Patient-centered assessment on disease burden, quality of life, and treatment satisfaction associated with acromegaly

Shuqian Liu,[1] Daphne T Adelman,[2] Yaping Xu,[3] Jillone Sisco,[4] Susan M Begelman,[3] Susan M Webb,[5,6,7] Xavier Badia,[7,8] Tina K Thethi,[9] Vivian Fonseca,[9] Lizheng Shi[1]

For numbered affiliations see end of article.

Correspondence to
Dr Lizheng Shi, School of Public Health and Tropical Medicine, Tulane University, 1440 Canal Street, Suite 1900, New Orleans, LA 70112, USA;
lshi1@tulane.edu

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ABSTRACT

The study aimed to assess the economic burden, health-related quality of life (HRQoL), and acromegaly treatment satisfaction in the USA. A web-based, cross-sectional survey was distributed to members of Acromegaly Community. Data related to comorbidities, treatment patterns, and treatment satisfaction were collected. The costs over the past 3 months included out-of-pocket cost, sick leave, leave of absence, direct loss of job due to acromegaly, unemployment, assistance to perform household chores, and family member loss of income. The HRQoL was assessed by Acromegaly Quality of Life (AcroQoL) and EQ-5D-3L questionnaires. Among 106 patients who completed the survey (mean age: 46 years, female: 76.4%), 44.3% presented with ≥5 comorbidities, and 90.6% reporting acromegaly-related symptoms. Compared with the low-symptom group 0–3 (n=41), the 4+ symptoms group (n=65) was more likely to have depression (OR=2.3, 95% CI 1.1 to 5.2) and cardiovascular disease (OR=5.8, 95% CI 2.0 to 16.7), and experienced higher costs (loss of job: $8874 vs $1717, P=0.02; unemployment disability: $17,102 vs $429, P=0.003; household chores: $2160 vs $932, P=0.0003; family members' income loss: $692 vs $122, P=0.03). The high-symptom group had lower HRQoL scores, compared with the low-symptom group (EQ-5D-3L: 0.53 vs 0.75, P<0.0001; AcroQoL: 27 vs 56, P<0.0001). Only 55.7% among patients requiring injections for acromegaly were satisfied. Patients with acromegaly who presented with multiple acromegaly-related symptoms were evidenced to have experienced higher economic burden and poorer quality of life than patients with the same diagnosis but fewer symptoms. The low rate of treatment satisfaction warrants need for further studies.

Significance of this study

What is already known about this subject?

- The disease burden and cost of acromegaly treatment emerge as a considerable topic for acromegaly management.
- Optimal disease management of acromegaly requires a highly coordinated approach involving numerous specialties and lifetime monitoring because of the complexity of comorbidities as well as the interactions of therapies and cost issues with different therapeutic options.
- However, disease control is suboptimal. Over 50% of patients with acromegaly are not effectively treated.

What are the new findings?

- The results of our study demonstrated patients with acromegaly who experience multiple comorbidities and acromegaly-related symptoms might have high economic burden and poor health-related quality of life.
- The significant impaired productivity was more than three times higher than that of cancer survivors reported in 2014.
- The average score of EQ-5D-3L observed in this particular population was much lower than that reported in patients with cancer and persons with osteoporosis-related fracture.

How might these results change the focus of research or clinical practice?

- In light of the multiple symptoms experienced by patients in this study, as well as the low patient treatment satisfaction rate among patients taking injectable somatostatin analogs/growth hormone-receptor antagonist, attention is needed to control or minimize symptoms that might have a positive impact on quality of life and economic burden.

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INTRODUCTION

Acromegaly is a chronic disorder characterized by autonomous overproduction of growth hormone (GH) predominantly due to a benign pituitary adenoma. Acromegaly is a rare disorder, with an estimated prevalence of 58–130 cases per million adults.[1] The excess GH results in increased secretion of insulin-like growth factor 1 (IGF-1), both of which are responsible for multiple significant

comorbidities. The course of the disease is insidious and slowly progressive, and results in most patients having a delay of 7–10 years in diagnosis from the time of first presentation of symptoms. As a result, patients with acromegaly usually present with advanced stages of disease and multiple comorbidities such as arthropathy, hypertension, diabetes, and cardiac diseases.[1 2] Optimal disease management of acromegaly requires a highly coordinated approach involving numerous specialties and lifetime monitoring.

It was evident that successful disease control potentially reduces mortality in a patient with acromegaly to as close as to that seen in the general population. However, disease control is suboptimal.[1 2] Over 50% of patients with acromegaly are not effectively treated because of the complexity of comorbidities as well as the interactions of therapies and cost issues with different therapeutic options.[2] Therefore, the disease burden and cost of acromegaly treatment emerge as a considerable topic for acromegaly management. The direct healthcare cost was $24,900 during the first 12 months of follow-up period following diagnosis of acromegaly reported in a cross-sectional cohort study in the USA.[3] Very few studies have assessed the impact on the disease burden of acromegaly, especially on treatment satisfaction and indirect costs such as work productivity/employment in the USA.

Most patients with acromegaly have poor health-related quality of life (HRQoL) because of its progressive nature and physical disability, which may be associated with psychological changes such as impairment in self-esteem, disruption in interpersonal relationships, depression, and/or anxiety.[4] The effect of disease control and comorbidities on patients' HRQoL is unclear.[2] This study aimed to assess economic burden, HRQoL, and treatment satisfaction with injectable somatostatin analogs (SSA)/growth hormone-receptor antagonist (GHRA) associated with acromegaly.

METHODS

A web-based, cross-sectional survey was conducted from August 2014 to October 2014. The survey link was directly distributed to the member lists of Acromegaly Community, which is a non-profit organization consisting of about 1300 patients with acromegaly in the USA. Patients with acromegaly who were 18 years of age or older and responded to the survey self-reported their demographic information (age, gender, race, marital status, education, household income, and medical insurance) and disease information (symptoms, age at diagnosis, duration of acromegaly from initial symptoms to diagnosis and/or treatment, treatments received such as surgery, radiotherapy, and concomitant medications, and comorbidities).

The frequency of the symptoms related to acromegaly, such as headache, excess sweating, fatigue, joint pain, swelling in soft tissue, tingling or numbness of the hand, snoring or sleep apnea, and visual problems, was assessed. The treatment satisfaction was evaluated by asking a question: 'Taking all things into account, how satisfied or dissatisfied are you with the injection?' The satisfaction rate was calculated as the number of patients who reported to be satisfied or very satisfied with injection over all patients requiring injections for acromegaly.

Use of resources for cost estimation

The direct cost was defined as the total out-of-pocket expense for acromegaly-related medical services or treatment over the past 3 months. The indirect costs over the past 3 months included four work-related items (ie, sick leave, leave of absence, direct loss of job due to acromegaly, and unemployment), assistance to perform household chores, and family member loss of income. The cost estimations of sick leave or leave of absence days were based on average weekly wage by age, gender, and race as reported by the US Department of Labor, Bureau of Labor Statistics in 2014.[5] The family members' loss of income due to patient's illness was also estimated using an average weekly wage of $464 for a full-time employee in 2014 based on the Bureau of Labor Statistics data.[6] The average weekly fringe benefit was also taken into account.[7] As for inability to perform household chores, patients reported the number of days they were unable to perform household chores. We assumed that they needed professional housekeeping services for 2 hours on each of the days. The median hourly wage of people providing housekeeping services was updated from the statistics reported by the US Department of Labor.[6] By multiplying this median hourly wage with the number of hours of housekeeping services, we estimated the costs due to inability to do household chores. In addition, the total out-of-pocket expense for acromegaly-related medical services or treatment over the past 3 months was also collected. All estimates of costs based on 3-month reports were then annualized.

Health-related quality of life

To provide a complimentary assessment on HRQoL, the EQ-5D-3L[6 8] and Acromegaly Quality of Life (AcroQoL) questionnaire[9–11] were used to provide a general and disease-specific descriptive profile for health status, respectively. The EQ-5D-3L comprises five dimensions of health (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) with three levels each (no problems, some/moderate problems, and extreme problems). The index value was calculated using the reference weights generated from a US population sample by Shaw *et al*[12] to provide an overall value of HRQoL. The AcroQoL has 22 items across physical dimension (8 items) and psychological dimension (14 items).[9–11] Psychological dimension contains two subdimensions, physical appearance and patient's personal relationships, which had seven items each. Each question has five possible answers on a 1–5 scale. The scores for each dimension or subdimension were quoted as a percentage with a minimal score of 0% and a maximal score of 100% equating worst and best HRQoL, respectively.[9–11] The reliability and validity of AcroQoL have been well evaluated and translated into many languages. It is a simple and validated tool used to assess acromegaly-specific HRQoL.[10 13–18]

Statistical analysis

Numbers and percentages were provided for categorical variables in descriptive analysis, including demographic characteristics, behavioral, and outcomes variables. Relevant measures of centrality such as means and medians were presented for continuous measures, as well as variance

measures such as SD and percentiles. Based on the distribution of acromegaly experiences reported by patients, the patients were then divided into a low-symptom group 0–3 and a high-symptom group with 4+ symptoms to further explore the impact on disease burden, HRQoL, and treatment satisfaction. Appropriate statistical tests (eg, t-test, Mann-Whitney U test, χ^2 test, and analysis of variance) were used based on the distribution of the data measured. Statistical analyses were performed using SAS V.9.4.

RESULTS

A total of 133 patients with acromegaly responded to the survey, of whom 106 (76.4% female) aged 22–72 years completed the questionnaire. The response rate was 10.2% (133/1300). Most of the patients were Caucasians (85.9%), married or engaged (60.4%), insured (91.5%), and with higher than high school education (58.5%). Patients' mean age at time of first acromegaly diagnosis was 37.7±11.8 years (median, 37 years), with 8.2±8 years of diagnostic delay (median, 5 years) from the time of onset of acromegaly symptoms (table 1).

Patients with acromegaly usually presented with multiple comorbidities; almost half of them (47/106) presented with five or more. The most common ones were depression (56.6%), hypertension (43.4%), musculoskeletal and connective tissue abnormalities (41.5%), sleep apnea (36.8%), cardiac and cardiovascular diseases (32.1%), and diabetes (32.1%). Among all patients, 90.6% had undergone surgery before the survey was conducted; none had undergone pituitary surgery within 6 months at the time of the survey; and 64.1% were currently on pharmacological therapy at the time of the survey (table 2).

There were 96 (90.6%) patients who still had symptoms including headache, excess sweating, fatigue, visual field defects, joint pain, and swelling in soft tissue in the past 3 months. The top three most frequent symptoms occurring every day were fatigue (84.4%), joint pain (77.1%), and headache (70.8%). Almost half of the patients experienced soft tissue swelling (44.8%) and excess sweating (43.7%) every day. Of the patients, 61.3% experienced more than four symptoms simultaneously (table 3).

The number of symptoms reported by patients in the past 3 months was then divided into two subgroups: 0–3 symptoms (low-symptom) and four or more symptoms (4+: high-symptom). Patients' demographic, comorbidities, and treatment were then compared by these two subgroups (table 1). There were no significant differences in demographics and medication uses between the two subgroups, except for age. Patients who had four or more symptoms were more likely to be younger than those with less than four symptoms (P=0.03) (table 1). As compared with the low-symptom group 0–3 (n=41), the high-symptom group with 4+ symptoms (n=65) were more likely to have depression (OR=2.3, 95% CI 1.1 to 5.2) and cardiovascular disease (OR=5.8, 95% CI 2.0 to 16.7). There was a non-significant tendency for the high-symptoms group to have a longer delay in reaching the diagnosis (5.7±4.6 vs 9.6±9.2 years, P=0.06).

Among patients on injectable medications (n=61), the rate of satisfaction with injectable SSA/GHRA treatment (satisfied/very satisfied) was 55.7%. Most of them were on SSA (53/61). There were no differences in treatment satisfaction between the low-symptom and high-symptom groups (59.3% vs 52.9%, P=0.62). No significant difference was found between those with/out SSA (56.6% vs 50.0%, P=1.00), either. The efficacy of injections was evaluated by asking if their symptoms became worse toward the end of an injection cycle (in the week or days before the next injection is due). Of the patients, 79% claimed this occurred, of whom 60.7% suffered this very frequently (table 4); 83.6% of the patients believed that symptoms interfered with daily life and work; 85.2% felt frustrated; and 37.7% requested medical intervention to alleviate symptoms, including additional daily injections, injection other than scheduled, oral drugs other than injections, or a later injection than scheduled. Consequently, 32.8% of the patients acknowledged they felt less confident (not/a little confident/somewhat confident) about the efficacy of injections; 57.4% complained about side effects (ie, pain at injection site sometimes/often to always); and 57.4% felt their current treatment is inconvenient or somewhat inconvenient (table 4). The patients' top preferences for new acromegaly treatments were to avoid injections (eg, oral formulation) (85.3%), improve disease management with more patients' support facilities (62.3%), and to provide better patient education (57.4%) (table 4).

Cost of acromegaly

The direct cost, defined as self-reported annualized healthcare out-of-pocket cost, was $1790 per person. The average number of days unable to work because of acromegaly was 34 days per person per year, resulting in $6702 loss of income per person. The total annual costs associated with loss of job and unemployment disability due to acromegaly was $6106 and $10,653 per person, respectively. The time patients were unable to perform household chores due to acromegaly, on average, was 89 days per patient every year, resulting in an annual loss of $1685. The total indirect cost per patient reached $25,145 per year. We also estimated annual loss of income of family members because they had to take work days off to take care of the patient. The annual loss was $472 for family members (table 5).

The impact of symptoms on indirect cost was assessed. Patients with four or more symptoms had significantly higher costs by category (loss of job: $8874 vs $1717, P=0.017; unemployment disability: $17,102 vs $429, P=0.003; household chores: $2160 vs $932, P=0.0003; family members' loss: $692 vs $122, P=0.028) as compared with the low-symptom group (table 5).

Health-related quality of life

The mean EQ-5D-3L QoL index was 0.62±0.23 out of 1, and the EQ-5D-3L visual analog scale was 51 out of 100. The mean AcroQoL global score was 39±22 (mean±SD) out of 100. The mean score was 37±23 in the physical dimension; within psychological dimension, the mean score was 34±23 and 46±26 in appearance and personal relationship, respectively (table 6). The scores of quality of life were much lower in the high-symptom subgroup compared with the low-symptom subgroup (EQ-5D-3L: 0.53 vs 0.75, P<0.0001; AcroQoL: 27 vs 56, P<0.0001). As compared with the low-symptom group, the high-symptom group

Table 1 Patients' reported demographics and disease characteristics by number of symptoms

n=106	n	%	0–3 symptoms	=4 symptoms	P value
% (n)			38.7 (41)	61.3 (65)	
Age					0.09
18–35 years	28	26.4	19.5 (8)	30.8 (20)	
36–50 years	35	33.0	26.8 (11)	36.9 (24)	
>50 years	43	40.6	53.7 (22)	32.3 (21)	
Female sex	81	76.4	65.9 (27)	83.1 (54)	0.59
Race/Ethnicity					0.90
Caucasian/non-Hispanic white	91	85.9	85.4 (36)	86.2 (56)	
Non-white	15	14.2	14.6 (6)	13.9 (9)	
Marriage status					0.18
Married/partner/engaged	64	60.4	68.3 (28)	55.4 (36)	
Other marriage status	42	39.6	31.7 (13)	44.6 (29)	
Household income before taxes					0.13
Less than $20,000	23	21.7	12.2 (5)	27.7 (18)	
$20,000–$49,999	19	17.9	14.6 (6)	20.0 (13)	
$50,000–$69,999	13	12.3	17.1 (7)	9.2 (6)	
$70,000–$99,999	17	16.0	19.5 (8)	13.9 (9)	
More than $100,000	17	16.0	24.4 (10)	10.8 (7)	
Did not wish to answer	17	16.0	12.2 (5)	18.5 (12)	
Education					0.10
High school or less	44	41.5	31.7 (13)	47.7 (31)	
More than high school	62	58.5	68.3 (28)	52.3 (34)	
Health insurance					0.51
Preferred provider organization	45	42.5	51.2 (21)	36.9 (24)	
Medicaid/Medicare	24	22.6	17.1 (7)	26.2 (17)	
Other insurance	25	23.6	24.4 (10)	27.7 (18)	
No insurance/did not answer	12	11.3	7.3 (3)	9.2 (6)	
Multi-insurance					0.93
No insurance	9	8.5	7.3 (3)	9.2 (6)	
1 insurance	81	76.4	78.1 (32)	75.4 (49)	
More than 1 insurance	16	15.1	14.6 (6)	15.4 (10)	
Smoking					0.76
Current smoker	12	11.3	9.8 (4)	12.3 (8)	
Non-smoker	94	88.7	90.2 (37)	87.7 (57)	
Comorbidities					
Depression	60	56.6	43.9 (18)	64.6 (42)	0.045
Hypertension	46	43.4	39.0 (16)	46.2 (30)	0.54
Musculoskeletal connective tissue	44	41.5	36.6 (15)	44.6 (29)	0.42
Sleep apnea	39	36.8	36.6 (15)	36.9 (24)	1
Cardiovascular	34	32.1	12.2 (5)	44.6 (29)	0.0005
Diabetes	34	32.1	34.2 (14)	30.8 (20)	0.83
Treatment pattern					
SSA	54	50.9	61.0 (25)	44.6 (29)	0.11
GHRA	9	8.5	4.9 (2)	10.8 (7)	0.48
DA	15	14.2	17.1 (7)	12.3 (8)	0.57
	Mean±SD	**Median (IQR)**	**Mean±SD**	**Mean±SD**	
Age (years)	45.7±12.0	44 (20)	49.0±12.3	43.7±11.5	0.03
Age at diagnosis (years)	37.7±11.8	37 (17)	40.1±13.1	36.1±10.8	0.13
Duration of acromegaly	8.1±7.5	5 (9)	8.9±7.1	7.6±7.8	0.14
Delay in diagnosis (years)	8.2±8.0	5 (8.5)	5.7±4.6	9.6±9.2	0.06

DA, dopamine agonists; GHRA, growth hormone-receptor antagonist; SSA, somatostatin analogs.

had considerably worse scores in physical dimension (26 vs 54), psychological subscale of appearance (23 vs 51), and subscale of personal relation (34 vs 64, all P<0.0001) (table 6).

DISCUSSION

The present study demonstrated high disease burden of acromegaly in respect to HRQoL and economic aspects as compared with the general population in the USA. Few

Table 2 Treatment pattern in patients with acromegaly

n=106	% (n)
Any treatment received	
No treatment	1.9 (2)
Surgery	90.6 (96)
Surgery only	15.6 (15)
Combine with radiotherapy/drugs	84.4 (81)
Radiotherapy	33.0 (35)
Pharmacological therapies/medicines	80.2 (85)
Current treatment type by drug class	
No medications	35.9 (38)
Current medications	64.2 (68)
SSA only	43.4 (46)
Long-acting SSA only	37.7 (40)
Short-acting SSA only	2.8 (3)
Long-acting + short-acting SSA	2.8 (3)
GHRA only	6.6 (7)
GHRA+SSA	0
DA only	5.7 (6)
SSA+DA	6.6 (7)
GHRA+DA	0.9 (1)
SSA+GHRA+DA	0.9 (1)
SSA (with/without other drugs)	50.9 (54)
GHRA (with/without other drugs)	8.5 (9)
DA (with/without other drugs)	14.2 (15)

DA, dopamine agonists; GHRA, growth hormone-receptor antagonist; SSA, somatostatin analogs.

Table 3 Symptoms related to acromegaly in the past 3 months among patients who had any symptoms

n=96	% (n)
Fatigue/day	
Less than one time per day	15.6 (15)
At least one time per day	84.4 (81)
Joint pain/day	
Less than one time per day	22.9 (22)
At least one time per day	77.1 (74)
Headache/day	
Less than one time per day	29.2 (28)
At least one time per day	70.8 (68)
Swelling in soft tissue/day	
Less than one time per day	55.2 (53)
At least one time per day	44.8 (43)
Excess sweating/day	
Less than one time per day	56.3 (54)
At least one time per day	43.7 (42)
Symptom related to carpal tunnel syndrome/day	
Less than one time per day	62.5 (60)
At least one time per day	37.5 (36)
Snore/day	
Less than one time per day	65.6 (63)
At least one time per day	34.4 (33)
Vision problem/day	
Less than one time per day	75.0 (72)
At least one time per day	25.0 (24)
Number of types of symptom, n=106	
No symptoms in the past 3 months	9.4 (10)
1–3	29.3 (31)
≥4	61.3 (65)

studies have been published regarding the indirect cost of acromegaly in the USA. In the present study, patients with acromegaly experienced significant impaired productivity, which resulted in per capita mean financial loss of $25,145 annually. The largest portion of this burden came from unemployment disability ($10,653), which was more than three times higher than that of cancer survivors (around $3000) reported in 2014.[19] Given the differences in proportion of age, sex, and race in different studies, it is difficult to compare income loss of missed work days among employed persons.[5] However, when it is compared with the estimation of lost productivity in performing household chores for cancer survivors, which was only $291/person/year,[19] it is higher among patients with acromegaly ($1685), indicating how severely this disease affects activities of daily living outside of work.

It is notable that four or more symptoms reported by study subjects were a great contributor to such an economic loss. Most of the patients (90.6%) still had symptoms, and 61.3% experienced more than four symptoms simultaneously (table 3). The high-symptoms group (4+ symptoms) incurred higher financial loss in loss of job (P=0.02) and unemployment disability (P=0.003) compared with the group of low symptoms (0–3 symptoms), indicating patients with high symptoms might suffer from disability or other severe conditions. The symptoms also interfered with patients' daily activities as patients in the high-symptoms group had to spend 2.3 times more money to pay for household chores services than those with low symptoms (P=0.0003). Furthermore, more symptoms required help or assistance from their family members, resulting in $570 extra financial loss per year in the high-symptoms compared with the low-symptoms group (P=0.03).

It is known that some reversible symptoms such as headache and excessive sweating improve when GH and IGF-1 are controlled in therapeutic intervention studies[15 20]; other symptoms related to prolonged chronic comorbidities such as cardiovascular disease, degenerative osteoarthropathy, and diabetes might persist or worsen despite treatment of acromegaly,[20] implying that the subjects in the present study are likely at an advanced stage of acromegaly. Likewise, in a prior report, younger patients are reported to have more aggressive tumors and higher GH concentrations,[20] which is supportive of our finding that the high-symptom group was more likely to be younger, and to have cardiovascular disease or depression, as compared with the low-symptom group. Further, the costs for patients with multiple comorbidities were considerably more than that of patients without comorbidity. For instance, it was reported that there were additional annual medical costs of $18,840 and $14,225 in patients with cardiovascular abnormalities or colon neoplasm, respectively.[3] In the present study, cardiovascular abnormalities increased 3.4 times missed work days; depression was responsible for $1658 extra cost due to inability to perform household chores.

Although the present study sample was recruited from Acromegaly Community, one of the largest acromegaly

Table 4 Treatment satisfaction among patients requiring injections for acromegaly

Total n=61	% (n)
Long-acting SSA only	65.6 (40)
Short-acting SSA only	4.9 (3)
Long-acting + short-acting SSA	3.3 (2)
GHRA only	11.5 (7)
GHRA+SSA	0
SSA+DA	11.5 (7)
GHRA+DA	1.6 (1)
SSA+GHRA+DA	1.6 (1)
Inconsistency between acromegaly symptoms and injections: sometimes they are better between the injections and sometimes they are worse.	
Never/rarely	21.3 (13)
Sometimes	36.1 (22)
Often to always	42.6 (26)
The symptoms become worse toward the end of an injection cycle (in the week or days before the next injection is due).	
Never/rarely	21.3 (13)
Sometimes	18.0 (11)
Often to always	60.7 (37)
The symptoms interfere with daily life and work (including both outside work and housework).	
Never/rarely	16.4 (10)
Sometimes	34.4 (21)
Often to always	49.2 (30)
The symptoms make the patient feel fed up and frustrated.	
Never/rarely	14.8 (9)
Sometimes	26.2 (16)
Often to always	59.0 (36)
The injection is very painful on the day of the injection at the injection site.	
Never/rarely	42.6 (26)
Sometimes	23.0 (14)
Often to always	34.4 (21)
The injection is still painful for 1–5 days after the injection at the injection site.	
Never/rarely	57.4 (35)
Sometimes	24.6 (15)
Often to always	18.0 (11)
Acromegaly symptoms lead to request medical intervention.	37.7 (23)
Symptoms led to request additional daily injection or injection other than scheduled.	9.8 (6)
Symptoms led to request another oral medicine other than injections.	19.7 (12)
Symptoms led to request a later injection than scheduled.	21.3 (13)
Satisfaction with injection	
Dissatisfied/very dissatisfied	8.2 (5)
Somewhat satisfied	36.1 (22)
Satisfied/very satisfied	55.7 (34)
How confident are you that taking these injections is a good thing for you?	
Not/a little confident	13.1 (8)
Somewhat confident	19.7 (12)
Confident/very confident	67.2 (41)
How convenient are your current treatments?	
Inconvenient/very inconvenient	29.5 (18)
Somewhat inconvenient	27.9 (17)
Convenient/very convenient	42.6 (26)
Patients' perspective	
Improvement in injection	54.1 (33)
Wish new medicine avoids injection	85.3 (52)
Improvement in patients' education	57.4 (35)
Improvement in patients' support	62.3 (38)
Improvement in daily medical treatment to control GH/IGF-1	21.3 (13)

DA, dopamine agonists; GH, growth hormone; GHRA, growth hormone-receptor antagonist; IGF-1, insulin-like growth factor 1; SSA, somatostatin analogs.

support groups in the USA,—patients who experience problems were more prone to participate in a patient advocacy group This was not representative of all patients with acromegaly in the USA and —these results support the evidence that costs are incurred for the management of comorbidities in patients with advanced stage/multiple symptoms, and indirect costs could further add to total costs.[2]

As a result, the prolonged and stressful multiple episodes of symptoms brought about adverse psychological reactions, both of which substantially interfere with quality of life. The average score of EQ-5D-3L was 0.62±0.23, which was lower than that reported in patients with cancer (0.79±0.15)[21] and persons with osteoporosis-related fracture (0.85±0.14).[22] HRQoL evaluated by AcroQoL was markedly impaired as the mean global score was only 39±22 in our sample, and much lower in the high-symptoms group than in the low-symptom group (table 6). It is worth noticing that 56.6% of our patients experienced depression/depressive symptoms, which might contribute to poor HRQoL. Psychopathological variables such as depressive symptoms and anxiety were reported to be common in acromegaly. There was a clear association between psychopathology and perceived HRQoL, indicating poor HRQoL might be persistent if a patient with acromegaly has a mental disorder.[23] Moreover, there is evidence that patients with active acromegaly, or presenting more comorbidities, have significantly worse HRQoL than those with biochemically controlled disease,[1 11 13 16 24] and it was markedly worse among patients who require prolonged pharmaceutical therapy with SSA[25]; in contrast, good control of GH/IGF-I excess improved the psychological subscale appearance of AcroQoL among patients with acromegaly.[26] In the study of Postma *et al*[18] comprising 108 patients with persistent acromegaly receiving postoperative combination therapy, the subscale scores in appearance and personal relations were extremely impaired (ranged from 21.1 to 26.9), which was interestingly similar to that in the high-symptom group in the current study (table 6).

The most striking result of the present study was that the rate of satisfaction for injectable SSA/GHRA treatment was only 55.7% among patients receiving injections with SSA and/or GHRA for acromegaly (n=61). In addition, most of the patients felt frustrated and preferred to avoid injections if a new therapy became available (table 4). All these factors may further contribute to the poor HRQoL regardless of the real clinical and biochemical efficacy of the treatment. Our study highlights that attention is needed for

Table 5 Direct and indirect costs among patients with acromegaly by number of symptoms

n=106	Mean±SD	Median (IQR)	0–3 symptoms Mean±SD (n=41)	≥4 symptoms Mean±SD (n=65)	P value
Direct cost in US dollars					
Out-of-pocket cost	1790±5212	200 (844)	1461±4920	1997±5415	0.21
Indirect cost in US dollars					
Work related: total cost of missed work	6702±18389	0 (730)	4088±12873	8350±21074	0.51
Direct loss of job	6106±14951	0 (0)	1717±5278	8874±17144	0.02
Unemployment disability	10,653±59,499	0 (0)	429±1927	17,102±75,476	0.003
Household chores	1685±2185	761 (2282)	932±1781	2160±2292	0.0003
Total indirect costs for patient	25,145±65,240	2282 (26,448)	7166±15,377	36,485±80,607	<0.0001
Family member loss of income	472±2335	0 (0)	122±781	692±2905	0.03

acromegaly-related symptoms, while treating comorbidities might improve treatment satisfaction and quality of life and reduce indirect cost of acromegaly.

In this study, we found a lower AcroQoL score than in previous reports, in which the average scores ranged from 50 to 68.[10 11 15–17 27] However, when comparing patients' characteristics, medical history, comorbidities, and treatment patterns with previous reports, our study population who presented more prevalent and multiple comorbidities was more likely to be on polytherapy, and has active acromegaly. Moreover, in comparison to most other AcroQoL results published where patients are recruited from reference centers, here the sample consists of members of a patients' advocacy group (ie, Acromegaly Community). Patients who feel fine usually do not search for patient support groups, while those who experience problems are much more prone to refer to them. On the other hand, reference centers usually have better outcome results of their patients with acromegaly[28]; this may explain, in part at least, the lower AcroQoL scores reported in our study sample. This is also consistent with the high percentage of symptoms reported by study subjects, as well as the characteristics of the present study.

Several relevant limitations of this study should be acknowledged. First, as mentioned before, this study was a non-probability sample because of limited knowledge of distribution of age, gender, and race in the Acromegaly Community, which was not representative of all patients with acromegaly in the USA. Further, a non-response bias might be present because of the low response rate. Non-internet users or people with limited literacy might not be included in the sample. Patients who participated/completed the survey might have a more severe or complicated disease condition, worse outcome results (ie, uncontrolled disease), less health awareness or knowledge, and so on. The sample size is relatively small, which reduces the strength of the statistical results. Yet acromegaly is a rare disease, which makes it difficult to recruit subjects.

The second is inherent to the nature of a cross-sectional survey design, in which results are only based on self-reported data and do not account for variability of outcomes over time. The biochemical measurements were not collected, making it impossible to identify whether the disease conditions were well controlled or not. Indeed, biochemical parameters were not always a good predictor of cost or HRQoL.[1 16 29] For example, studies indicate that comorbidities and persistence of certain symptoms might continue to impair HRQoL, regardless of the treatment and the biochemical control of acromegaly.[15 29] Moreover, the estimation of cost was based on reports in the past 3 months, which might not be representative of all the long-term outcome of the patients. However, this method is commonly used in self-reported surveys of disease burden.

Third, although we did not further verify the diagnosis of acromegaly in our subjects, they were more likely to be a patient with confirmed acromegaly since they were from a patients' advocacy group. There were possibilities of memory errors in recall of medical history, or misdiagnosis of comorbidities or mistakes due to lack of knowledge of the disease. Nonetheless, our report of patient demographic and medical characteristics is in concordance with prior epidemiological reports[1 20] and the American Association of Clinical Endocrinologists guidelines for diagnosis and treatment of acromegaly updated in 2011.[30] Our study further confirms that

Table 6 Health-related quality of life among patients with acromegaly by number of symptoms

n=106	Mean±SD	Median (IQR)	0–3 symptoms Mean±SD (n=41)	≥4 symptoms Mean±SD (n=65)	P value
EQ-5D-3L					
QoL index	0.62±0.23	0.71 (0.36)	0.75±0.19	0.53±0.21	<0.0001
QoL VAS	51±23	54 (39)	64±19	42±21	<0.0001
AcroQoL					
Acro score	39±22	35 (25)	56±22	27±14	<0.0001
Physical dimension	37±23	38 (31)	54±23	26±15	<0.0001
Psychological subdimension appearance	34±23	29 (25)	51±25	23±14	<0.0001
Psychological subdimension personal relation	46±26	43 (32)	64±26	34±18	<0.0001

AcroQoL, Acromegaly Quality of Life; QoL, quality of life.

comorbidities, symptoms, as well as treatment patterns may have great impact on cost and HRQoL for patients with acromegaly. To the best of our knowledge, this is the first study that reports indirect costs in the USA.

CONCLUSION

Patients with acromegaly who experienced multiple comorbidities and acromegaly-related symptoms might have high economic burden and poor HRQoL compared with the general population, especially for those who need combination therapy throughout their lifetime. Acromegaly-related symptoms result in huge indirect costs and severely impair HRQoL for people living with acromegaly. Although some symptoms might be persistent because of prolonged duration of chronic comorbidities, necessary attention is needed to control or minimize symptoms during disease management, which may benefit HRQoL and the economic burden. The low rate of satisfaction with injectable SSA/GHRA treatment deserves further studies. In light of the multiple symptoms experienced by patients in this study, as well as the low patient treatment satisfaction rate and expressed patient treatment preferences, this study substantiates that there may be need for improved medical therapy, or new medications would be needed from an economic point of view as well as that of the patient experience and quality of life perspective.

Author affiliations
[1]Department of Global Health Management and Policy, School of Public Health and Tropical Medicine, Tulane University, New Orleans, Louisiana, USA
[2]Department of Endocrinology, Northwestern University Feinberg School of Medicine, Chicago, Illinois, USA
[3]US Medical Affairs, Genentech, South San Francisco, California, USA
[4]President, Acromegaly Community, Grove, Oklahoma, USA
[5]Endocrinology/Medicine Departments, Hospital de la Santa Creu i Sant Pau, Barcelona, Catalunya, Spain
[6]Department of Endocrinology, Universitat Autònoma de Barcelona (UAB), Barcelona, Spain
[7]Centro de Investigación Biomédica en Red de Enfermedades Raras, Instituto de Salud Carlos III, Madrid, Spain
[8]Omakase Consulting and University of Barcelona, Barcelona, Spain
[9]Department of Medicine, Tulane University Health Sciences Center, New Orleans, Louisiana, USA

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