Clinical features and complications of acromegaly at diagnosis are not all the same - data from two large referral centers

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Compliance with ethical standards

Conflict of interest MF reports serving as an investigator with research grants to Oregon Health & Science University (OHSU) for Chiasma, Crinetics, Ionis, Novartis; and serving as an occasional consultant to Chiasma, Crinetics, Ionis, Ipsen, Pfizer, Recordati. CP has received research funding to Carol Davila University of Medicine and Pharmacy as a Principal Investigator from Novartis. All other authors have no conflict of interest to report.

Ethical approval This retrospective chart review study involving human participants was in accordance with the ethical standards of the institutional research committees and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The OHSU and C. I. Parhon National Institute of Endocrinology Institutional Review Boards approved the data collection.

Informed consent Institutional Review Board approval with a waiver of informed consent for this two-institution, retrospective, HIPAA-compliant study was obtained.
Abstract

Purpose The number of international acromegaly-related registries is increasing; however, heterogeneity of acromegaly symptoms and signs across countries is not well described. We compared clinical disease manifestations at diagnosis between two large University referral centers from two continents.

Methods Retrospective, comparative epidemiological study of acromegaly patients at two centers; 1) C. I. Parhon National Institute of Endocrinology, “Carol Davila” University of Medicine and Pharmacy Bucharest, Romania (Parhon), and 2) Pituitary Center, Oregon Health & Science University, Portland, Oregon, United States (OHSU) from approved registries was undertaken. Data were extracted from medical charts and questionnaires. Binary logistic regression analysis was undertaken for the most frequently noted symptoms and clinical signs.

Results Study included 216 patients (87 Parhon, 129 OHSU). Age, sex and median delay in diagnosis were similar between centers. IGF-1 index was higher in patients at Parhon (3.3 vs 2.1, p < 0.001). The top five symptoms at both centers were; enlarged hands/feet, headache, arthralgia, fatigue, and irregular menses in women. A significant difference was noted for multiple signs and symptoms frequency, often >20 percentage points between centers. Center was a predictor of many signs and symptoms, independent of acromegaly biochemical severity or disease duration.

Conclusion We show in the first comparative study that differences in medical practice, documentation, and likely cultural differences can influence patients’ symptom(s) reporting and screening patterns in geographically different populations. Pooling data into large multicenter international registries databases may lead to loss of regional characteristics and thus a mixed overall picture of combined cohorts.
Keywords [4-6] Acromegaly, growth hormone excess, diagnosis, symptoms, signs, complications.
Introduction

Acromegaly is a rare disease that is caused by excessive growth hormone (GH) secretion by a pituitary adenoma (1-3). The clinical picture of active acromegaly is characterized by a combination of symptoms, signs and comorbidities related to the tumor itself (e.g. headache, oculomotor nerve palsy or hypopituitarism) or to GH and insulin-like growth factor-1 (IGF-1) excess (arthralgia, morphologic changes or obstructive sleep apnea (OSA), cardiovascular disease, and secondary diabetes mellitus (DM)) (2-4). Long-standing acromegaly is relatively easy to diagnose due to multiple pathognomonic signs and symptoms. However, milder disease cases pose a great challenge, and an acromegaly diagnosis is eventually considered after numerous non-endocrine evaluations. Clinical manifestations are insidious and a diagnosis is usually delayed by years 6-10 years (5-8); although a few publications reported a shorter time to diagnosis, 2.5-5.5 years (9-11) and a decline of the diagnostic delay overtime (5). Interestingly, in most cases, an evaluation is initiated by primary care providers (PCP) (10).

Several studies have identified a clinical profile that accompanies active acromegaly along with the severity and frequency of various signs, symptoms and complications, often with vast differences between studies (4, 5, 12-15). Many investigators, because acromegaly is a rare disease, have attempted to increase subject number and statistical accuracy by aggregating data from national or international acromegaly data registries (5, 12, 16). Although the importance of these studies is without question, some have uncovered significant differences between countries and/or centers in the diagnosis and treatment of acromegaly and disease-related complications (5, 16, 17). This might be one reason for the relative lack of success of studies that have attempted to determine a specific combination of signs and symptoms most indicative of acromegaly (12, 14).
While differences in clinical presentation in patients from different countries and centers could be due to genetic variation, other important socio-economic factors such as access to medical care, trust in medical care providers, imaging modalities used, type of IGF-1 assays, local practice of medicine, provider bias, and cultural factors such as family influence on decision-making, and misconceptions and/or misinterpretations regarding symptoms likely also play a role (18-21). If these differences are inherent to the studied populations, data pooling into national and international registries might lead to inappropriate result generalization (22), and local relevance could be lost.

We aimed to compare the acromegaly clinical picture, at diagnosis, between two university referral centers; 1) Department of Pituitary and Neuroendocrine Disorders, C. I. Parhon National Institute of Endocrinology, “Carol Davila” University of Medicine and Pharmacy Bucharest, Romania (Parhon), and 2) Pituitary Center, Oregon Health & Science University, Portland, Oregon, United States (OHSU). We also aimed to assess any differences, and if any such differences were disease-related *per se* or due to factors such as specific medical practice(s), medical record chart documentation, or culture.

**Methods**

*Study Design and Patients*

This is a retrospective, comparative epidemiological study of newly diagnosed and previously untreated acromegaly patients who presented to two university referral centers; Parhon (years; 2012 – 2020) and OHSU (years; 2006 –2018).

Parhon maintains an approved repository of all patients with pituitary adenomas followed by the institution since 1990. The present cohort includes patients with acromegaly (*n* = 87)
assessed before any treatment (years; 2012 – 2020). Patients presenting prior to 2012 were excluded as IGF-1 measurements were performed with various assays that are no longer in use. Patients assessed after 2012 had serum IGF-1 measured with the same IGF-1 assay.

OHSU maintains an institutional review board approved repository of all patients with pituitary adenomas; those prior to 2006 not included here due to transition to electronic medical records (EMR) in 2006.

Clinical Evaluation

At Parhon, patients were clinically assessed by history and clinical examinations; there were no pre-printed questionnaires or checklists. All medical staff working at Parhon have large experience treating acromegaly patients as it is the largest Pituitary Center in Romania serving most of country’s population (23).

At OHSU, the majority of patients were assessed by the same neuroendocrinologist (MF) using a standard acromegaly documentation template in the EMR. A pituitary symptoms questionnaire written in lay terms was completed by patients. Quality of life (QoL) questionnaires were not routinely evaluated at diagnosis and thus, not included.

Data on symptoms and physical exam findings were extracted from clinic chart notes and questionnaires. Age, sex, and delay in diagnosis (determined as time between the first symptom and official diagnosis) were also recorded.

Biochemical Evaluation

Biochemical diagnosis of acromegaly was made based on elevated IGF-1 and/or non-suppressible growth hormone (GH) on oral glucose tolerance test when applicable. In Parhon
patients, GH and IGF-1 were measured with an automated chemiluminescent analyzer (Liaison XL, Diasorin). Measuring ranges were 3 – 1,500 ng/ml for IGF-1, and 0.05 – 80 ng/ml for GH, respectively. At OHSU, the majority of GH and IGF-1 were measured as previously published (24). Growth hormone values that were below the detection limit were reported as the lower limit of normal and the values that were above the assay reading capacity were reported as the maximum reading capacity (for example, GH >100 ng/ml was reported as 100 ng/ml). Some patients had IGF-1 performed at an outside laboratory and reference range differed between laboratories.

To normalize the values across the IGF-1 assays and adjust for the age- and sex-related differences, IGF-1 values were expressed as IGF-1 index (IGF-1/upper limit of normal (ULN) for each patient). This is a common approach undertaken in most multicenter acromegaly studies, both prospective and retrospective in the absence of a central lab (5, 12).

**Imaging Evaluation**

In both OHSU and Parhon patients, magnetic resonance imaging (MRI) was performed at various facilities and the data on tumor size at diagnosis were extracted from imaging reports. Maximum tumor diameter was recorded.

**Comorbidity Evaluation**

At Parhon, patients’ medical history was obtained at presentation and the following comorbidities were routinely recorded: hypertension, DM, dyslipidemia, arrhythmia and thyroid nodules. Data on obstructive sleep apnea (OSA), coronary artery disease (CAD), heart failure, colonic polyps, bone mass (by dual-energy X-ray absorptiometry) and spinal fractures were not
routinely collected as screening information, but were performed as clinically indicated and recorded if a patient mentioned it at the visit. At OHSU, patients’ medical history was obtained at presentation and the following comorbidities were recorded: OSA, hypertension, coronary artery disease, heart failure, arrhythmia, DM, dyslipidemia, colonic polyps, thyroid nodules, and spinal fractures. Patients without history of these comorbidities were referred for sleep study evaluation, echocardiogram (ECHO), colonoscopy, thyroid ultrasound – if a palpable thyroid abnormality was present, – and spinal x-rays, and bone mass (by dual-energy X-ray absorptiometry) since 2011. Hemoglobin A1c and lipid panel were either measured or requested to be obtained by a PCP. Prevalence of comorbidities was calculated as the number of patients with identified comorbidity divided by the total number of patients in the cohort.

Statistical analysis

Statistical analysis was performed using SPSS 25. Mann-Whitney test was used to evaluate continuous variables (age, delay in diagnosis, IGF-1 index, GH, maximum tumor diameter). Chi square test was used to evaluate categorical variables (sex, symptoms, and physical exam findings at presentation). Binary logistic regression analysis was performed for symptoms and physical exam findings with occurrence of >20% using center (institution), age, sex, delay in diagnosis, IGF-1 index, and GH as independent predictors. Forward LR stepwise method was utilized.

Results

Eighty-seven acromegaly patients from Parhon and 129 from OHSU were included. There was no significant difference in age, sex and median delay in diagnosis between the two centers.
Interestingly, median age in males (45 years) at Parhon was 9 years younger than females (54 years) at diagnosis while males and females at OHSU were diagnosed around the same age (51.5 vs 51 years, respectively). Patients at Parhon presented with significantly higher IGF-1 index (3.3 x ULN) and nadir GH (5.3 ng/mL) compared with OHSU patients (2.1 x ULN and 2.1 ng/mL, respectively). There was no difference in random GH levels and tumor diameters (Table 1).

The descending order of the aggregate (Parhon plus OHSU) percentages for reported symptoms were; large extremities (66.7%), headache (59.7%), arthralgia (52.8%), fatigue (52.3%), weight gain (35.6%), snoring (32.9%), memory loss (29.2%), frontal bossing (25%), hirsutism (25%), jaw changes (24.5%), excessive sweating (23.6%), coarse facies (21.8%), skin tags (21.3%), carpal tunnel syndrome (20.4%), round face (19.4%), back neck pain (19%), spread teeth (18.1%), oily skin (18.1%), increased nose (17.6%), and enlarged lips (15.3%). Loss of libido, peripheral neuropathy, depression, macroglossia, visual defects, acne, constipation, shortness of breath, hyperpigmentation, increased head, galactorrhea, thick skin, and gigantism had each an aggregate frequency of < 15%.

The descending order of the aggregate (Parhon plus OHSU) percentages for physical exam findings were; hand enlargement (68.5%), frontal bossing (67.6%), protruding jaw (58.8%), coarse facies (38.4%), sweaty or oily skin (37.5%), skin tags (33.8%), gaps between teeth (32.4%), macroglossia (31.9%), facial rounding (26.4%), truncal obesity (25.5%), skin thickening (23.6%), hand edema (20.8%), and goiter (17.1%). Dental articulation problems, abnormal visual field, hirsutism, galactorrhea, arthropathy, husky voice, acne, plethora, acanthosis nigricans, hyperpigmentation, leg edema, and gynecomastia had each an aggregate
frequency of < 15%. Figure 1 compares the frequencies of symptoms and the corresponding physical exam findings at Parhon vs. OHSU (with aggregate frequency of at least 20%).

A significant difference was found in multiple symptoms at presentation between the two centers (Figure 1). Symptoms that were more commonly documented in OHSU patients included headache, arthralgia, fatigue, weight gain, snoring, memory and concentration problems, coarse facies, frontal bossing, jaw changes, spreading of the teeth, macroglossia, hirsutism, acne, oily skin, skin tags, hyperpigmentation, irregular menses, carpal tunnel syndrome (CTS), back and neck pain, loss of libido, depression, constipation, and galactorrhea. Nose enlargement, lip enlargement, and increased head size were more commonly documented in Parhon patients. There was no difference in documented frequency of enlarged extremities, excessive sweating, rounding of the face, peripheral neuropathy, thickening of the skin, visual defects, shortness of breath, and gigantism.

With regards to physical exam findings, hand enlargement, frontal bossing, coarse facies, gaps between the teeth, facial rounding, truncal obesity, skin thickening, hand edema, abnormal thyroid exam, and dental articulation problems were more frequently documented in Parhon patients, whereas skin tags were more frequently documented in OHSU patients (Figure 1). There was no difference in documented protruding jaw, oily/sweaty skin, macroglossia, abnormal visual field, hirsutism, acne, galactorrhea, arthropathy, husky voice, facial plethora, acanthosis, hyperpigmentation, leg edema, and gynecomastia.

Logistic regression analysis was performed to determine which independent variables (center, age, sex, delay in diagnosis, IGF-1 index, and GH) could serve as predictors of reported symptoms and physical exam findings with an aggregate prevalence of at least 20% (Table 2). Patients at OHSU were more likely than patients at Parhon to report headache, arthralgia,
fatigue, weight gain, snoring, memory/concentration problems, hirsutism, jaw changes, and
carpal tunnel syndrome. Endocrinologists at OHSU were more likely to document skin tags,
macroglossia, and hirsutism and less likely to document hand enlargement, coarse facies, gaps
between the teeth, truncal obesity, skin thickening, and hand edema. Higher IGF-1 index
predicted symptoms of enlarged extremities and protruding jaw and several physical exam
findings (hand enlargement, frontal bossing, protruding jaw, sweaty/oily skin, and macroglossia).
Longer delay in diagnosis was the independent predictor only for symptom of hand enlargement
and for physical findings of hand enlargement, protruding jaw and truncal obesity, however, the
odds ratio (OR) for this predictor was essentially 1. When multiple predictors were retained in
the regression model, center had the highest impact based on the OR (Table 2).

Frequency of comorbidities before the diagnosis of acromegaly and total (at any time up
until last follow up) are presented in Figure 2. We found variable prevalence of comorbidities in
patients at Parhon and OHSU; hypertension, hyperlipidemia, and DM/impaired glucose tolerance
being most common at both centers. Numerically, hypertension, myocardial hypertrophy and
thyroid nodules were more prevalent at Parhon while diabetes, sleep apnea, colonic polyps and
vertebral fractures were more prevalent at OHSU. Of note, percent of patients screened with
sleep study, ECHO, x-rays, colonoscopy and thyroid ultrasound differed considerably between
the centers, contributing to difference in the prevalence of comorbidities.

Discussion

To our knowledge, this is the first study to perform comparative analysis in two
geographically and culturally different populations of patients with acromegaly; we assessed
clinical presentation of newly diagnosed acromegaly patients at two high volume academic
Pituitary referral Centers; one in Romania and one in the US and examined whether any
differences noted were related to disease or other factors, such as medical practice,
documentation, culture and, thus, Center.

We demonstrated important differences, in both physical exam findings and symptoms,
between acromegaly patients at the two centers. Notably, the top five symptoms at presentation
were the same; 1) enlarged hands/feet, 2) headache, 3) arthralgia, 4) fatigue, and 5) irregular
menses in women. However, the frequency of these symptoms (except enlarged hands/feet)
differed by > 20 percentage points (enlarged hands/feet; 64.4% and 68.2%, headache; 47.1% and
68.2%, arthralgia; 34.6% and 65.1%, fatigue; 19.5% and 74.4%, and irregular menses in women
30.4% and 65.6% at Parhon and OHSU respectively). This was observed in multiple other
symptoms such that, frequency of reported snoring, skin tags, weight gain, memory loss or
depression at OHSU was at least 20 percentage points higher than at Parhon. While reported
increased size of nose and lips was at least 20 percentage points higher at Parhon. We also found
differences in the physical exam findings, with a significantly higher prevalence of hand
enlargement, coarse facies, gaps between teeth, facial rounding, skin thickening, and dental
articulation problems at Parhon; at least 20 percentage points higher than at OHSU.

Multiple factors are likely responsible for such differences. While it is possible that genetic
differences may affect the disease manifestation, this probably accounts for small
differences. Sex and overall age distribution, were similar at both centers. Interestingly, males
were younger than females at Parhon but not at OHSU. Similarly, younger age at diagnosis in
males has been observed in some (25) but not all studies (13, 25, 26).

Among other factors, severity and duration of disease may be responsible for some
differences. We found that patients at Parhon had worse biochemical disease, though similar
delay in diagnosis as OHSU patients. However, this would not explain why frequency of multiple symptoms was significantly higher at OHSU compared with Parhon. We suggest that cultural differences affecting patients’ perception of their disease and recognition or validation of symptoms by physicians may explain some of the larger differences. Differences in the illness perception in different populations have been observed in different diseases and may be related to not only to cultural, but also socio-economic, healthcare, and geographic differences (18, 20, 21). Lastly, documentation of the symptoms, including use of questionnaires and EMR templates versus manual symptoms entry could likely also create major differences in reporting of the symptoms.

In the logistic regression analysis, we found that the respective center emerged as an important predictor, both positive and negative, of many signs and symptoms, independently of disease characteristics such as biochemical severity or disease duration. Patients at OHSU had higher likelihood of reporting various symptoms, with greatest odds found for reporting memory/concentration problems (19.69), weight gain (17.12) and fatigue (10.4). As these symptoms are not specific to acromegaly, the drastic difference between the centers suggests that there are major underlying differences in conducted clinical visits/interviews, clinical documentation, cultural and social characteristics of the studied populations.

Interestingly, our study showed important discrepancies between self-reported symptoms and their corresponding physical exam findings. As a general rule, the frequency of symptoms was lower than that of their corresponding signs. However, there were some exceptions such as reported frequency of arthralgia and hirsutism which was 65.1% and 40.3% but only 3.9% and 3.1% respectively at the physical exam documentation at OHSU (possibly due to lack of attention to joint exam by physicians and hair removal by patients). The most important
differences between signs and symptoms, > 20 percentage points, were recorded for frontal bossing, jaw changes, coarse facies, round face, spread teeth, macroglossia and skin thickening at Parhon. These differences between symptoms and signs are in accordance with previous studies (12) that demonstrated up to 40% differences at the time of first presentation. Some authors suggest that the perceived body changes in acromegaly are less related to objective findings at the physical exam, but more related to depressive symptoms (27). A recent study of oro-dental state in acromegalic patients also reported a discrepancy between a relatively good objective exam and unsatisfactory self-assessment of oral heath-related QoL (28).

Prevalence of comorbidities was also drastically different between centers. This is likely largely related to the differences in the medical practices and implemented protocols for screening for comorbidities. Evaluation for OSA, cardiomyopathy (ECHO), vertebral fractures and colonoscopy is recommended for every acromegaly patient at OHSU, while thyroid ultrasound is performed on as needed basis as per guidelines (4, 29, 30) to prevent overdiagnosis of clinically irrelevant nodules. Conversely, at Parhon thyroid ultrasound is performed essentially in every patient with a diagnosis of acromegaly in accordance with recommendations by some authors (31) and country’s mild iodine deficiency(32, 33), thus, a much higher frequency of thyroid nodules was found. Myocardial hypertrophy was diagnosed by electrocardiogram or ECHO at Parhon, which could account for the higher frequency. Even prior to diagnosis, OSA and colonic polyps were observed more frequently at OHSU likely because of higher number of sleep studies and colonoscopies performed in the general populations in the US at 50 years of age. Interestingly, while evaluation of hypertension, diabetes and lipid disorders are likely similar, hypertension was more prevalent at Parhon, DM more prevalent at OHSU, and lipid disorders were similar in prevalence.
The cohort of patients examined here was similar to other cohorts from national or international databases. Median patient age was 51 years, similar to 51.9 years in the ACROPOLIS study (12), 47 years in the German Registry (34), 45.2 years in the Liège Acromegaly Survey (LAS) database (5), and 46 years in a Canadian study (13). The percentage of females we report, 59.2%, is slightly higher than the range 53%–57.6% reported in the above mentioned studies (5, 12, 13, 34). Compared with registries that provided disease activity at diagnosis (35), our patients had lower GH values (5.7 vs. 10 ng/mL), a similar IGF-1 index (2.68 vs. 2.77), and similar tumor diameter (15 mm) (5). The top signs and symptoms recorded at diagnosis were similar to other studies (12, 13), with acral and facial morphological changes the most prevalent. However, frequencies vary across studies with acral enlargement reported in 55–100% (this cohort, 66.7%), sweating 52–91% (this cohort, 23.6%), and snoring/sleep apnea 7–81% (this cohort, 32.9%). This is likely explained by differences in clinical assessment, data documentation and extraction.

Comorbidities reported prior to acromegaly diagnosis in our cohort were generally lower than those reported in the international LAS database (5) at diagnosis; however, there is significant heterogeneity of data collection in different studies (e.g. based on chart review vs. diagnostic codes), which may in part be responsible for observed differences (Table 3) (5, 36, 37). Importantly, the frequency of most comorbidities in this study almost doubled after screening, suggesting that targeted screening can improve diagnosis of comorbidities and subsequent treatment. Comprehensive documentation templates might help keep track of acromegaly comorbidities in EMR and improve rates of assessment of comorbidities.

Taken together, our findings suggest that cultural and medical practice/documentation differences are important determinants of the clinical evaluation of acromegaly as demographics
and disease characteristics remain merely constant across countries (5). As a result, pooling of data on signs and symptoms in international registries (5) might lead to a loss of equally important regional characteristics. Additionally, it is possible that diagnosis instruments like ACROSCORE (14), which includes specific symptoms and comorbidities (colonic polyps, thyroid hyperplasia, and diabetes mellitus), may not be applicable in populations other than in those for which they were developed. The results we present also suggest that symptoms included in specific instruments, such as SAGIT (38) and ACRODAT (39), designed to assess disease control and disease activity, and may need to be assessed by specific local questionnaires as perceived intensity could be different from one patient population to another.

The study has some limitations due to retrospective design, relatively small sample size per center, heterogeneous reporting of the data, and absence of a uniform questionnaire for every patient. This has a potential to “miss” some symptoms and signs, however, we believe that, given the centers’ experience (both are large Pituitary Centers of excellence (40)) in treating patients with acromegaly, the number of clinical features present, but not documented should be small. Also, this furthermore highlights the differences between centers in the real-world.

Future studies should focus on clinical presentation between populations using standardized comprehensive questionnaires and a cross-sectional design at the initial evaluation by an endocrinologist. We hypothesize that such a study might demonstrate more similar frequencies of symptoms and signs between the populations. However, this might “erase” some of the differences related to individual’s perception of the disease. While the patients in different regions may have similar symptoms and signs, the way they relay their symptoms to the physicians and the way physicians collect the information may be different due to cultural, socioeconomic and other factors.
In conclusion, we show important differences in symptoms, signs and complications of acromegaly at diagnosis between university referral centers that are not associated with differences in disease characteristics (GH, IGF-1 or tumor size). These suggest that local medical practice, EMR documentation, and cultural and possible socio-economic differences cannot be overlooked when various cohorts of patients with acromegaly are compared. We believe that understanding and addressing diversity and socio-economic differences can improve medical care. Targeted screening for comorbidities may improve assessment for comorbidities.
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Figure Legends

Figure 1. Reported symptoms (gray bars) and corresponding physical exam findings (white bars) in Parhon (clear bars) and OHSU patients (shaded bars). *p value < 0.05 between Parhon and OHSU patients.

Figure 2. Frequency of comorbidities at diagnosis (black bars) and at final assessment (white bars) in OHSU (left side) or Parhon (right side) patients. DM = diabetes mellitus; IGT = impaired glucose tolerance.
Figure 1. Reported symptoms (gray bars) and corresponding physical exam findings (white bars) in Parhon (clear bars) and OHSU patients (shaded bars). *p value < 0.05 between Parhon and OHSU patients.
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Table 1. Patient Baseline Characteristics

| Characteristic                        | All patients (n = 216) | Parhon, Romania (n = 87) | OHSU, United States (n = 129) | p-value |
|---------------------------------------|------------------------|---------------------------|-------------------------------|---------|
| Females (%)                           | 59.2                   | 65.1                      | 55.0                          | NS      |
| Age (years)                           | 51.0 (38.0, 61.0)      | 51.0 (41.5, 62.0)         | 51.0 (34.0, 60.0)             | NS      |
| Age, females                          | 52.5 (38.0, 61.0)      | 54.0 (46.0, 62.0)         | 51.0 (32.5, 58.0)             | 0.035   |
| Age, males                            | 48.5 (39.8, 60.0)      | 45.0 (39.3, 55.0)         | 51.5 (40.0, 61.0)             | NS      |
| Delay in diagnosis (months)           | 60.0 (23.8, 119.0)     | 59.0 (13.5, 115.3)        | 60.0 (24.0, 119.0)            | NS      |
| IGF-1 (ng/mL)                         | 659 (416, 948)         | 740 (508, 963)            | 596 (409, 926)                | 0.07    |
| IGF-1 (x ULN)                         | 2.7 (1.6, 3.7)         | 3.3 (2.2, 3.9)            | 2.1 (1.4, 3.4)                | < 0.001 |
| Random GH (ng/mL)                     | 5.7 (2.0, 20.7)        | 7.6 (3.4, 16.4)           | 4.7 (1.4, 22.8)               | NS      |
| Nadir GH on oral glucose tolerance test (ng/mL) | 3.6 (1.3, 10.2)  | 5.3 (2.0, 11.2) | 2.1 (0.5, 7.9) | 0.007 |
| Maximum tumor diameter (mm)           | 15 (10, 22)            | 16 (10, 24)               | 15 (9, 21)                    | NS      |

All data are presented as median (25, 75 percentile) except Females (percent).
Abbreviations: GH, growth hormone; IGF-1, insulin-like growth factor-1; ULN, upper limit of normal.
NS, not significant.
### Table 2. Predictors of Symptoms and Physical Exam Findings in Acromegaly Patients – Results of Binary Logistic Regression Analysis

| Symptoms/Physical Exam Findings | Dependent Variable | Independent Predictors | Odds Ratio | OR 95% CI | P value | Dependent Variable | Independent Predictors | Odds Ratio | OR 95% CI | P value |
|---------------------------------|--------------------|------------------------|------------|-----------|---------|--------------------|------------------------|------------|-----------|---------|
| Symptoms                        |                    |                        |            |           |         |                    |                        |            |           |         |
| Large extremities               | Delay in dx        | 1                      | 1.01       | 1.004-1.016 | 0.001   | Hand enlargement   | OHSU                   | 0.16       | 0.05-0.45 | < 0.001 |
|                                 | IGF-1 index        | 1.7                   | 1.22       | 1.22-2.35  | 0.001   |                    |                        |            |           |         |
|                                 | Female sex         | 5.10                  | 2.26       | 2.26-11.53 | < 0.001 |                    |                        |            |           |         |
|                                 |                    |                        |            |           |         |                   |                        |            |           |         |
| Headache                        | OHSU               | 2.09                  | 1.09       | 1.09-4.02  | 0.026   | Frontal bossing    | Delay in dx            | 1.005      | 1.000-1.01 | NS      |
|                                 | Delay in dx        | 0.99                  | 0.99       | 0.99-0.999 | 0.014   |                    | OHSU                   | 1.34       | 1.26-2.36 | 0.001   |
|                                 |                    |                        |            |           |         |                   |                        |            |           |         |
| Arthralgia                      | OHSU               | 3.62                  | 1.87       | 1.87-7.03  | < 0.001 | Protruding jaw     | Delay in dx            | 1.006      | 1.001-1.011 | 0.011   |
|                                 | Age                | 1.02                  | 1.00       | 1.00-1.05  | 0.040   |                    | IGF-1 index            | 2.21       | 1.607-3.058 | 0.001   |
|                                 |                    |                        |            |           |         |                   |                        |            |           |         |
| Fatigue                         | OHSU               | 10.4                  | 5.0        | 5.0-21.6   | < 0.001 | Coarse facies      | OHSU                   | 0.051      | 0.023-0.113 | < 0.001 |
|                                 |                    |                        |            |           |         |                   |                        |            |           |         |
| Weight gain                     | OHSU               | 17.12                 | 6.338      | 6.338-46.267 | < 0.001 | Dry/sweaty/oily skin | Female sex         | 2.365      | 1.188-4.707 | 0.014   |
|                                 |                    |                        |            |           |         |                   | IGF-1 index            | 1.478      | 1.143-1.912 | 0.003   |
|                                 |                    |                        |            |           |         |                   |                        |            |           |         |
| Snoring                         | OHSU               | 5.46                  | 2.522      | 2.522-11.842 | < 0.001 | Skin tags          | OHSU                   | 3.225      | 1.588-6.547 | 0.001   |
|                                 | Age                | 1.03                  | 1.007      | 1.007-1.059 | < 0.012 |                    |                        |            |           |         |
|                                 |                    |                        |            |           |         |                   |                        |            |           |         |
| Memory/concentration            | OHSU               | 19.69                 | 5.799      | 5.799-66.866 | < 0.001 | Gaps between teeth | OHSU                   | 0.405      | 0.211-0.776 | 0.006   |
|                                 |                    |                        |            |           |         |                   |                        |            |           |         |
| Hirsutism                       | OHSU               | 7.58                  | 2.123      | 2.123-27.100 | 0.002  | Macrogllossia      | IGF-1 index            | 1.508      | 1.164-1.953 | 0.002   |
|                                 | Age                | 0.97                  | 0.936      | 0.936-1.000 | NS     |                    |                        |            |           |         |
|                                 |                    |                        |            |           |         |                   |                        |            |           |         |
| Jaw changes                     | OHSU               | 3.38                  | 1.492      | 1.492-7.645 | 0.003  | Facial rounding   | OHSU                   | 0.100      | 0.045-0.221 | < 0.001 |
|                                 | IGF-1 index        | 1.41                  | 1.068      | 1.068-1.864 | 0.016  |                    |                        |            |           |         |
|                                 |                    |                        |            |           |         |                   |                        |            |           |         |
| Carpal tunnel symptoms          | OHSU               | 7.08                  | 2.365      | 2.365-21.170 | < 0.001 | Truncal obesity    | Delay in dx            | 0.056      | 0.022-0.464 | < 0.001 |
|                                 |                    |                        |            |           |         |                   | GH                     | 1.005      | 1.000-1.010 | 0.038   |
|                                 |                    |                        |            |           |         |                   |                        |            |           |         |
| Amenorrhea/irregular menses,    |                    |                        |            |           |         | Skin thickening    | OHSU                   | 0.045      | 0.016-0.126 | < 0.001 |
| Frontal bossing, Coarse facies, |                    |                        |            |           |         |                   |                        |            |           |         |
| Excessive sweating, Skin tags   | NS                 |                        |            |           |         |                   |                        |            |           |         |
|                                 |                    |                        |            |           |         |                   | Hand edema             | 0.081      | 0.033-0.199 | < 0.001 |
|                                 |                    |                        |            |           |         |                   | OHSU                   | 1.012      | 1.001-1.024 | 0.040   |
|                                 |                    |                        |            |           |         |                   | GH                     | 2.482-36.122 | 0.001   |
|                                 |                    |                        |            |           |         |                   |                        |            |           |         |
| Abbreviations: CI, confidence interval; IGF-1, insulin-like growth factor-1; OR, odds ratio; OHSU; Oregon Health and Science University; dx, diagnosis; NS, not significant; GH, Growth hormone.
Table 3. Frequency of Comorbidities in Studies of Geographically Different Cohorts

| Comorbidities                              | Present study (% before diagnosis/% total) | Petrossians, et al (Europe) [5] | Matsubayashi, et al (Japan) [30] | AlMalki, et al (Saudi Arabia) [29] |
|--------------------------------------------|------------------------------------------|---------------------------------|---------------------------------|----------------------------------|
| Hypertension (%)                           | 46.2/55.5                                | 28.8                            | 42.9                            | 50                               |
| Diabetes Mellitus or Impaired Glucose Tolerance (%) | 23.2/41.8                                | 29.6                            | 37.1                            | 51.7                             |
| Hyperlipidemia, (%)                        | 24.45/52.5                               | -                               | 26.7                            | -                                |
| Myocardial hypertrophy (%)                 | 3.2/26.8                                 | 15.5                            | -                               | -                                |
| Sleep apnea (%)                            | 18.9/32.4                                | 25.5                            | 17.8                            | 47.8                             |
| Colonic polyps (%)                         | 10.1/23.6                                | 13                              | -                               | 22.7                             |
| Thyroid nodules or goiter (%)              | 5.56/30.6                                | 34.0                            | -                               | 37.5                             |

Comorbidity data was collected as follows:

- Present study – OHSU and Parhon combined; chart review; % before diagnosis/% total
- Petrossians, et al. – international database; % at diagnosis
- Matsubayashi, et al. – diagnostic codes in national database; % before diagnosis
- AlMalki, et al. – chart review; % total before and after diagnosis