Burden of acromegaly in the United States: increased health services utilization, location of care, and costs of care

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ABSTRACT

Background: Limited information is available on the utilization and healthcare costs among patients with acromegaly. The purpose of this study was to assess the impact of acromegaly on healthcare utilization and costs by locations of care (LoC).

Methods: Patients with acromegaly and controls were identified from an analysis of drug and medical claims filed from January 2010 to April 2019 from a US employer database. Each patient with acromegaly was matched with 20 random controls (without acromegaly) selected from the database. Claims were tracked for 12 months postdiagnosis (or matched date for controls). Outcomes by LoC, including costs, services, and likelihood of use, were compared using two-stage regression models or logistic regression models, controlling for demographic and job-related variables, and Charlson comorbidity index scores.

Results: Claims from 60 patients with acromegaly and 1,200 controls were analyzed. Compared with the control group, patients with acromegaly had significantly higher likelihoods of receiving care in a physician’s office [odds ratio > 1,000], inpatient [OR = 8.010], outpatient [OR = 12.656], laboratory [OR = 3.681], and ‘other’ locations [OR = 4.033] (all p < .001), except in an emergency department (ED). Significantly more services were performed at each LoC for those with acromegaly (p < .01) but not in an ED. Total costs were more than 5-fold higher for the acromegaly cohort compared with controls (p < .05). Costs by LoC were consistently higher (p < .001) for patients with acromegaly vs. controls, with mean annual cost differences greatest in outpatient hospital/clinic ($9,611 vs $1,355), inpatient ($8,646 vs $739), physicians’ office ($4,762 vs $1,301), other ($2,001 vs $367), and laboratory ($508 vs $66). ED-related treatment costs were not significantly different between cohorts.

Conclusions: Compared with matched controls, patients with acromegaly were more likely to utilize healthcare services in nearly all LoCs and accrue higher expenditures at each LoC, with the exception of ED services.

Introduction

Acromegaly is a chronic debilitating disorder caused, in most cases, by excessive endogenous growth hormone (GH) hypersecretion from a pituitary adenoma that results in the overproduction of insulin-like growth factor 1 (IGF-1). The primary manifestation of acromegaly is abnormal tissue growth, but it is also associated with several serious comorbid conditions (e.g., type-2 diabetes, osteoarthritis, cardiovascular disease, sleep apnea). The life expectancy of untreated patients with acromegaly may also be shorter than the general population.

Acromegaly is a rare disease, with a reported prevalence of up to 13.7 per 100,000 people. Most patients with acromegaly are diagnosed between 18 and 64 years of age, with a peak during the fourth decade of life, coinciding with their most productive working years.

The disease is associated with multiple comorbidities that are present often long before the diagnosis is made. Many of these comorbidities are often not optimally treated despite achieving biochemical control, resulting in impairment in quality of life. The goal of therapy is to normalize the circulating levels of GH and IGF-1, and thereby reduce comorbidities and normalize the excess mortality. Treatment options include surgery, pharmacotherapy, and lifelong monitoring is necessary to monitor for disease control, to assess for therapeutic efficacy and medical therapy side-effects, and to detect disease recurrence after successful surgery.

Research has been published recently on the economic impact of acromegaly, including health services utilized by patients with acromegaly and health expenditures associated with the condition. In an effort to bolster this information, Yuen and colleagues evaluated how...
acromegaly influenced direct medical and prescription costs, indirect costs, and lost work time associated with absences and disability. However, one health economic area has not been fully explored: the patterns of healthcare utilization in patients with acromegaly by locations of care (LoC). Related to this is whether these LoC patterns differ from that of the general population. Studying utilization of LoC is essential for efficient resource allocation and healthcare funding, especially as the costs of treating acromegaly can be exorbitant. The main objective of this analysis was to evaluate the likelihood, number, and cost of healthcare services used, according to LoC, by individuals with acromegaly and a matched control group.

Methodology

This retrospective study was conducted using the Workpartners (formerly known as Human Capital Management Services) Research Reference database (RRDb), a proprietary health claims database that includes claims information on 2.9 million de-identified US employees and 1.7 million dependents. Prescription drug and medical (including LoC) claims data are available, as well as human resource information from January 2001 to the present.

The retrospective patient identification methodology utilized specific International Classification of Diseases (ICD) codes to highlight potential acromegaly claims. This methodology was also used in a previous study of patients with acromegaly by the authors. Claims using ICD-9 code 253.0 (short description, acromegaly or gigantism) or ICD-10 code E22.0 (short description, acromegaly or pituitary gigantism), identified patients with acromegaly. The identified population included employees with acromegaly in addition to any identified spouses (including domestic partners) with acromegaly receiving health benefits through the employee. To be included in the study, patients (age range, 18–64 years) had to have at least 12 continuous months of eligibility for healthcare (and prescription drugs). Additionally, all eligible patients had to meet the following criteria:

- At least two diagnoses of acromegaly at least 30 days apart
- One diagnosis of acromegaly plus either a diagnosis of pituitary adenoma or one claim for pituitary surgery (hypophysectomy) or stereotactic radiosurgery

Evidence of any other nonacromegaly pituitary disorders in the claims information, such as prolactinoma, non-functioning pituitary adenoma, Cushing disease, and craniopharyngioma, resulted in patient exclusion.

Patients were assigned an index date based on the initial date of acromegaly diagnosis. Each patient with acromegaly was matched to 20 controls. The 1:20 matching process reduced the standard errors of the outcome variables for the control group, strengthening the power of the between-group comparisons. The control group comprised randomly selected employees and spouses who did not have any acromegaly diagnoses during the patient selection period and were continuously covered by health insurance during the 12-month follow-up period. Controls were matched by demographics (age, percent female, marital status, self-reported racial information), region of the country, and index date. Furthermore, employees with acromegaly were matched with control employees, and spouses with acromegaly were matched with control spouses.

The claims data from patients with acromegaly and their matched controls were collected for 12 months following their index date. These data formed the basis for the analysis of healthcare utilization and costs.

Medical claims were assigned to LoCs based on identifiers on the claim and included physician’s office, inpatient hospital, outpatient hospital or clinic, emergency department, laboratory, and “other” (which includes ambulance claims and claims without a specific location code). Medical claim outcomes that were analyzed by LoC included costs, number of services (potentially more than one chargeable activity per visit; for example, blood work, evaluation and management, radiology, diagnostic tests, etc.), and likelihood of use. The costs and number of services were compared using separate two-stage stepwise regression models (logistic followed by generalized linear regression) for each outcome. The models only used logistic regression. Prescription claims were analyzed in total and for non-acromegaly agents. The two-stage regression models were chosen, because they can effectively account for the non-normal distributions of outcomes variables, such as cost and number of services.

In each case, the multivariate regression models controlled for the impact of such confounding factors as age, gender, marital status, race, employment status of the covered worker, region of the country based on the zip code first digit, employee versus spouse indicator, and the Charlson Comorbidity Index score (a risk-adjusting score built from claims data indicators of serious comorbid conditions that are predictive of mortality). A subanalysis of the patients with acromegaly was included to explore the impact of hypopituitarism on costs.

Based on the primary ICD code listed, all medical claims were assigned to one or more of 284 specific categories defined by the Agency for Health Research and Quality (AHRQ). These categories were developed to help understand the patterns of diagnoses and procedures so that health plans, policymakers, and researchers can analyze costs, utilization, and outcomes associated with particular illnesses and procedures. The most prevalent categories in the cohort with acromegaly were compared with the controls using two-sample proportion tests.

In an effort to normalize costs over the 10 years of claims analysis, cost data were adjusted to constant 2019 dollars using the medical Consumer Price Index (CPI) and the prescription drug cost CPI from the US Bureau of Labor Statistics. All models and statistics were generated via SAS Enterprise Guide, version 7.15 (SAS Institute Inc, Cary, North Carolina). A p value of .05 was considered the threshold for statistical significance.
**Results**

A total of 60 patients with acromegaly were identified, including 47 employees from the US employee database and 13 spouses (Table 1). These patients with acromegaly were matched to 1,200 controls.

There were no significant socioeconomic or demographic differences between those with acromegaly and their matched controls (Table 2). Nine of the patients with acromegaly (15%) had hypopituitarism.

Statistically significant differences were demonstrated upon analysis of how individuals with acromegaly accessed healthcare services compared with their matched controls (Table 3). For example, patients with acromegaly had a higher likelihood of seeking health care services in the physician’s office (odds ratio [OR] >1,000; 95% CI [>0.001, >1,000], p < .0001), inpatient setting (OR 8.010; [0.943, 3.506], p < .0005), outpatient facility (OR 12.656; [5.715, 28.024], p < .0001), laboratory (OR 3.681; [2.084, 6.502], p < .0001), and “other” locations (OR 4.033; [2.327, 6.990], p < .0001).

In addition, the number of healthcare services associated with each LoC, except the emergency department, was greater for patients with acromegaly than for matched controls (Table 4). This was especially prominent in the office, outpatient, and laboratory settings. For example, patients with acromegaly had a mean of 31.6 chargeable services in the physician’s office over the 12-month study period compared with the controls, who had a mean of 13.6 services (p < .0001). In the outpatient/hospital/clinic setting, the mean number of chargeable services was significantly greater for those with acromegaly compared with those without acromegaly (p < .0001). Statistically significant differences between the cohorts were also apparent for laboratory services (p < .0001), inpatient services (p = .0013), and “other” services (p < .0001). This was not the case for emergency department services (a mean of 0.6 for patients and controls).

Total costs were higher for the patients with acromegaly compared with their matched controls (p < .05). When evaluated by LoC, costs were consistently higher except in the emergency department (all others statistically significant at p < .0001) for the cohort with acromegaly (Table 5). Cost differences by LoC were greatest for care given in the outpatient hospital/clinic (p < .0001), inpatient setting (p = .0009), and physicians’ office (p < .0001). Laboratory costs were nearly eight-fold higher as well for patients with acromegaly compared with controls (p < .0001). As expected, none of the matched controls utilized acromegaly-indicated medications.

In the subanalysis of patients with acromegaly presenting with hypopituitarism, ED costs for the patients without hypopituitarism were $232 higher than for those with hypopituitarism ($279 ± 86 vs $47 ± 43, p = .0154) and were similar at all other LoCs.

The medical claims for both patients with acromegaly and their matched controls for the 12-month follow-up were categorized according to AHRQ class definitions. An analysis revealed the 30 most common reasons for visits, listed in Table 6. After removing the “other endocrine disorders” category, which included acromegaly and applied to all patients with the condition and 1.2% of controls, the next condition with the greatest difference in prevalence between groups was “other and unspecified benign neoplasm” (63% vs. 7%, respectively) and “unspecified nature or uncertain behavior” (38.5% vs. 3.5%, respectively). Many other comorbidity prevalence differences were statistically significant, including those for connective tissue disorders and arthritic conditions, diabetes mellitus (with or without complications), and neurologic problems.

**Discussion**

A majority of patients with acromegaly require lifelong medical therapy to control the disease and its associated comorbidities. This retrospective study evaluated whether patients with acromegaly utilized more healthcare services (and in different care locations) than individuals without acromegaly. Both groups utilized the physician’s office most often, followed by outpatient facilities, laboratory services, and other sites of care, even though the frequency of use was quite different between groups for most venues. Finding that healthcare service use in general was significantly greater (in many cases, several-times greater) for patients with acromegaly, this analysis corroborates and builds upon previous estimates of the economic burden of acromegaly.

Evidence on this topic is limited. Utilizing another database of health claims, Placzek and colleagues found that 99% of patients with acromegaly visited a physician office during the 12-month study period (75% visited physician offices as a result of an acromegaly-related problem). Twenty percent utilized emergency room services, and 33% were admitted to an inpatient facility (for any reason). Their analysis did not include a comparison with a control group, but it did illustrate the health services that tend to be consumed by individuals with acromegaly (both acromegaly-related and all-cause). The present study found that 19% of patients with acromegaly used the ED, which was similar to the finding above, and not significantly different than that of the control group.

Our study analyzed the number of services used in these LoCs. Clearly, patients with acromegaly utilized more ambulatory care–based services than individuals without acromegaly. In this investigation, all patients with acromegaly visited a physician’s office during the 12-month follow-up compared with 91% of those without acromegaly. Yet, the number of chargeable services ordered/performed at the physician office was far greater for those with acromegaly, which was also observed of hospital inpatient and outpatient services (but not for emergency department utilization). Furthermore, acromegaly was associated with significantly higher costs in nearly all sites of care analyzed compared with controls.

None of the controls had pituitary surgery claims. Patients with acromegaly had pituitary surgery claims for current procedural terminology (CPT) Code 61548 (hypophysectomy or excision of pituitary tumor, transnasal or transseptal approach, nonsterotactic transnasal or transseptal using a microscope) was found in 11.7% of the cohort, and CPT code 62165 (neuroendoscopy, intracranial; with excision of pituitary tumor, transnasal or transsphenoidal approach, transnasal or trans-sphenoidal using an endoscope) was found in 6.7% of the cohort.
During the study year, 31.7% of the patients with acromegaly used a single agent to treat the primary disease, 5.0% used two compounds, and 1.7% used three different compounds (38.3% overall used acromegaly-specific medications). These medications included somatostatin analogs, dopamine agonists, and a growth hormone receptor–antagonist.

Though not significant, the subanalysis of our data found the total 12-month direct costs for patients with acromegaly and hypopituitarism were $48,442 higher than for those without hypopituitarism. Upon further analysis of individual patients, it was determined that this large difference was due to a single outlier patient with an injectable medication (J1569, Injection, immune globulin [Gammagard liquid], non-lyophilized [e.g. liquid], 500 mg) during the study period, accounting for almost $400,000 of cost. When this outlier was excluded from the overall analysis, the resulting effect

Table 1. Patient population inclusion criteria.

| Description | Number |
|-------------|--------|
| Employees in the database | 2,844,389 |
| Employees in the database with claims after 1/1/2010 | 1,201,197 |
| Employees with acromegaly, 2 acromegaly diagnoses ≥ 30 days apart | 52 |
| Employees with acromegaly, ≥ 1 acromegaly diagnosis plus 1 pituitary adenoma diagnosis within 1 year plus 1 claim for pituitary surgery | 8 |
| Employees with acromegaly excluded due to a diagnosis of other pituitary disorder | (1) |
| Employees with acromegaly excluded due to non-continuous eligibility | (12) |
| Employees with acromegaly ≥ 1 year continuous post-index date eligibility | 47 |
| Spouses* with acromegaly, 2 acromegaly diagnoses ≥ 30 days apart | 9 |
| Spouses with acromegaly, 1 acromegaly diagnosis plus 1 pituitary adenoma diagnosis within 1 year plus 1 claim for pituitary surgery (hypophysectomy or stereotactic radiosurgery) | 9 |
| Spouses with acromegaly excluded due to a diagnosis of other pituitary disorder | (2) |
| Spouses with acromegaly excluded due to non-continuous eligibility | (3) |
| Spouses with acromegaly with ≥ 1 year continuous post-index date eligibility | 13 |
| Total study population with acromegaly | 60 |

*Spouses also included domestic partners.

Table 2. Characteristics of the study population with or without acromegaly.

| Variable | Patients with acromegaly (N = 60) | Matched controls (N = 1,200) | p Value* |
|----------|-----------------------------------|-------------------------------|----------|
|          | Mean or percent | Standard error | Mean or percent | Standard error |         |
| Age (years)b | 47.0 | 1.5 | 45.4 | 0.3 | .2779 |
| % Female | 45.0% | 6.5% | 49.5% | 1.4% | .4963 |
| % Employees (vs. spouses) | 78.3% | 5.3% | 78.3% | 5.3% | 1.0000 |
| % Exempt from overtimea,e | 33.3% | 6.1% | 33.3% | 1.4% | 1.0000 |
| Annual salaryb,c,e | $78,279 | $6,736 | $78,263 | $1,490 | .9981 |
| % Full timeb,e | 71.7% | 5.9% | 71.8% | 1.3% | .9777 |
| Charlson Comorbidity Index (study period) | 0.80 | 0.19 | 0.29 | 0.03 | <.0001 |
| Region of the country, employee’s first digit Zip: | | | | | |
| 0 | 13.3% | 4.4% | 6.2% | 0.7% | .0381f |
| 1 | 8.3% | 3.6% | 2.4% | 0.4% | .0058g |
| 2 | 6.7% | 3.2% | 8.3% | 0.8% | .6471 |
| 3 | 10.0% | 3.9% | 7.4% | 0.8% | .4595 |
| 4 | 0.0% | 0.0% | 1.8% | 0.4% | .3014 |
| 5 | 8.3% | 3.6% | 8.2% | 0.8% | .9633 |
| 6 | 8.3% | 3.6% | 14.1% | 1.0% | .2077 |
| 7 | 10.0% | 3.9% | 11.3% | 0.9% | .7499 |
| 8 | 23.3% | 5.5% | 23.3% | 1.2% | 1.0000 |
| 9 | 11.7% | 4.2% | 17.0% | 1.1% | .2803 |
| Index year | | | | | |
| 2010 | 28.3% | 5.9% | 29.1% | 1.3% | .9006 |
| 2011 | 15.0% | 4.6% | 15.2% | 1.0% | .9720 |
| 2012 | 11.7% | 4.2% | 14.3% | 1.0% | .5637 |
| 2013 | 5.0% | 2.8% | 4.7% | 0.6% | .9051 |
| 2014 | 0.0% | 0.0% | 0.0% | 0.0% | .8070 |
| 2015 | 6.7% | 3.2% | 7.6% | 0.8% | .7930 |
| 2016 | 23.3% | 5.5% | 19.1% | 1.1% | .4155 |
| 2017 | 5.0% | 2.8% | 5.8% | 0.7% | .8070 |
| 2018 | 5.0% | 2.8% | 4.3% | 0.6% | .8052 |

*An indicator of the percentage of the employee population who are classified as not eligible for overtime versus other employees.

bAt index date.

cFor annual salary, data were based on 44 patients and 880 matched controls.

dFor patients and controls who are spouses, racial and job-related information are for the associated employee.

eCategorical and binary variables were compared using chi-square ($\chi^2$) tests. Means of continuous variables were compared using t-tests.

fStatistically significant.

gNote. Sums may not equal 100.0% because of rounding.

During the study year, 31.7% of the patients with acromegaly used a single agent to treat the primary disease, 5.0% used two compounds, and 1.7% used three different compounds (38.3% overall used acromegaly-specific medications). These medications included somatostatin analogs, dopamine agonists, and a growth hormone receptor–antagonist.

Though not significant, the subanalysis of our data found the total 12-month direct costs for patients with acromegaly and hypopituitarism were $48,442 higher than for those without hypopituitarism. Upon further analysis of individual patients, it was determined that this large difference was due to a single outlier patient with an injectable medication (J1569, Injection, immune globulin [Gammagard liquid], non-lyophilized [e.g. liquid], 500 mg) during the study period, accounting for almost $400,000 of cost. When this outlier was excluded from the overall analysis, the resulting effect
did not change the overall findings, that is, the magnitude of difference was reduced, but costs were still higher for patients with acromegaly (with or without hypopituitarism) compared with controls.

Patients with hypopituitarism and concurrent secondary adrenal insufficiency may be at a greater risk of developing episodes of adrenal crisis. This may prompt visits to the ED, which then subsequently drive up the ED costs\(^3\). However, we found that the ED costs for patients with acromegaly and hypopituitarism were not higher than for those without hypopituitarism. A possible explanation for this finding is that the patients with acromegaly and hypopituitarism may have a low prevalence of adrenal insufficiency, as the recovery of the hypothalamic–pituitary–adrenal axis is more frequent in these patients than patients with non-functioning adenoma after surgery\(^3\), and thus not needing to present to the ED as frequently as anticipated for possible episodes of adrenal crisis.

Compared with controls, a likely contributor to the higher costs and utilization of patients with acromegaly is related to its other comorbidities. This study found significantly greater Charlson Comorbidity Index scores for those with acromegaly than individuals without the disorder (mean score, 0.80 vs. 0.29, respectively; \(p < .0001\)) and many statistically significant

### Table 3. Likelihood of utilization by location of care for subjects with or without acromegaly.

| Location of care | Patients with acromegaly (N = 60) | Matched controls (N = 1,200) | p Value |
|------------------|-----------------------------------|-----------------------------|---------|
|                   | Adjusted\(^a\) likelihood of utilization (%) | Standard error (%) | Adjusted\(^a\) likelihood of utilization (%) | Standard error (%) |
| Physician’s office | 100 | 0.0 | 91 | 0.8 | <.0001\(^b\) |
| Inpatient hospital | 22 | 5.4 | 3 | 0.5 | .0005\(^b\) |
| Outpatient hospital or clinic | 89 | 4.1 | 38 | 1.4 | <.0001\(^b\) |
| Emergency department | 19 | 5.1 | 11 | 0.9 | .1417 |
| Laboratory | 62 | 6.3 | 31 | 1.3 | <.0001\(^b\) |
| Other | 55 | 6.4 | 23 | 1.2 | <.0001\(^b\) |

\(^a\)Likelihoods were adjusted using separate stepwise logistic regression models controlling for age, self-reported gender, marital status, race of the associated employee, employment status of the associated employee, region of the country based on the first digit zip code, employee vs. spouse indicator, and the Charlson Comorbidity Index score.

\(^b\)Statistically significant.

### Table 4. Chargeable services\(^a\) provided at each location of care during 12-month follow-up for subjects with or without acromegaly.

| Location of care | Patients with acromegaly (N = 60) | Matched controls (N = 1,200) | p Value |
|------------------|-----------------------------------|-----------------------------|---------|
|                   | Adjusted\(^a\) mean utilization | Standard error | Adjusted\(^a\) mean utilization | Standard error |
| Physician’s office | 31.6 | 4.2 | 13.6 | 0.4 | <.0001\(^b\) |
| Inpatient hospital | 4.0 | 1.1 | 0.6 | 0.1 | .0013\(^b\) |
| Outpatient hospital or clinic | 20.5 | 2.9 | 4.0 | 0.2 | <.0001\(^b\) |
| Emergency department | 0.6 | 0.2 | 0.6 | 0.0 | .7067 |
| Laboratory | 9.8 | 1.6 | 2.3 | 0.1 | <.0001\(^b\) |
| Other | 6.4 | 1.1 | 1.0 | 0.1 | <.0001\(^b\) |
| Total (sum of above)\(^b\) | 72.9 | – | 22.1 | – | |

\(^a\)Utilization is number of services (it includes all individual services provided at each visit to a location of care).

\(^b\)Means were adjusted using separate two-part stepwise regression models (logistic followed by generalized linear models) controlling for age, gender, marital status, race of the associated employee, employment status of the associated employee, region of the country based on the first digit zip code, employee vs. spouse indicator, and the Charlson Comorbidity Index score.

\(^b\)Sum of the adjusted means for components with varying sample sizes; therefore no standard error and \(p\) values were calculated.

### Table 5. Costs by location of care for subjects with or without acromegaly.

| Location of care | Patients with acromegaly (N = 60) | Matched controls (N = 1,200) | p Value |
|------------------|-----------------------------------|-----------------------------|---------|
|                   | Adjusted\(^a\) mean cost | Standard error | Adjusted\(^a\) mean cost | Standard error |
| Physician’s office | $4,762 | $678 | $1,301 | $43 | <.0001\(^b\) |
| Inpatient hospital | $8,646 | $2,388 | $739 | $115 | .0009\(^b\) |
| Outpatient hospital or clinic | $9,611 | $1,793 | $1,355 | $74 | <.0001\(^b\) |
| Emergency department | $242 | $70 | $231 | $20 | .8860 |
| Laboratory | $508 | $93 | $66 | $4 | <.0001\(^b\) |
| Other | $2,001 | $583 | $367 | $29 | .0052\(^b\) |
| Total (sum of above)\(^b\) | $25,770 | – | $4,059 | – | |

\(^a\)Costs were adjusted using separate two-part stepwise regression models (logistic followed by generalized linear models) controlling for age, gender, marital status, race of the associated employee, employment status of the associated employee, region of the country based on the first digit zip code, employee vs. spouse indicator, and the Charlson Comorbidity Index score.

\(^b\)Statistically significant.

\(^b\)Sum of the adjusted means for components with varying sample sizes; therefore no standard error and \(p\) values were calculated.

\(^b\)The non-acromegaly drug costs category is based on regression-adjusted data. The acromegaly drug costs are actual unadjusted costs. Therefore, the total drug costs are not the sum of these two variables.
differences in the number of services utilized to treat comorbid conditions, such as rheumatologic diseases, diabetes mellitus, and neurological diseases. In the previous study utilizing the same claims database, Yuen et al.\textsuperscript{19} found that patients with acromegaly had significantly higher prevalence of other medical conditions such as arthritis, chronic lung disease, diabetes, hyperlipidemia, hypertension, and thyroid disease than matched controls. The information on health services utilization seems to indicate the potential for improved management of acromegaly. Previous studies have also consistently demonstrated that effective biochemical control of IGF-1 can help mitigate or reduce the effects of these comorbid conditions (as well as the acromegaly itself) and improve symptoms\textsuperscript{32–34}. This could translate into ramifications for patterns of care implementation, intensity of care, and overall health expenditures. Nevertheless, the present study was not designed to correlate quality of care factors or adherence to acromegaly drug therapy with use of health-care services.

We acknowledge that our study has several strengths and limitations. This retrospective study utilized a commercial claims database to assess services and patterns of acromegaly. One strength of this methodology is that claims analysis can efficiently identify populations with acromegaly or other rare diseases. The database utilized in the present study is a large national sample and enables tracking of employees (through assignment of unique employee identification numbers), spouses, and their dependents if they change health plans. The Workpartners database included health resources information and self-reported demographic information (e.g., marital status, employee racial identification). Using administrative coding for patient identification, this methodology permitted exclusion of patients with other conditions, such as Cushing’s disease, without relying on patient recall or subjective measures. By contrast, previous studies\textsuperscript{7,16,18,29} did not exclude patients with Cushing’s disease or other pituitary disorders. Though not the primary focus, this study also explored the impact of concurrent hypopituitarism.

The limitations of our study on the other hand include a small sample size, largely related to the low prevalence of acromegaly. The study used commercial claims provided through employers, which may have excluded patients with acromegaly whose families do not receive employment-based coverage. As with any study utilizing retrospective claims analyses, the relevance of the findings rely heavily on accurately recorded claims data\textsuperscript{35}. This could potentially affect the validity of the comorbid relationships with acromegaly. In addition, the use of administrative databases for research purposes could result in limited generalizability of findings (i.e., fee-for-service vs. a capitated population)\textsuperscript{36}. However, the Workpartners database is national in scope. The investigation also did not assess the ramifications of treatment (and treatment types) or the impact of new versus existing acromegaly diagnoses and treatment paradigms. Nor did the analysis examine how specialist office visits were assessed relative to visits to primary care providers, as this could be important to the extent that acromegaly is often complicated by comorbid conditions\textsuperscript{1}.
MRI scanning, and healthcare costs or utilization was not attempted. Such analyses may be better served through prospective or observational cohort studies.

The present study results also raise additional questions. For example, are patients with acromegaly efficiently accessing care? The majority of individuals diagnosed with this disorder are of working age; therefore, is there an opportunity for worksite-based care settings to improve overall patient management, especially since acromegaly is highly associated with outpatient care utilization? Lastly, what are the significant relationships between acromegaly and its comorbid conditions; how does adequate management of those conditions affect overall costs?

Conclusion

Acromegaly poses a significant burden on healthcare utilization and costs by LoC. Our findings further corroborate previous estimates of the economic burden of acromegaly and provide a further insight: This disease is associated with substantially greater likelihood of healthcare services utilization in nearly all LoCs compared with controls. Our data also indicate significantly higher costs incurred for patients with acromegaly throughout the healthcare system compared with the general population, and a significantly greater number of services and costs associated at each LoC, with the exception of ED services. Further studies are warranted to better understand whether effective patient care for acromegaly can reduce this burden, and to assess short- and long-term costs associated with specific therapeutic modalities and at which LoC those costs tend to be incurred to enable better planning of healthcare funding for these patients.

Transparency

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Conflicts of interest/competing interests

KCJY has received research grants to his institution for clinical research studies from Ionis, Cinetics, and Novartis. RAB, IAB, NLK, and KCJY are consultants to Ipsen.

KCJY has served on advisory boards for Pfizer, Ipsen, Cinetics and Chiasma.

AR-O Jr, KAM, and JDW are employees of Ipsen and hold company stock.

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Author contributions

RAB directed the study, wrote and refined the analysis plan, drafted the initial manuscript, and coordinated the team’s revisions. KAM, AR-O Jr, IAB, and JDW helped develop the initial analysis plan. All authors revised the protocol, interpreted the results, provided input to revise the manuscript, and approved the version submitted. IAB was the primary analyst with the assistance of NLK. KCJY and AR-O Jr were responsible for clinical guidance and oversight throughout the study process.

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