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ORIGINAL ARTICLE

Family caregivers of rare disease: A survey on health-related quality of life in family caregivers for Gaucher disease patients in China

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Abstract

Background: Rare diseases affect the health-related quality of life (HRQoL) of patients and their family caregivers (FCs). However, limited evidence is available on the HRQoL of FCs of patients with Gaucher disease (GD). This study aimed to assess HRQoL and related factors among FCs of patients with GD in China.

Methods: A cross-sectional online survey was conducted with 49 FCs recruited by convenience sampling. Participants completed the Medical Outcome Study Short Form-36 (SF-36), Zung's Self-Rating Anxiety Scale, Zung's Self-Rating Depression Scale, the Multi-dimensional Scale of Perceived Social Support, the Herth Hope Index, and a questionnaire about FCs' and patients' sociodemographic characteristics. Single-sample t tests, one-way analysis of variance, and multivariate linear regression analysis were used to analyze the data analysis.

Results: Participating FCs had significantly lower scores in all eight SF-36 domains compared with the general population in China ($p < 0.01$). FCs' gender, education, daily care time, anxiety, and the perceived disease severity of patients were significant predictors of SF-36 physical component summary scores. Caregiving help from others, anxiety, perceived disease severity, and medical insurance type were significant predictors of SF-36 mental component summary scores.

Conclusion: The findings showed FCs of patients with GD had lower HRQoL. There is an urgent need to address the health concerns of FCs of people with rare diseases including their HRQoL.

KEYWORDS
China, family caregiver, Gaucher disease, health-related quality of life, SF-36

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1 | INTRODUCTION

Gaucher disease (GD) is a rare metabolic disorder which is caused by autosomal recessive inheritance of mutations in the GBA gene encoding the lysosomal enzyme acid β-glucosidase (Alioto et al., 2020; Cormand et al., 1998; Rosenbloom & Weinreb, 2013; Sheth et al., 2019). Patients with GD usually suffer severe symptoms including enlargement of the liver and spleen, anemia, reduced platelets, bone pain, bone infarctions, and potentially permanent disability or even death (Cox, 2010). GD is classified into three types based on the presence and degree of nervous system involvement. The overall incidence of GD ranges from 0.39 to 5.80 per 100,000 people and the prevalence ranges from 0.70 to 1.75 per 100,000 people (Nalysnyk et al., 2017; Zuckerman et al., 2007). However, no definite statistics for GD are available in China. Data from the China Charity Federation (updated in January 2016) indicated that around 370 patients had been registered (Lei et al., 2018).

In addition to the personal experience of suffering, rare diseases are also a family event. As is the case with most chronic conditions, rare diseases have a major impact on the daily life of a patient's whole family. These health conditions pose unique challenges for both affected patients and the family caregivers (FCs) who care for these patients (Cardinali et al., 2019). The FCs are usually relatives (often a patient's parents or spouse) who take on most of the physical and emotional burdens of care for a patient without receiving any financial compensation (Wang et al., 2020). The FCs play an important role in daily disease management, and their physical and psychological conditions directly affect the care level they can provide for patients. This critical caregiving role is also influenced by the weak care system currently available for people with rare diseases (Graf von der Schulenburg & Frank, 2015), and the shortage of nursing professionals. In addition, FCs of patients with rare diseases may face more challenges than FCs of patients with common diseases, including unusual healthcare issues, lack of disease-specific information, diagnostic delays, inadequate treatment options, and limited access to healthcare (Vitale, 2017).

Most published studies on FCs have focused on cancer (Choi et al., 2016; Yu et al., 2017), Alzheimer's dementia (Zhao et al., 2012), schizophrenia (Hsiao et al.,2017), stroke (Yu et al., 2013), and other common chronic diseases (Xie et al.,2016). These studies revealed that long-term care for an affected family member can influence FCs' emotional, social, and physical well-being and often result in reduced health-related quality of life (HRQoL). These previous studies also noted that the HRQoL of FCs was affected by several variables, including their sociodemographic characteristics, the patients' clinical characteristics, personal resources, and caregiving factors.

Recently, attention has been directed to FCs of patients with rare diseases. Although these FCs are important for care provision, their HRQoL is potentially negatively affected by the caregiving role, especially as rare diseases often have difficult diagnoses, complex conditions, and difficult and expensive treatment regimens (Feltmate et al., 2015; Pelentsov et al., 2016). Some previous studies assessed the HRQoL of FCs of patients with rare diseases. For example, Kim et al. (2010) found that the FCs of patients with mitochondrial disease experienced poorer HRQoL and greater levels of depression and anxiety compared with the general population. Weng et al. (2012) reported that FCs that cared for patients with rare genetic disorders, such as Russell–Silver syndrome, were susceptible to physical and mental problems.

GD is a rare, inherited, chronic disease that is multisystemic, clinically heterogeneous, and requires lifelong management (Nalysnyk et al., 2014). These characteristics distinguish the caregiving role from that in many other health conditions and place a huge strain on FCs. Comprehensive assessment of the HRQoL of FCs of patients with GD is needed, but no such study has yet been conducted. Therefore, this study aimed to (1) assess the HRQoL of FCs caring for patients with GD disease in China, (2) compare the HRQoL of these FCs with that of the general population, and (3) identify factors that predicted HRQoL.

2 | MATERIALS AND METHODS

2.1 | Study design and data collection

There is no official registration system or database for rare disease patients and families in China. However, FCs of rare disease patients voluntarily join in rare disease communication groups for information communication and mutual assistance. The China Gaucher disease family exchange group (C-GDFEG) is currently the largest GD information exchange platform in China. As an administrator, the sponsor of the C-GDFEG is responsible for reviewing the qualifications of each patient's family before their application to join the group is accepted. As GD is a rare condition, there are only a small number of FCs in China. A cross-sectional online survey of primary FCs of patients with GD based on convenience sampling was conducted for data collection. From May to June in 2018, a total of 98 families with GD patients in C-GDFEG were invited to complete the electronic questionnaire. Up to June 2018, 51 of 98 respondents had completed the questionnaire, of which 49 questionnaires met the final inclusion criteria.

The researchers published the recruitment letter through the administrator of C-GDFEG. The recruitment letter explained the purpose of the survey, the inclusion criteria, as well as emphasized voluntary participation in the study. The inclusion criteria are listed as follows: he/she was the primary FC, he/she was aged 18 or older, and he/she was able to understand the content of the questionnaire. The administrator of C-GDFEG sent an e-questionnaire link to those who met the inclusion criteria and were willing to participate in the survey. The contact information of researchers was also sent to them for information communication. To ensure the quality of the survey, we used an enterprise version of the e-questionnaire developed by Questionnaire Star Company. To express gratitude to the respondents, each respondent would receive an automatic electronic red envelope worth 20 Yuan after completing the questionnaire. The study was approved by the Ethics Committee of Harbin Medical University (No. HMUIRB20200001).

The e-questionnaire consisted of four parts (the detail of the questionnaire can be referred in Appendix S1). Part I was informed consent. Each FC then continued to fill out the e-questionnaire after reading the informed consent form and pressing the button "accept" on their web link. Part II focused on gathering basic demographic information of the FCs, such as gender, age, residence, religious belief, level of education, marital status, employment, relationship to the patient, annual household income, number of family members with GD, hours of caregiving per day, perceived disease severity, if there was anyone else taking care of the patient with GD, if the FC is diagnosed with any chronic disease, attitude toward caregiving, and knowledge of the disease. Part III focused on collecting basic demographic information of patients including gender, age, residence, religious belief, level of education, disease duration, therapeutic regimen, and medical insurance type. In Part IV, instruments were used to assess the health status of caregivers, including the Medical Outcome Study Short Form-36 (SF-36), Zung's Self-Rating Anxiety Scale (SAS), Zung's Self-Rating Depression Scale (SDS), the Multidimensional Scale of Perceived Social Support (MSPSS), and the Herth Hope Index (HHI).

2.2 | Measurements

2.2.1 | SF-36

The 36-Item Short-Form Health Survey Questionnaire (SF-36) is a set of generic, coherent, and easily administered instruments for evaluating health-related quality of life year (Brazier et al., 1992; Kamenskaya et al., 2017; Rösler-Schidlack et al., 2011). The questionnaire contains 36 items and measures eight dimensions including physical function (PF), role limitations due to physical problems (RP), bodily pain (BP), general health (GH), vitality (VT), social function (SF), mental health (MH), and role limitations due to emotional problems (RE). The dimensions of PF, RP, BP, and GH can be summarized as physical component scores (PCS), whereas the other four dimensions (VT, SF, MH, and RE) can be summarized as mental component scores (MCS). The Chinese version of SF-36 was used to measure FCs' HRQoL. The Chinese version was shown to have sound reliability and validity in the survey of Mainland China (Li et al., 2003). The PCS and MCS scores were calculated using the standard scoring algorithms (McHorney et al., 1993; Ware et al., 1998).

2.2.2 | Zung's Self-Rating Anxiety Scale (SAS)

Zung's Self-Rating Anxiety Scale (SAS) is a self-administered instrument for measuring levels of anxiety in respondents who answered the questions according to last week's experience (Zung, 1971). The SAS consists of 20 items with a 4-point scale from never (1) to often (4) as a response option. Thus, the total score *1.25 is the final score (<50, normal range; 50–59, mild anxiety; 60–69, moderate anxiety; ≥70, severe anxiety). The Chinese version of SAS had been widely used among Chinese populations and its validity has been demonstrated (Cronbach's $\alpha = 0.85$) (Wang et al., 2017).

2.2.3 | Zung's Self-Rating Depression Scale (SDS)

Zung's Self-Rating Depression Scale (SDS) is a norm-referenced instrument to the potential presence of depressive disorders in adults (Zung, 1965). The SDS includes 20-items and each question is scored on a scale of 1–4 (a little of the time, some of the time, a good part of the time, and most of the time). The total score *1.25 is the final score (<50, normal range; 50–59, mildly depressed; 60–69, moderately depressed; ≥70, severely depressed) (Chen et al., 2020; Guo, 2012). The Chinese version of the SDS is one of the most widely used measures for depression in China, and its psychometric properties had been well documented (Cronbach's $\alpha = 0.83$) (Chen et al., 2020).

2.2.4 | Multidimensional Scale of Perceived Social Support (MSPSS)

MSPSS (Dahlem et al.,1991) includes 12 items that cover three dimensions ("family," "friends," and "significant

others"). Each item is rated on a 7-point Likert scale with the responses ranging from 1 representing "very strongly disagree" to 7 representing "very strongly agree"; thus, the total scores range from 12 to 84 with the cumulative sum of score in each item. The higher total scores indicate the respondents perceiving greater social support. The Chinese version of the MSPSS was used to measure the perceived social support of FC, as it had been widely used and demonstrated good psychometric properties in prior studies (Cronbach's $\alpha = 0.88$) (Huang et al., 1996).

2.2.5 | Herth Hope Index (HHI)

The HHI contains three subscales involving 12 items: temporality and future, positive readiness and expectancy, and interconnectedness; 12 items measure various dimensions of hope using a 4-point Likert scale (1 = strongly disagree, 2 = disagree, 3 = agree, and 4 = strongly agree). The total possible scores thus range from 12 to 48, with a higher score indicating greater hopefulness (Herth, 1992). The HHI is a short and concise instrument and is applicable to various populations including FCs (Duggleby et al., 2011; Herth, 1992). The Chinese version of HHI was widely used to measure the optimism of the family caregivers, and validity had been demonstrated for the Chinese version of HHI (Cronbach's $\alpha = 0.85$) (Li & Wu, 2004).

2.3 | Statistics analysis

The characteristics of FCs and patients were reported using frequencies and percentages for categorical variables and means and standard deviations (SDs) for continuous variables. The scores for the eight subscales, PCS, and MCS were calculated following the standard SF-36 scoring algorithms. Then, a single-sample t test was performed to compare the score for each of the eight subscales in SF-36 of FCs of patients with GD with its norm for the Chinese general population (Pan et al., 2011). In addition, group comparisons of PCS and MCS were conducted using student t tests for two groups and one-way ANOVA tests for three or more groups. More specifically, we tested the associations of HRQoL (PCS and MCS) of the FCs with the sociodemographic characteristics of FCs and patients of FCs (the gender, age, residence, religious belief, level of education, marital status, employment, relationship to patient, annual household income, other family members with GD, hours of caregiving per day, perceived disease severity, caregiving help from others, FCs' chronic disease, attitude toward caregiving, and

knowledge of disease), emotional distress (anxiety and depress) of FCs, the levels of support and hope of FCs, and the basis of patients (gender, age, residence, religious belief, level of education, the illness time after the diagnosis, therapeutic regimen, GD covered by medical insurance, and types of medical insurance). To avoid omitting the important variables, less stringent selection criteria of univariate analysis were adopted, and those variables with $p \leq 0.2$ in univariate analysis were entered into the multivariate linear models for further exploration (Chen, 2018), with the PCS and MCS serving as dependent variables. Statistical analyses were conducted using SAS version 9.3(SAS Institute, Cary, CN).

3 | RESULTS

3.1 | Sample characteristics

The majority of FCs were parents of the patients (89.8%), female (73.47%), living in rural areas (61.22%), atheists (79.59%), and married (93.88%). In addition, 59.18% of the FCs were from families with a yearly income of <30,000 RMB. Nearly, one-third (34.69%) of FCs cared for the patients for 6–12 h/day, and 57.14% had not received help with caregiving from others. In addition, the FCs reported emotional distress, with 30.62% reporting moderate/severe anxiety and 63.27% reporting moderate/severe depression. The occurrence rates of anxiety and depression were 67.35% and 83.67%, respectively. The mean total SAS and SDS score were 54.77 ± 10.88 and 59.73 ± 11.84, respectively. Over half (55.1%) of the FCs received moderate levels of social support, with a mean MSPSS score of 58.04 ± 11.68. The mean HHI total score was 31.02 ± 5.67, with 71.43% of participating FCs reporting a moderate level of optimism. The mean age of the patients was 11.81 ± 12.26 years with the range from 2 to 45, and 79.59% were younger than 18 years. Almost half (48.98%) of the patients had lived with GD for 4 months to 2 years since diagnosis. Although all patients had medical insurance, only 10.2% had medical insurance that covered their GD.

3.2 | HRQoL of FCs for GD patients

The comparisons between the eight dimensions of the SF-36 of FCs with the general norms are reported in Table 1. The FCs of GD had significantly lower scores in all eight SF-36 domains ($p < 0.001$) than the Chinese national norms, which were calculated using 17,754 subjects who were randomly selected from six cities in China (Pan et al., 2011). Furthermore, the most significant reduction of score occurred in the RP (27.55 ± 24.07 vs. 77.50 ± 34.86,

TABLE 1 Mean total score of FCs' SF-36, SAS, SDS, MSPSS, and HHI compared with Chinese norms

	FCs of GD (mean ± SD)	General population (mean ± SD)	T	P
Physical function (PF)	63.78 ± 30.21	87.92 ± 16.98	5.59	<0.0001
Role physical (RP)	27.55 ± 24.07	77.50 ± 34.86	14.48	<0.0001
Bodily pain (BP)	53.57 ± 24.17	82.22 ± 16.98	8.29	<0.0001
General Health (GH)	38.93 ± 21.91	62.51 ± 17.88	7.52	<0.0001
Vitality (VT)	45.31 ± 18.58	68.17 ± 17.63	9.06	<0.0001
Social function (SF)	48.98 ± 26.63	80.67 ± 19.98	8.32	<0.0001
Role emotional (RE)	20.41 ± 18.15	67.86 ± 39.44	18.18	<0.0001
Mental health (MH)	48.33 ± 16.02	68.47 ± 16.90	8.33	<0.0001
SAS	54.77 ± 10.88	37.23 ± 12.58	11.29	<0.0001
SDS	59.73 ± 11.84	41.88 ± 1.57	10.55	<0.0001
MSPSS	58.04 ± 11.68	—	—	—
HHI	31.02 ± 5.67	—	—	—

Note: There is no norm of health Chinese people for MSPSS and HHI.

$p < 0.001$) and followed by the RE (20.41 ± 18.15 vs. 67.86 ± 39.44, $p < 0.001$).

3.3 | Factors associated with HRQoL of FCs

Table 2 shows the comparison of PCS and MCS scores by different caregiving characteristics. At a significance level of $p = 0.20$, significant differences in PCS scores were found for gender ($p = 0.041$), age ($p = 0.048$), education ($p = 0.068$), employment ($p = 0.055$), daily care time ($p = 0.125$), chronic disease ($p = 0.147$), perceived disease severity ($p = 0.002$), anxiety ($p = 0.035$), depression ($p = 0.006$), and hope ($p = 0.012$). Significant differences in MCS scores were found for residence ($p = 0.111$), daily care time ($p = 0.186$), availability of other caregivers ($p = 0.040$), perceived disease severity ($p = 0.007$), anxiety ($p = 0.062$), depression ($p = 0.004$), and hope ($p = 0.017$). Moreover, duration since diagnosis ($p = 0.075$) and medical insurance type ($p = 0.082$) scores were associated with FCs' MCS scores. The multivariate linear regression model further confirmed that gender, education, daily care time, anxiety, and perceived disease severity were significant predictors of PCS scores (Table 3). Significant predictors of MCS scores were help from others with caregiving, anxiety, perceived disease severity, and medical insurance type (Table 4).

4 | DISCUSSION

Compared with FCs of patients with other chronic health problems, FCs of individuals with rare diseases faced additional caregiving challenges. To our knowledge, this was the first study to evaluate the HRQoL and related factors in FCs caring for GD patients.

The HRQoL of FCs has generally been found to be lower than that of the general population (Yu et al., 2017). For example, FCs who cared for older people with chronic diseases (Xie et al., 2016) and who cared for stroke patients (Yu et al., 2013) had significantly lower scores ($p < 0.05$) than the general Chinese population in six SF-36 domains (RP, GH, VT, SF, RE, and MH) and seven SF-36 domains (except for RE), respectively. In addition, Minaya Flores et al. (2014) reported that caregivers, providing care for patients with gliomas in France, had lower scores for six SF-36 domains (RP, BP, VT, SF, RE, and MH) than the French norms ($p < 0.05$). Similarly, Nguyen et al. (2015) reported that in the United States, caregivers of patients with chronic liver disease had lower SF-36 scores in four domains (RE, VT, MH, and SF) than the national norms ($p < 0.05$). However, in the present study, FCs' scores for all eight SF-36 domains were significantly lower than the national norms, indicating that FCs of patients with GD experienced lower HRQoL than the general population. Therefore, policymakers should consider providing more health resources for FCs of patients with rare diseases.

In this study, the perceived disease severity of the patient was the most important factor that affected FCs' HRQoL as reflected in both the PCS and MCS scores. This indicated that the poor health status of patients with GD could lead to a negative impact on the mental and physical functioning of FCs. This finding was consistent with previous studies that also revealed, providing care for patients with rare conditions had a greater impact on families than providing care for more common conditions

TABLE 2 Comparison of scores of PCS and MCS among different caregiving characteristics

Characteristics	N (%)	PCS	t/F	P	MCS	t/F	P
Family caregivers							
Gender			4.402	**0.0413**		0.54	0.4642
Female	36 (73.47)	40.53 ± 21.47			37.27 ± 20.42		
Male	13 (26.53)	55.44 ± 23.34			42.01 ± 19.66		
Age			3.239	**0.0482**		0.96	0.3908
≤30	25 (51.02)	54.12 ± 24.81			33.22 ± 13.98		
31–39	10 (20.41)	41.13 ± 18.69			41.94 ± 19.76		
≥40	14 (28.57)	36.87 ± 16.85			44.01 ± 22.97		
Residence			0.12	0.729		2.64	**0.1111**
Urban	19 (38.78)	46.85 ± 22.41			44.34 ± 18.79		
Rural	30 (61.22)	44.53 ± 23.12			35.09 ± 20.41		
Religious belief			1.25	0.2685		0.19	0.6646
No	39 (79.59)	38.88 ± 20.11			40.13 ± 18.73		
Yes	10(20.41)	47.78 ± 22.94			43.21 ± 24.37		
Education			3.49	**0.068**		0.25	0.6202
College and above	15 (30.61)	54.76 ± 26.56			42.89 ± 24.00		
College bellow	34 (69.39)	42.07 ± 19.63			39.812 ± 17.91		
Marital status			0.48	0.465		0.48	0.452
Married	46 (93.88)	44.63 ± 22.11			38.99 ± 18.18		
Not married	3 (6.12)	48.33 ± 21.68			40.76 ± 27.66		
Employment			3.88	**0.0549**		0.01	0.9099
Employed (full time and part time)	23 (46.94)	52.48 ± 21.87			41.1 ± 23.31		
Unemployed	26(53.06)	40.18 ± 21.80			40.44 ± 16.46		
Relationship to patient			2.16	**0.134**		0.33	0.7223
Mother	33 (67.35)	40.09±21.79			36.8 ± 21.03		
Father	11 (22.45)	54.95 ± 23.49			41.48 ± 17.96		
Other (spouse)	5 (10.2)	56.05 ± 22.40			44.61 ± 30.52		
Annual family income (RMB)			1.17	0.2846		0.05	0.8211
≤30,000	29 (59.18)	43.08 ± 20.82			40.22 ± 19.18		
>30,000	20 (40.82)	50.14 ± 24.64			41.54 ± 21.06		
Whether other family members have Gaucher disease			0.33	0.5697		0.03	0.8615
No	40 (81.63)	46.83 ± 23.26			40.99 ± 20.67		
Yes	9 (18.37)	42.05 ± 19.34			39.70 ± 16.07		
Daily care time			2.18	**0.1245**		1.74	**0.1863**
<6 h	9 (18.37)	51.66 ± 25.44			46.08 ± 21.07		
6-12 h	17 (34.69)	48.00 ± 19.53			38.61 ± 16.39		
>12 h	23 (46.94)	37.16 ± 17.45			34.68 ± 18.56		
Perceived disease severity			7.34	**0.0017**		5.62	**0.0065**
Mild	20 (40.82)	55.64 ± 16.55			47.32 ± 24.64		
Moderate	17 (34.69)	47.4 ± 24.23			43.58 ± 12.88		
Severe	12 (24.49)	27.79 ± 18.58			25.79 ± 8.88		

(Continues)

TABLE 2 (Continued)

Characteristics	N (%)	PCS	t/F	P	MCS	t/F	P
Whether others help with caregiving			0.32	0.5753		4.48	**0.0396**
No	28 (57.14)	42.11 ± 21.94			28.59 ± 16.04		
Yes	21 (42.86)	46.83 ± 22.79			43.49 ± 19.65		
Chronic disease			2.17	**0.1471**		0.03	0.874
No	34 (69.39)	49.06 ± 22.50			41.05 ± 18.14		
Yes	15 (30.61)	38.91 ± 21.50			40.07 ± 23.71		
Caregiving attitude			0.61	0.4386		0.03	0.8547
Positive	31 (63.27)	47.87 ± 22.92			41.44 ± 20.18		
Negative	18 (36.73)	42.65 ± 21.93			40.35 ± 19.84		
Understanding of disease			0.05	0.9539		0.33	0.7214
Fully	11 (22.45)	47.72 ± 19.24			44.28 ± 28.37		
Partially	13 (26.53)	45.72 ± 24.39			41.84 ± 16.58		
Lacking	25 (51.02)	44.92 ± 22.78			38.63 ± 17.23		
Anxiety (SAS score)			3.12	**0.0351**		2.62	**0.0624**
Normal	16 (32.65)	52.2 ± 21.97			49.01 ± 21.22		
Mild	18 (36.73)	51.5 ± 19.97			41.88 ± 20.46		
Moderate	9 (18.37)	36.05 ± 25.46			34.18 ± 9.45		
Severe	6 (12.25)	27.2 ± 13.20			28.21 ± 14.31		
Depression (SDS score)			4.73	**0.0059**		5.16	**0.0038**
Normal	8 (16.33)	60.20 ± 21.64			57.71 ± 30.99		
Mild	10 (20.40)	56.72 ± 25.20			49.38 ± 10.41		
Moderate	22 (44.90)	42.53 ± 16.80			35.08 ± 14.05		
Severe	9 (18.37)	28.94 ± 21.96			29.98 ± 16.21		
Social support (MSPSS score)			0.81	0.4519		1.43	0.2504
Low	3 (6.12)	43.93 ± 22.73			38.08 ± 19.66		
Moderate	27 (55.10)	46.40 ± 23.11			41.85 ± 20.13		
High	19 (38.78)	61.33 ± 13.71			57.87 ± 12.23		
Hope (HHI score)			4.91	**0.0116**		4.76	**0.017**
Low	4 (8.16)	16.56 ± 15.43			20.72 ± 10.90		
Moderate	35 (71.43)	46.77 ± 20.18			38.81 ± 18.45		
High	10 (20.41)	54.85 ± 24.54			51.57 ± 23.83		
Patients							
Duration since diagnosis			0.23	0.7981		2.74	**0.0748**
0–3 months	9 (18.37)	44.44 ± 17.85			29.24 ± 18.12		
4 months−2years	24 (48.98)	48.17 ± 25.42			40.35 ± 17.39		
>2 years	16 (32.65)	43.48 ± 20.99			47.83 ± 21.84		
Treatment option			0.44	0.509		0.88	0.3529
Treated	27 (55.10)	44.02 ± 21.83			43.14 ± 19.94		
Untreated	22 (44.90)	48.34 ± 23.54			37.81 ± 19.58		
Whether GD had been covered by medical insurance			0.02	0.8924		0.34	0.5641
No	44 (89.80)	44.65 ± 28.14			35.85 ± 23.36		

(Continues)

TABLE 2 (Continued)

Characteristics	N (%)	PCS	t/F	P	MCS	t/F	P
Yes	5 (10.20)	46.10 ± 22.14			41.31 ± 19.54		
Medical insurance type			0.72	0.4929		2.65	**0.0816**
Medical insurance for urban workers	4 (8.16)	58.87 ± 23.47			57.65 ± 23.99		
Medical insurance for urban residents	12 (24.49)	45.52 ± 18.26			41.61 ± 19.45		
New rural cooperative medical care	33 (67.35)	44.55 ± 23.85			32.75 ± 16.43		

Note: Bold indicates $p < 0.2$ in group comparisons (Student's t test for two groups or one-way ANOVA test for multiple groups).

TABLE 3 Factors associated with health-related quality of life of FCs in PCS domain

Variables	Coefficients	SE of coefficients	χ^2	P
Male (vs. female)	10.5984	4.9372	4.61	0.0318
Age (vs. ≤30)				
31–39	−3.3909	5.2342	0.42	0.5171
≥40	−10.9213	5.7636	3.59	0.0681
College above (vs. College below)	10.7432	5.2212	4.23	0.0396
Employed (vs. Unemployed)	8.7930	5.2648	2.79	0.0949
Daily care time (vs. <6 h)				
6-12 h	−0.5914	5.8266	0.01	0.9192
>12 h	−13.1566	5.4854	5.02	0.0250
Perceived disease severity (vs. mild)				
Moderate	−0.3523	4.9070	0.01	0.9428
Severe	−17.5888	6.0234	8.53	0.0035
Chronic disease (vs. No)	−1.6381	4.7976	0.12	0.7328
SAS (vs. normal)				
Mild	−4.9562	7.3578	0.45	0.5006
Moderate	−8.0484	8.1782	0.97	0.3251
Severe	−15.6474	9.3208	4.44	0.0350
SDS (vs. normal)				
Mild	3.5276	5.5052	0.41	0.5217
Moderate	−2.2302	9.0178	0.06	0.8047
Severe	−12.2436	7.5486	2.63	0.1048
Hope (vs. low)				
Moderate	3.6337	5.7414	0.40	0.5268
High	8.2300	9.3240	0.78	0.3774

Note: Multivariate linear regression models were adopted to identify factors associated with quality life of FC in PCS domain.

(Anderson et al., 2013; Chio et al., 2005). Patients with more severe symptoms usually require more support from their FCs. Therefore, it can be expected that the HRQoL scores reported by FCs caring for patients with serious conditions would be lower than those of FCs caring for patients with milder symptoms (Chen et al., 2015; Nipp et al., 2016).

Consistent with the findings of previous studies (Angst et al., 2002; Ozono et al., 2007), we found that gender was associated with FCs' HRQoL in the PCS domain, with male caregivers reporting better physical health than females. In China, some studies revealed that when care for patients was undertaken by family members, females generally took on more tasks and expended more energy

TABLE 4 Factors associated with health-related quality of life of FCs in MCS domain

Variables	Coefficients	SE of coefficients	χ^2	P
Urban (vs. rural)	4.6316	6.9037	0.45	0.5023
Daily care time (vs. <6 h)				
6-12 h	−1.6679	5.1674	0.07	0.7868
>12 h	−9.2114	5.3353	2.11	0.1460
Perceived disease severity (vs. mild)				
Moderate	−10.9227	4.3592	6.21	0.0129
Severe	−18.9908	5.8860	10.41	0.0013
Caregiving help from others (vs. No)	12.0261	4.9945	5.32	0.0208
SAS (vs. normal)				
Mild	−9.2567	3.5894	6.43	0.0081
Moderate	−14.1012	5.5976	5.64	0.0140
Severe	−17.2604	7.1905	10.93	0.0037
SDS (vs. normal)				
Mild	−8.1565	7.2627	1.26	0.2614
Moderate	−11.5207	8.5640	1.81	0.1785
Severe	−13.3189	8.0654	2.73	0.0987
Hope (vs. low)				
Moderate	0.5381	5.9190	0.01	0.9276
High	2.0735	9.7029	0.05	0.8308
Medical insurance type (vs. medical insurance for urban workers)				
Medical insurance for urban residents	−7.1913	6.0923	1.03	0.3106
New rural cooperative medical care	−20.2540	8.5042	6.42	0.0116
Duration since diagnosis (vs. 0-3 months)				
4 months−2 years	7.8569	6.4002	1.51	0.2196
>2 years	5.0216	6.0403	0.69	0.4058

Note: Multivariate linear regression models were adopted to identify factors associated with quality life of FC in MCS domain.

and time than males, meaning they also experienced more pressure (Liu et al., 2017; Wong et al., 2019).

Some studies reported that the education level of caregivers could influence their HRQoL (Alshubaili et al., 2008; Moradi et al., 2015; Ndikuno et al., 2016). The present study confirmed that FCs of patients with GD with a higher level of education had better physical component scores than those with lower education levels. A possible explanation for this finding is that FCs with a higher education level may have better knowledge of rare diseases and therefore be better at coping with the patient's care demands and managing patient's health (especially in crises), and be able to self-regulate when the patient's disease worsens.

Another factor that positively affected the mental health of FCs in this study was cocaregiving, which was consistent with previous research on FCs of patients with

breast cancer in China (Zhu et al., 2014). Having other people to help care for the patient gives FCs a break from the demanding work of daily caregiving. Moreover, cocaregiving gives FCs the opportunity to help, encourage, and support each other. To some extent, the presence of cocaregiving could reduce the negative perceptions of FCs about providing care to patients, thereby increasing the FCs' confidence in coping with difficulties, and improving their HRQoL. Longer daily caring time can impact FCs' physical health, potentially resulting in a lower general health condition. In this study, the multivariate regression models revealed a negative correlation between daily caring time and FCs' HRQoL, with worse PCS scores for those within longer daily caring time (>12 h/day).

Caregivers of patients with rare diseases were found to experience heightened feelings of emotional distress such as anxiety and depression (Creemers et al., 2014). Previous

research confirmed that emotional distress was associated with low HRQoL among FCs of patients with chronic diseases (Doubova & Infante-Castaneda, 2016; Grov et al., 2005). Therefore, as serious diseases such as GD are long term, the need for lifelong medication could result in a huge economic burden for caregivers. In turn, this may take a toll on the caregiver's physical and mental health, which could lead to psychological problems (anxiety and depression). As expected, our study demonstrated that FCs of patients with GD had significantly lower SAS and SDS scores compared with the Chinese national norms, and anxiety was a significant factor associated with FCs' HRQoL.

Our study showed that the type of medical insurance for patients had different impacts on the HRQoL of FCs in the MCS domain; compared with FCs with medical insurance for urban workers, FCs with New Rural Cooperative Medical Care insurance had lower MCS scores ($p = 0.012$). This may be related to the current reimbursement system for drugs for patients with GD. In some developed areas in China, UEBMI covers the drugs needed for GD, which could relieve caregivers' economic burden. However, patients in rural areas without such coverage had huge financial burdens (Fu et al., 2018). This highlighted an urgent need for reasonable and impartial medical insurance to help ease family financial burdens across regions.

4.1 | Limitations

There were some limitations in the current study. First, the sample size was relatively small. However, the incidence and prevalence of GD in China are low. The research team also made sure to obtain data via the best channel, which is via the C-GDFEG. In future, we will deepen the research by enlarging the sample size. Second, this study only verified the rare disease status of a sample of FCs by the design on voluntary participation in C-GDFEG. This sample may be biased, toward FCs with active participation. Besides, there was also a possibility that the participants may underestimate their health status to elicit more support and help, introducing biases. Third, the study did not investigate the HRQoL of GD patients and explore the relationship between patients' HRQoL and FCs' HRQoL, because most of the patients in the study were children and the HRQoL assessment instrument adopted in this study could not be applied to children. It is valuable to carry out research focusing on the HRQoL of patients with GD in future.

5 | CONCLUSION

FCs of patients with GD in China report low HRQoL in all eight SF-36 domains. This study revealed that gender,

education, daily care time, anxiety, and perceived disease severity are significant predictors of PCS scores. Significant predictors of MCS scores are help from others with caregiving, anxiety, perceived disease severity, and medical insurance type. The present findings also highlighted that FCs of patients with GD and other rare diseases should receive more support. The results of this study could assist policymakers in decision-making when allocating health resources.

CONFLICT OF INTEREST
The authors declare that they have no competing interests.

AUTHORS CONTRIBUTIONS
JX and HB designed the study, performed the statistical analysis, and drafted the manuscript. XYQ and JHW compiled the questionnaires. HY and CYS contributed to the study design and revised the questionnaires. RLYT was involved in drafting the manuscript. QHW and WDH participated in the design of the study and finalized the manuscript with inputs from all authors. All authors read and approved the final manuscript.

CONSENT
All voluntary participants in this study provided electronic informed consent and the Ethics Review Board of Harbin Medical University approved this study. Family caregivers had read the informed consent form and pressed the button "accept" which representative informed consent on their web link prior to the initiation of the study.

ETHICAL APPROVAL
The study was approved by the Ethics Committee of Harbin Medical University.

DATA AVAILABILITY STATEMENT
Data sets generated and/or analyzed during the current study are not publicly available as the data also form part of an ongoing study but are available from the corresponding author on reasonable request.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the Supporting Information section.

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