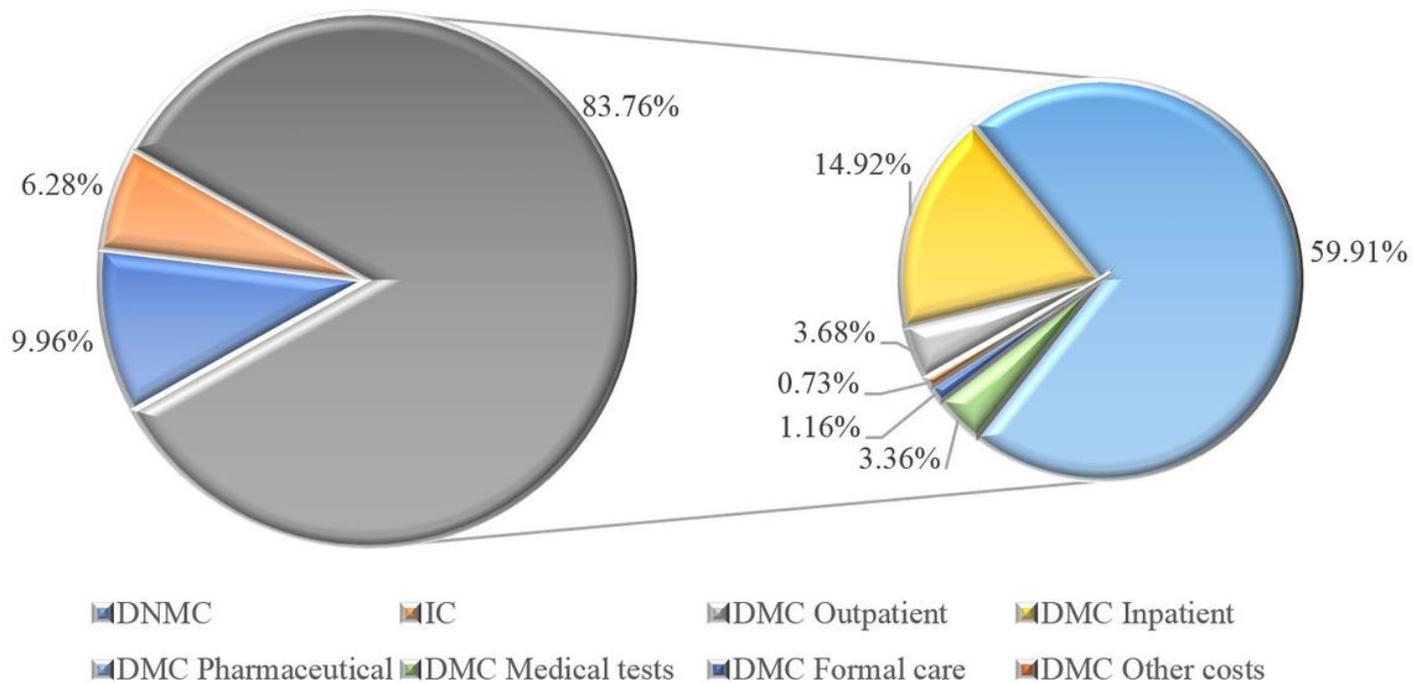


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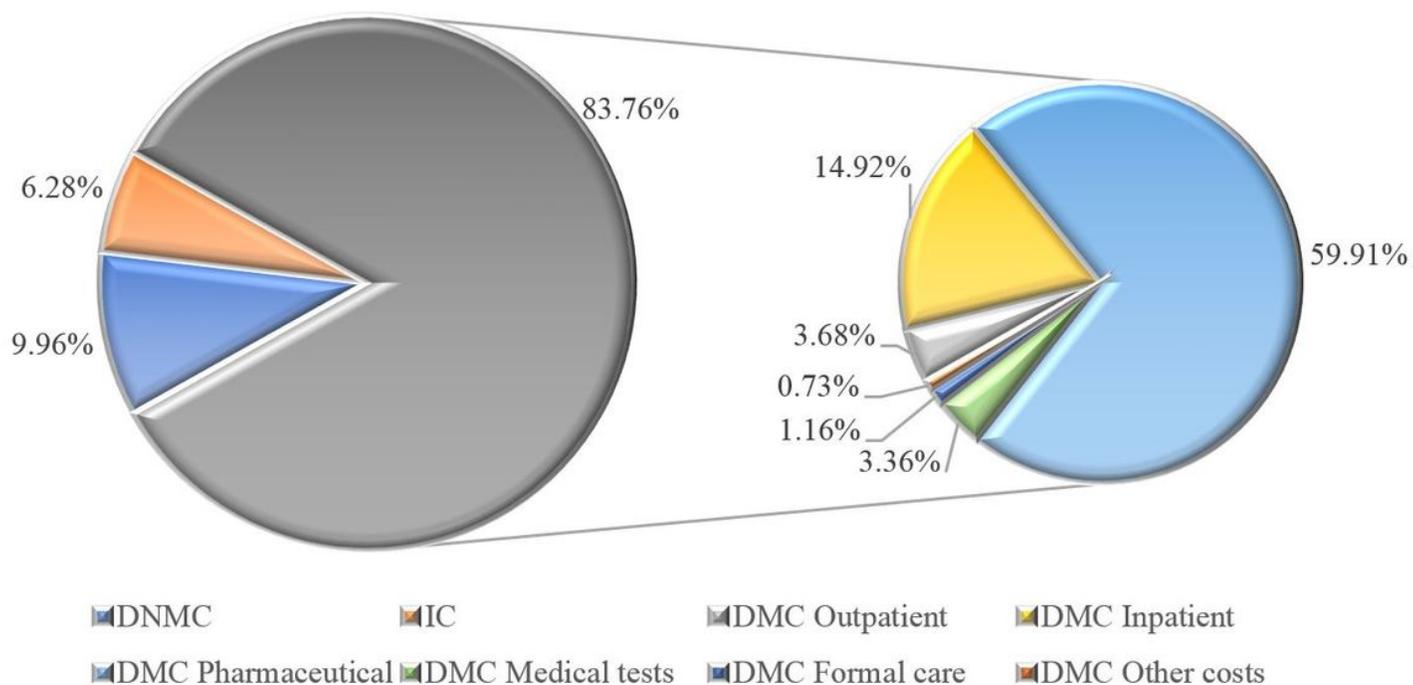


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