Prevalence, incidence, comorbidities, and treatment patterns among Japanese patients with acromegaly: a descriptive study using a nationwide claims database

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Abstract. Epidemiological data of rare diseases are important for understanding disease burden, improving treatment, and planning healthcare systems. However, those of acromegaly in Japan are not well known. Our study aimed to describe the prevalence, incidence, prediagnostic comorbidities, and treatment patterns of patients with acromegaly in Japan. Using the National Database of Health Insurance Claims and Specific Health Checkups of Japan, we retrospectively identified 12,713 patients with acromegaly aged ≥20 years between January 2014 and December 2017 (the prevalence cohort), 2,552 newly diagnosed patients between January 2013 and December 2017 (the incidence and comorbidity cohort), and 2,125 patients enrolled in the database at least 365 days after the diagnosis (the treatment-pattern cohort). The average annual prevalence in 2015–2017 was 9.2 cases per 100,000 in the prevalence cohort, and the average annual incidence in 2013–2017 was 0.49 cases per 100,000 in the incidence and comorbidity cohort. The most common prediagnostic comorbidities included hypertension (43%), diabetes (37%), and hyperlipidemia (27%). In the treatment-pattern cohort, 54% and 45% of patients received surgery and medical treatment as the primary treatment, respectively. Between the first surgery and 365 days after diagnosis, 15% of the patients in this cohort received medical treatment as the secondary treatment, mostly with somatostatin analogs (83%). Of the 1,569 patients who underwent surgery, 29% received medical treatment before surgery. The prevalence and incidence of acromegaly in Japan were similar to those in other countries. This epidemiological study provides the basis for better management of acromegaly nationwide.

Key words: Acromegaly, Prevalence, Incidence, Comorbidities, Treatment pattern

ACROMEGALY is a rare endocrine disease caused by the excessive secretion of growth hormone (GH). It is characterized by clinical manifestations such as acral enlargement and modification of facial appearance, and complications, including hypertension, impaired glucose intolerance, and sleep apnea [1, 2]. Its symptoms gradually develop over many years, and its complications, such as hypertension and glucose intolerance, are common to age-related diseases in the general population.

As a result, the diagnosis of acromegaly often lags years behind the onset of symptoms [3]. Patients with acromegaly have a high risk of mortality if the disease is left untreated. In contrast, lowering the serum IGF-1 concentration and improving metabolic comorbidities can normalize mortality rates [4-7]. Therefore, patients should be diagnosed and treated without delay after the onset of symptoms of acromegaly.

Previous studies on the epidemiology of acromegaly have reported the prevalence of 1.8–13.7 per 100,000 people, the annual incidence of 0.2–1.2 per 100,000 people, and the ratio of males to females is roughly 1:1 [8-23]. In Japan, a questionnaire survey of large hospitals nationwide in 1993 reported 815 cases with acromegaly within the past five years [24], but few recent epidemiological data on acromegaly have been reported. The epidemiology of acromegaly is likely to have changed with the recent progress in the diagnosis and treatment of this disease and revisions to clinical guidelines [25]. The description of current prediagnostic comorbidities and treatment patterns may contribute to better management of acromegaly.
Japan has hitherto not established any nationwide acromegaly registry database. In the present study, we used the National Database of Health Insurance Claims and Specific Health Checkups of Japan (NDB), including almost all the administrative claims data under the universal healthcare insurance system in Japan [26]. In the present study, we aimed to describe the prevalence and incidence of acromegaly in Japan using this nationwide administrative claims database. We also reported the prediagnostic comorbidities and treatment patterns of patients with acromegaly.

Materials and Methods

Data source

We conducted a retrospective observational study using the NDB from January 2012 to March 2018. This database contained almost all claims related to medical care services provided by healthcare institutions, except services fully covered by public expenses such as medical assistance. The NDB includes information on patient identification numbers (ID1 and ID2); types of public insurance, sex, and age group (5-year age bands); diagnostic codes based on the 10th Revision of the International Statistical Classification of Diseases (ICD-10); clinical practice identification codes; treatment codes, including those of surgery and radiation therapy; date of treatment; drug codes; and date of prescriptions. ID1 is generated from the insurance identification number, date of birth, and sex, whereas ID2 from the name, date of birth, and sex. In the same individual, ID1 and ID2 may change, depending on employment or marital status. To increase traceability, we identified patients with acromegaly by assuming that they were a single patient if either their ID1 or ID2 matched. In this identification method, if the name, sex, and date of birth are the same, one ID2 can be assigned to more than one individual. This can lead to the underestimated number of patients [27]. However, among patients with rare diseases such as acromegaly, it is unusual to misidentify individuals with the same name, sex, and date of birth. Clinical practice identification codes enable the distinction between drugs used for testing and those for treatment. The study was conducted in accordance with the Declaration of Helsinki, and was approved by the Institutional Review Board of the University of Kyoto (No. R1675). Due to the anonymous nature of the data, the requirement for informed consent was waived in accordance with the Japanese ethical guidelines.

Acromegaly case identification and study cohorts

We selected three cohorts to describe the prevalence, incidence, prediagnostic comorbidities, and treatment patterns of acromegaly. To include patients present at annual follow-up visits for the prevalence cohort, we identified patients with acromegaly for 2 years. All patients aged ≥20 years were selected during the three periods of 2014–2015, 2015–2016, and 2016–2017 to form the prevalence cohort. They had to meet one of the three acromegaly selection criteria as follows: 1) at least two diagnostic codes of acromegaly (ICD-10: E220) in two different months; 2) one diagnostic code of acromegaly in combination with one diagnostic code of hyperfunction of pituitary gland (ICD-10: E229); or 3) one diagnostic code of acromegaly in combination with one treatment code or one drug code. Treatment options included pituitary surgery (i.e., transsphenoidal resection and intracranial tumor resection), radiotherapy (i.e., stereotactic radiosurgery and intensity-modulated radiation therapy), and acromegaly-related medical therapy. For the first two options, the treatment codes are listed in the Supplementary Table S1. Regarding medical therapy, we only assessed three types of medication, namely somatostatin analogs (SSA), dopamine agonists (DA), and GH receptor antagonists (GHRA). We only included drugs used for acromegaly treatment while excluding those for pituitary function tests and short-acting SSA. In addition, we calculated the prevalence of acromegaly in 2015, 2016, and 2017 corresponding to the three 1-year periods of 2014–2015, 2015–2016, and 2016–2017. To do that, we also included patients with at least one claim in the database after January of each of these 3 years, respectively.

To calculate the incidence of acromegaly and the frequencies of prediagnostic acromegaly-related comorbidities, we identified newly diagnosed cases between January 2013 and December 2017 (the incidence and comorbidity cohort). They were defined as patients who met the acromegaly selection criteria (3) for the first time in this 5-year period. We defined the index date as the date of the earliest claim for a diagnostic code of acromegaly, treatment code, or drug code during this period. If only data for years and months were available, the first day of the month was used to determine the index dates. To avoid selecting patients who were previously diagnosed with acromegaly, we only included cases enrolled in the database at least 365 days before the index date. At the same time, we excluded patients who had diagnostic codes of acromegaly between January 2012 and the index date.

To explain the treatment pattern of acromegaly, we selected newly diagnosed cases enrolled in the database at least 365 days after the index date. This selection helped ensure the follow-up of the treatment pattern (the treatment-pattern cohort).
Prevalence

We calculated the prevalence of acromegaly as the division of the number of patients with acromegaly in the prevalence cohort in a particular period (i.e., 2014–2015, 2015–2016, or 2016–2017) by the population aged ≥20 years in October of the later year of that period (i.e., 2015, 2016, or 2017) estimated by the Cabinet Bureau of Statistics [28].

Incidence and acromegaly-related comorbidities

Regarding the incidence of acromegaly, we calculated this measure by dividing the number of new acromegaly cases in the incidence and comorbidity cohort in a selected year by the population aged ≥20 years in October of that year estimated by the Cabinet Bureau of Statistics [28]. Besides, we evaluated acromegaly-related comorbidities, such as hypertension, diabetes mellitus, or carpal tunnel syndrome, during 365 days before the index date. Their diagnostic codes are listed in Supplementary Table S2.

Treatment patterns

Treatment was classified into five categories: 1) surgery (i.e., transsphenoidal resection, endoscopic transsphenoidal resection, and intracranial tumor resection); 2) SSA therapy (i.e., octreotide, lanreotide, and pasireotide); 3) DA therapy (i.e., cabergoline [off-label use] and bromocriptine); 4) GHRA therapy (i.e., pegvisomant); and 5) radiation therapy (Supplementary Table S1). In the treatment-pattern cohort, the primary treatment was defined as the first code of surgery, drug, or radiation therapy from the index date. The date of the primary treatment was defined as the date of the first code of surgery, drug, or radiation therapy from the index date. The secondary treatment after surgery was assessed among patients who underwent the first surgery. It was defined as the first code of drug or radiation therapy between the index date and 365 days after the index date. Medical therapy before the first surgery was defined to involve all drug codes between the index date and the date of the first surgery code.

Statistical analyses

In this study, all statistical analyses were descriptive and performed using SAS version 9.4 for Windows (SAS Institute, Cary, NC, USA). The prevalence of acromegaly for each of the three years, namely 2015, 2016, and 2017 is expressed as a number of cases per 100,000 inhabitants in the prevalence cohort. The annual incidence of acromegaly for each year from 2013 to 2017 is presented as a number of cases per 100,000 inhabitants in the incidence and comorbidity cohort. Both the prevalence and incidence were stratified by sex (male and female) and age group (20–34, 35–44, 45–54, 55–64, and ≥65 years). The number of newly diagnosed cases was described by age group, sex, type of public insurance (i.e., Society managed, Association Kempo, Mutual aid associations, National Health Insurance, and Long life medical care system), and year of the index date (i.e., 2013, 2014, 2015, 2016, and 2017). Acromegaly-related comorbidities up to 365 days before the index date (i.e., prediagnostic comorbidities) are presented as frequencies. For the treatment-pattern cohort, the time from the index date to the primary treatment and that from the index date to the first surgery are displayed as medians, while primary treatment options (i.e., “transsphenoidal resection”, “endoscopic transsphenoidal resection”, “intracranial tumor resection”, “SSA”, “DA or GHRA”, or “radiation therapy”), secondary treatment options (i.e., “SSA”, “DA or GHRA”, or “radiation therapy”) after the first surgery, and medical treatment options (“SSA”, “SSA + DA”, or “DA or GHRA”) before the first surgery as percentages.

Results

Prevalence

Among 12,713 patients aged ≥20 years who had at least one diagnostic code of acromegaly between January 2014 and December 2017 in the prevalence cohort, we identified about 9,700 patients in each of the three periods, ranging from 9,459 to 9,793 (Table 1). Females accounted for 56.7% (16,419/28,936), and the age distribution by sex was similar. The prevalence of acromegaly was 9.2 cases per 100,000 on average (from 9.0 to 9.3 cases per 100,000). The prevalence in females was higher than that in males. In particular, the male-to-female ratio was 1:1.2. The prevalence of acromegaly varied by age and was found highest in the 55–64 year age group and the 65+ age group (12.8 cases per 100,000), followed by that in the 45–54 year age group (9.2 cases per 100,000).

Incidence

Among 5,117 patients aged ≥20 years who had at least one diagnostic code of acromegaly in Japan, the annual incidence of acromegaly was 0.49 per 100,000, dropping from 0.69 per 100,000 in 2013 to 0.32 per 100,000 in 2017. The incidence in females was higher than that in males, with
cases per 100,000), and the 35–44 year age group (0.56 
incident cases up to 365 days before diagnosis. The 
cohort). The median time from index date to the primary 
treatment in 53.6% (n = 1,138) and 45.2% (n = 961) of these patients, respectively (Table 4). Endo-
soscopic transphenoidal resection was undertaken for 
87.0% (n = 990) of patients initially treated with surgery, 
and SSA was prescribed for 77.0% (n = 740) of patients 
initially treated with medications. During the observation 
period of 365 days after the index date, 1.2% of patients 
(n = 26) received radiation therapy or no treatment fol-
lowing diagnosis. In 1,569 newly diagnosed cases who 
underwent first surgery, the median time from index 
date to first surgery was 88 days (IQR: 52 to 136 days).

**Comorbidities**

Table 3 shows acromegaly-related comorbidities among 
incident cases up to 365 days before diagnosis. The five most common prediagnostic comorbidities included hypertension (42.9%), diabetes mellitus (37.1%), hyper-
lipidemia (26.7%), sleep apnea (21.1%), and arthropathy 
(17.8%).

**Treatment pattern**

Among 2,352 newly diagnosed cases aged ≥20 years 
between January 2013 and December 2017, we identified 
2,125 patients who enrolled in the database at least 365 
days after the index date (Fig. 1; the treatment-pattern 
cohort). The median time from index date to the primary 
treatment was 77 days (interquartile range [IQR]: 24–110 
days). Surgery and medical therapy were chosen as the 
primary treatment in 53.6% (n = 1,138) and 45.2% (n = 961) of these patients, respectively (Table 4). Endo-
soscopic transphenoidal resection was undertaken for 
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lowing diagnosis. In 1,569 newly diagnosed cases who 
underwent first surgery, the median time from index 
date to first surgery was 88 days (IQR: 52 to 136 days).

### Table 1: Prevalence of acromegaly in Japan

| Year    | Male Cases | Prevalence* (in millions) | Female Cases | Prevalence* (in millions) |
|---------|------------|---------------------------|--------------|---------------------------|
| 2015    | 1,289      | 10.2                      | 279          | 2.8                       |
| 2016    | 1,544      | 9.3                       | 492          | 5.5                       |
| 2017    | 1,867      | 8.0                       | 789          | 9.5                       |
| Average | 1,658      | 11.3                      | 2,616        | 13.6                      |

* The prevalence of acromegaly was calculated as the number of patients with acromegaly in the period 2014–2015, 2015–2016, 2016–2017 in the prevalence cohort divided by the population aged ≥20 years in October of 2015, 2016, 2017 estimated by the Cabinet Bureau of Statistics.
Discussion

We found that the average annual prevalence and incidence of acromegaly for persons aged ≥20 years in Japan was 9.2 per 100,000 and 0.49 per 100,000. These results were obtained by analyzing data between 2012 and 2018 extracted from a nationwide claims database, which covers almost all of the Japanese population. To accurately estimate the epidemiology of rare diseases, a large sample size is required. To our knowledge, this present study is among those assessing the epidemiology of acromegaly that have the largest sample sizes. In addition, we figured out that prior to the diagnosis of acromegaly, many people visited healthcare institutions to receive treatment for hypertension, diabetes, hyperlipidemia, and sleep apnea. A total of 54% of incident acromegaly cases underwent surgery as the primary treatment. Before the first surgery, 30% of incident cases received medical treatment, and after the first surgery, SSA being the most common secondary treatment.

The prevalence and incidence of acromegaly in Japan in the present study were comparable to those reported in other countries by previous studies [8-23]. A nationwide hospital survey in South Korea, a country adjacent to Japan, provided with the corresponding rates of 2.8 cases per 100,000 and 0.4 cases per 100,000 [14]. In two studies in the United States that used the healthcare insurance claims database, the prevalence was between 7.1 and 8.8 cases per 100,000, and the incidence was between 0.83 and 1.17 cases per 100,000 [19, 20]. In the present study, the incidence decreased from 0.69 cases per 100,000 in 2013 to 0.32 cases per 100,000 in 2017. This decline may be due to the exclusion criteria for newly diagnosed cases. More precisely, we did not include any patient with a diagnostic code of acromegaly between January 2012, when the database was available, and the index date. In other words, the 2017 incidence may have been more accurately estimated because patients with a history of acromegaly were identified and excluded over a longer period. Interestingly, it was quite similar to that in the previous study in South Korea [14].

The guidelines for acromegaly treatment recommend surgery as the first-line treatment [25, 29]. In the present study, 54% of patients underwent surgery as the primary treatment option. According to a review paper of population-based studies on acromegaly, this proportion remained relatively stable at 67–90%, while that of patients initially treated with medications ranged from 0% to 78%, with significant differences across countries [30]. In Japan, anterior pituitary function can sometimes be assessed using octreotide or bromocriptine before treatment for acromegaly. In the administrative claims
# Table 2: Incidence of acromegaly in Japan

| Year | Both sexes | Male | Female |
|------|------------|------|--------|
| Cases Incidence* | Population (in millions) | Cases Incidence* | Population (in millions) | Cases Incidence* | Population (in millions) |
| 2013 | 84 | 0.41 | 84 | 0.41 | 0.35 | 0.35 |
| 2014 | 207 | 0.71 | 207 | 0.71 | 0.61 | 0.61 |
| 2015 | 259 | 0.87 | 259 | 0.87 | 0.82 | 0.82 |
| 2016 | 320 | 1.15 | 320 | 1.15 | 1.08 | 1.08 |
| 2017 | 381 | 1.31 | 381 | 1.31 | 1.33 | 1.33 |

* The Incidence of acromegaly were calculated as the number of new acromegaly cases in a selected year in the incidence and comorbidity cohort divided by the population aged ≥20 years in October of that year estimated by the Cabinet Bureau of Statistics.
data, the drugs used for pituitary function tests might also be assigned the same code as those for treatment. Therefore, to avoid misclassifying these two categories of drugs, we used not only drug codes but also clinical practice identification codes and excluded short-acting SSAs to define medical treatment. However, the validity of this clinical practice identification code has not been verified, which may lead to misclassification. This means that the proportion of medical treatment as the primary treatment option might be high, making that of surgery low.

Our study has several limitations. First, the diagnostic code of acromegaly has not been validated. The claims database is generated for administrative purposes (i.e., reimbursement of healthcare services), not for research purposes; therefore, diagnostic codes for payment might have been used instead of the actual clinical diagnosis. Thus, we may have overestimated or underestimated the prevalence or incidence of acromegaly in the present study. However, some of the estimation inaccuracies could be reduced as we identified patients with acromegaly by combining the diagnostic codes with acromegaly-related treatment codes and drug codes. Validation studies were also challenging to perform because the NDB contains anonymous data, and acromegaly is a rare disease. Second, the database lacks relevant clinical information, such as GH, IGF-1, or size of adenoma. With its availability, we could describe the prevalence and incidence of acromegaly with higher accuracy, and establish the association between treatment and its response. Third, the prevalence and incidence may be underestimated due to the difficulties in tracing individual patients in the NDB. We might have identified different individuals with the same name and age as one single person. Finally, we did not consider other treatment options for acromegaly such as proton therapy. However, during the implementation of this study, proton therapy was available only as one of the advanced medical care services and not covered by health insurance.

This nationwide-claims database study showed that the prevalence and incidence of acromegaly among people aged ≥20 years in Japan were similar to those reported by previous studies. Although recommended by the guidelines for acromegaly treatment, surgery remained underused as the first treatment option. Our results are expected to help in appropriately allocating medical resources, including personnel and equipment, to acromegaly treatment, and evaluating the quality of care, such as compliance with clinical practice guidelines. The reliability of our results can be improved through the development of a nationwide disease registry or a combination of the NDB and clinical data.

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### Table 3 Patients characteristics and comorbidities among newly diagnosed patients with acromegaly

|                          | n   | (%)  |
|--------------------------|-----|------|
| **Total**                | 2,552 |     |
| **Age group**            |     |      |
| 20–34                    | 317  | (12.4) |
| 35–44                    | 505  | (19.8) |
| 45–54                    | 526  | (20.6) |
| 55–64                    | 557  | (21.8) |
| 65+                      | 647  | (25.4) |
| **Sex**                  |     |      |
| Male                     | 1,143 | (44.8) |
| Female                   | 1,409 | (55.2) |
| **Insurance type**       |     |      |
| Society managed          | 543  | (21.3) |
| Association Kempo        | 728  | (28.5) |
| Mutual aid associations  | 208  | (8.2)  |
| National Health Insurance| 886  | (34.7) |
| Long life medical care system | 187  | (7.3)  |
| **Year of the index date**|     |      |
| 2013                     | 725  | (28.4) |
| 2014                     | 526  | (20.6) |
| 2015                     | 499  | (19.6) |
| 2016                     | 461  | (18.1) |
| 2017                     | 341  | (13.4) |
| **Comorbidity**          |     |      |
| Hypertension             | 1,094 | (42.9) |
| Diabetes Mellitus        | 948  | (37.1) |
| Hyperlipidemia           | 682  | (26.7) |
| Sleep apnea              | 538  | (21.1) |
| Arthropathy              | 455  | (17.8) |
| Hypopituitarism          | 266  | (10.4) |
| Menstrual abnormality    | 87   | (3.4)  |
| Carpal tunnel syndrome   | 62   | (2.4)  |
| Cardiomyopathy           | 24   | (0.9)  |
Table 4  Treatment pattern of patients with acromegaly

| Primary treatment                                      | n  | (%) |
|--------------------------------------------------------|----|-----|
| Total                                                  | 2,125 |     |
| Time from index date to primary treatment, median (IQR), days | 77  | (24–110) |
| Surgery                                                |     |     |
| Transsphenoidal resection                              | 1,138 | (53.6) |
| Endoscopic transsphenoidal resection                   | 128  | (6.0) |
| Intracranial tumor resection                           | 990  | (46.6) |
| SSA                                                    | 20   | (0.9) |
| DA or GHRA                                             |     |     |
| Radiation or none                                      | 26   | (1.2) |
| Medication                                             |     |     |
| SSA                                                    | 961  | (45.2) |
| DA or GHRA                                             | 740  | (34.8) |
| Radiation or none                                      | 221  | (10.4) |
| Total                                                  | 1,569 |     |
| Time from index date to surgery, median (IQR), days     | 88  | (52–136) |
| Medication                                             |     |     |
| SSA                                                    | 240  | (15.3) |
| DA or GHRA                                             | 200  | (12.7) |
| Radiation or none                                      | 22   | (1.4) |
| Medication before surgery                              |     |     |
| SSA                                                    | 462  | (29.4) |
| SSA + DA                                               | 358  | (22.8) |
| DA or GHRA                                             | 55   | (3.5) |

Data are n (%) unless otherwise stated.  
SSA, somatostatin analog; DA, dopamine agonist; GHRA, growth hormone receptor antagonist; IQR, interquartile

Supplementary Table S1  Acromegaly related-surgery and radiotherapy codes

| Types of treatment | Description                                          | Treatment code                          |
|--------------------|-------------------------------------------------------|-----------------------------------------|
| Surgery            | Transsphenoidal resection                             | 150071010                               |
|                    | Endoscopic transsphenoidal resection (pituitary tumor) | 150355310, 150384610                     |
|                    | Intracranial tumor resection                          | 150284510                               |
| Radiosurgery       | Stereotactic radiosurgery with Gamma Knife            | 180018910, 190197910, 190198010          |
|                    | Linear accelerator radiation therapy (stereotactic radiotherapy) | 180019710                              |
|                    | External-beam irradiation (Intensity Modulated Radiation Therapy) | 180031910, 180032010                     |
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**Supplementary Table S2**  
ICD-10 codes for acromegaly-related prediagnostic comorbidities

| Comorbidity                  | ICD-10 codes |
|------------------------------|--------------|
| Hypertension                 | I10-I15, R030|
| Diabetes Mellitus            | E11, E14, R73|
| Hyperlipidemia               | E780-E785    |
| Sleep apnea                  | G47          |
| Arthropathy                  | M15-M19      |
| Hypopituitarism              | E230, E237   |
| Menstrual abnormality        | N91, N92     |
| Carpal tunnel syndrome       | G560, G569   |
| Cardiomyopathy               | I42          |

ICD, International Classification of Diseases
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