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Patient Characteristics, Disease Burden, Treatment Patterns and Outcomes in Patients with Acromegaly: Real-World Evidence from the Malaysian Acromegaly Registry

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Abstract

Objective. This study aims to report the demographic features of patients with acromegaly, the disease burden, and the corresponding treatment patterns and outcomes in Malaysia.

Methodology. This is a retrospective study that included patients from the Malaysian Acromegaly registry who were diagnosed with acromegaly from 1970 onwards. Data collected included patient demographics, clinical manifestations of acromegaly, biochemical results and imaging findings. Information regarding treatment modalities and their outcomes was also obtained.

Results. Registry data was collected from 2013 to 2016 and included 140 patients with acromegaly from 12 participating hospitals. Median disease duration was 5.5 years (range 1.0 – 41.0 years). Most patients had macroadenoma (67%), while 15% were diagnosed with microadenoma. Hypertension (49.3%), diabetes (37.1%) and hypopituitarism (27.9%) were the most common co-morbidities for patients with acromegaly. Majority of patients had surgical intervention as primary treatment (65.9%) while 20.7% were treated medically, mainly with dopamine agonists (18.5%). Most patients had inadequate disease control after first-line treatment regardless of treatment modality (79.4%).

Conclusion. This registry study provides epidemiological data on patients with acromegaly in Malaysia and serves as an initial step for further population-based studies.

Key words: acromegaly, Malaysian registry, healthcare resource utilization, treatment outcomes

INTRODUCTION

Acromegaly is a rare endocrine disease resulting from excessive growth hormone (GH) production and affects both men and women equally.[1] In Western countries, the reported prevalence is approximately 70 to 80 cases per million population with an incidence of 3-11 cases per million population per year,[2-5] although the cases reported from Asia are lower at a prevalence of 28 and incidence of 4 cases per million population/year.[6]

Acromegaly is mainly caused by the presence of GH-secreting pituitary tumours. Elevated GH and insulin-growth factor 1 (IGF-1) result in anatomical changes and metabolic dysfunction.[1] Dysregulation of both hormones results in acromegaly-associated symptoms such as changes in facial appearance, overgrowth of hands and feet, headache, endocrine dysfunction and cardiovascular diseases.[7-11] Due to its insidious nature, the diagnosis of acromegaly is often delayed, at least 4 to 10 years after disease onset.[12-14] Unfortunately, diagnostic delays often lead to poor patient quality of life as well as increased morbidity and mortality.[15,16]

Clinical features that are suggestive of acromegaly such as headaches, diabetes mellitus, hypertension and heart disease of unknown aetiology warrant biochemical screening with GH and IGF-1 to confirm a diagnosis of

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acromegaly. Magnetic resonance imaging of the pituitary is also requested.[17] Main treatment goals include tumour removal and normalisation of GH and IGF-1 levels, accompanied by the resolution of clinical symptoms and eventually, a reduction in long-term mortality.[17] The main therapeutic options for acromegaly include surgical resection of adenomas, medical treatment with dopamine agonists and somatostatin analogues, and radiotherapy.[8,11,17] Transsphenoidal surgery is often considered the first-line treatment for most patients, with medical therapy being reserved as second-line treatment for patients who refuse surgery to control hormone production and tumour growth.[8,17-19]

Patient presentation, demographics and treatment modalities vary greatly amongst countries and regions. There was no prior data on acromegaly in Malaysia, hence, the Malaysian Endocrine and Metabolic Society (MEMS) established the acromegaly disease registry in 2013. Data were collected from 12 participating hospitals, including patients diagnosed with acromegaly from 1970 onwards. There is currently also no published literature on acromegaly in Malaysia. This study aims to report the demographic features of patients with acromegaly, the burden of the disease, the different treatment modalities and the corresponding treatment outcomes in Malaysia using data from the acromegaly disease registry.

METHODOLOGY

Data were collected from 2013 to 2016 from the Malaysian Acromegaly Registry with permission obtained from MEMS. Any patient diagnosed with acromegaly from 1970 onwards was included in the registry, whether they were identified at routine clinical appointments or upon reviewing hospital records. A diagnosis of acromegaly was made based on radiographic evidence of a pituitary adenoma plus any one of the following biochemical criteria: 1) Documented elevated IGF-1 level; 2) Failure of GH suppression with oral glucose tolerance test (OGTT); 3) Elevated GH levels in the presence of clinical features of acromegaly. Patients were excluded if either biochemical evidence or pituitary imaging was negative or unavailable.

Data collected included demographic, clinical (symptoms, signs, and comorbidities), biochemical and hormonal profiles, imaging results, as well as information regarding treatment modalities and their therapeutic outcomes. Outcomes were categorized as either controlled disease defined by an age-adjusted normal IGF-1 level and a random GH concentration <1 μg/L, or persistent disease if either GH or IGF-1 remained above the normal range.

All data was collected, stored and used in strict accordance with current Malaysia legislation on data protection, ethics and written informed patient consent. The study was approved by Malaysia Medical Research and Ethics Committee (MREC no: NMRR-12-1324-13746).

Statistical methods

In general, categorical variables were presented as count and percentages, while continuous variables were presented as count and median with range (min-max), stratified by tumour size.

RESULTS

A total of 140 patients with acromegaly from 12 participating hospitals were included in the registry. The median disease

Table 1. Patient baseline characteristics

Characteristics	Overall	Size of pituitary tumour*	
		Macro-adenoma	Micro-adenoma
Total patients, N (%)	140 (100.0)	95 (67.9)	21 (15.0)
Median age, years, (range)	52.0 (20.0 – 80.0)	49.0 (20.0 – 80.0)	58.0 (31.0 – 75.0)
Age groups at diagnosis, n (%)			
<18 years	0 (0.0)	0 (0.0)	0 (0.0)
18 - <30 years	11 (7.9)	9 (9.5)	0 (0.0)
30 - <50 years	51 (36.4)	39 (41.1)	6 (28.6)
≥50 years	77 (55.0)	46 (48.4)	15 (71.4)
Gender, n (%)			
Female	68 (48.6)	45 (47.4)	11 (52.4)
Male	70 (50.0)	48 (50.5)	10 (47.6)
n	138	93	21
Median Disease duration, years (range)	5.5 (1.0 – 41.0)	4.0 (1.0 – 41.0)	8.0 (1.0 – 19.0)
Categorized disease duration, n (%)			
<5 years	62 (44.3)	51 (53.7)	7 (33.3)
5 – 10 years	36 (25.7)	23 (24.2)	8 (38.1)
>10 years	40 (28.6)	19 (20.0)	6 (28.6)
n	94	77	13
Median IGF-1 at diagnosis, μg/L (range)	627.0 (4.5 – 1115.0)	601.0 (4.5 – 1115.0)	724.0 (400.0 – 892.0)
n	66	54	9
Median GH at diagnosis, measured post-OGTT, μg/L (range)	13.9 (0.2 – 730.0)	17.2 (0.2 – 730.0)	4.0 (1.0 – 36.0)
n	64	48	12
Median GH at diagnosis, measured post fasting, μg/L (range)	17.0 (0.0 – 104.0)	18.5 (0.2 – 104.0)	9.1 (0.2 – 32.9)
Clinical manifestations of acromegaly, n (%)			
Hypertension	69 (49.3)	40 (42.1)	15 (71.4)
Diabetes	52 (37.1)	33 (34.7)	10 (47.6)
Hypopituitarism	39 (27.9)	27 (28.4)	2 (9.5)
Dyslipidemia	19 (13.6)	13 (13.7)	4 (19.0)
Arthritis	17 (12.1)	13 (13.7)	3 (14.3)
Sleep apnea	10 (7.1)	6 (6.3)	3 (14.3)
Toxic MNG + Hyperthyroidism	10 (7.1)	9 (9.5)	1 (4.8)
Visual field detect	5 (3.6)	4 (4.2)	0 (0.0)
Thyroid Carcinoma	4 (2.9)	2 (2.1)	2 (9.5)
Co-secreting prolactin + hPL	5 (3.6)	5 (5.3)	0 (0.0)
Cardiac (LVH + MR)	3 (2.1)	3 (3.2)	0 (0.0)
Carpal Tunnel Syndrome	2 (1.4)	2 (2.1)	0 (0.0)
Renal Calculi	2 (1.4)	2 (2.1)	0 (0.0)
Osteoporosis	2 (1.4)	0 (0.0)	1 (4.8)
Stroke	1 (0.7)	0 (0.0)	1 (4.8)
Apoplexy	1 (0.7)	1 (1.1)	0 (0.0)
Migraine	1 (0.7)	1 (1.1)	0 (0.0)
Others	11 (7.9)	5 (5.3)	2 (9.5)

*Tumour size was not documented for 24 patients
Abbreviation: GH, growth hormone; hPL, human placental lactogen; IGF-I, insulin growth factor-I; LVH, left ventricular hypertrophy; MNG, multinodular goiter; MR, mitral regurgitation

Table 2. Primary treatment modalities

Characteristics	Overall	Size of pituitary tumour*	
		Macro-adenoma	Micro-adenoma
Total patients, N	140	95	21
Received primary healthcare treatment, M (%)	135 (96.4)	91 (95.8)	21 (100.0)
Type of treatment regimens, n (%)			
Single treatment modality	121 (89.6)	81 (89.0)	20 (95.2)
Medical	28 (20.7)	18 (19.8)	9 (42.9)
Surgery	89 (65.9)	61 (67.0)	11 (52.4)
Transfrontal	3 (2.2)	2 (2.2)	0 (0.0)
Transsphenoidal	84 (62.2)	58 (63.7)	11 (52.4)
Others or undefined	2 (1.5)	1 (1.1)	0 (0.0)
Radiotherapy	4 (3.0)	2 (2.2)	0 (0.0)
Conventional	2 (1.5)	2 (2.2)	0 (0.0)
Stereotactic	2 (1.5)	0 (0.0)	0 (0.0)
Others or undefined	0 (0.0)	0 (0.0)	0 (0.0)
Dual treatment modalities	12 (8.9)	10 (11.0)	0 (0.0)
Medical and surgery	8 (5.9)	8 (8.8)	0 (0.0)
Surgery and radiotherapy	4 (3.0)	2 (2.2)	0 (0.0)
Triple treatment modalities	2 (1.5)	0 (0.0)	1 (4.8)
Type of medical regimens, n (%)			
Single medication	34 (25.2)	24 (26.4)	8 (38.1)
Dopamine agonists	25 (18.5)	17 (18.7)	7 (33.3)
Somatostatin analogues	7 (5.2)	5 (5.5)	1 (4.8)
Others or undefined	2 (1.5)	2 (2.2)	0 (0.0)
Double medications	4 (3.0)	2 (2.2)	2 (9.5)
Dopamine agonists and Somatostatin analogues	4 (3.0)	2 (2.2)	2 (9.5)

*Tumour size was not documented for 24 patients
NB: Percentage calculated using denominator "received primary healthcare treatment, M"

Table 3. Current treatment modalities

Characteristics	Overall	Size of pituitary tumour	
		Macro-adenoma	Micro-adenoma
Total patients, N	140	95	21
Received current healthcare treatment, M (%)	71 (50.7)	49 (51.6)	14 (66.7)
Type of treatment regimens, n (%)			
Single treatment modality	71 (100.0)	49 (100.0)	14 (100.0)
Medical	67 (94.4)	46 (93.9)	14 (100.0)
Surgery	3 (4.2)	2 (4.1)	0 (0.0)
Transsphenoidal	1 (1.4)	1 (2.0)	0 (0.0)
Others or undefined	2 (2.8)	1 (2.0)	0 (0.0)
Radiotherapy	1 (1.4)	1 (2.0)	0 (0.0)
Others or undefined	1 (1.4)	1 (2.0)	0 (0.0)
Type of medical regimens, n (%)			
Single medication	62 (87.3)	43 (87.8)	13 (92.9)
Dopamine agonists	27 (38.0)	16 (32.7)	8 (57.1)
Somatostatin analogues	35 (49.3)	27 (55.1)	5 (35.7)
Double medications	5 (7.0)	3 (6.1)	1 (7.1)
Dopamine agonists and Somatostatin analogues	3 (4.2)	1 (2.0)	1 (7.1)
Others or undefined	2 (2.8)	2 (4.1)	0 (0.0)

NB: Percentage calculated using denominator "received primary healthcare treatment, M"

Table 4. First line treatment outcomes

	Treatment outcome*	
	Controlled disease (N=28)	Persistent disease (n=81)
First line treatment, n (%)		
Medical only	3 (10.7)	13 (16.0)
Surgical only	19 (67.9)	57 (70.4)
Radiotherapy only	1 (3.6)	3 (3.7)
Medical + surgical	4 (14.4)	3 (3.7)
Surgical + radiotherapy	1 (3.6)	3 (3.7)
Medical + surgical + radiotherapy	0	2 (2.5)

*There was no information on treatment outcome in 29 patients. 1 patient had deficiency in hormone levels post-removal of pituitary tumour.

duration was 5.5 years (range 1.0 – 41.0 years). Median age of patients was 52 years, with equal distribution across gender (female 68 [48.6%]; male 70 [50.0%]). Over 67% of patients were diagnosed with macroadenoma, while a minority of patients had microadenoma (n=21, 15%). Tumour size was not documented in 24 patients. IGF-1 levels were available for 94 patients at diagnosis, but only 66 patients had an OGTT with GH measurement at diagnosis.

Hypertension (49.3%), diabetes (37.1%) and hypopituitarism (27.9%) were the most common co-morbidities for patients with acromegaly. Patients with microadenoma were more frequently found to have hypertension and diabetes compared to those with macroadenoma (71.4% vs 42.1%; 47.6% vs 34.7%). Some patients with macroadenomas had co-secretion of prolactin and human placental lactogen (5%, 5.3% respectively). Unexpectedly, there were 2 cases of hypopituitarism (9.5%), which is not usually associated with microadenomas. The full list of clinical manifestations of acromegaly is presented in Table 1.

Regardless of adenoma size, majority of patients received monotherapy with most patients undergoing surgery alone (65.9%) while 20.7% had medical treatment alone as first-line intervention (Table 2). A minority of patients required dual therapy with either a combination of medical and surgical intervention (5.9%) or a combination of surgery and radiotherapy (3.0%). In terms of medical intervention, dopamine agonists were more frequently used (18.5%) in contrast to somatostatin analogues (5.2%).

Currently, the majority of the patients are receiving monotherapy with medical treatment being the dominant choice (94.4%). There are no patients on dual or triple therapy. Somatostatin analogues are used slightly more than dopamine agonists (49.3% vs 38.0%) (Table 3).

A total of 109 patients reported treatment outcomes after first-line treatment (Table 4). Regardless of the treatment modality, most patients had persistent disease.

DISCUSSION

The acromegaly registry was established to obtain epidemiological data on patients with acromegaly in Malaysia. It was funded and supported by MEMS. From this current study, data collected between 2013 and 2016 showed that there were only 140 patients listed in the registry were diagnosed with acromegaly from 1970 onwards. The Malaysian Consensus Statement for the Diagnosis and Management of Acromegaly highlights the condition as an underrecognised and underdiagnosed condition in the country.[17] Clinicians face major challenges in management due to the delayed diagnosis.[20-22] Median duration of disease to diagnosis was 5.5 years, although nearly a third were only diagnosed after 10 years, with a majority of patients having macroadenomas (68%). As a result of this finding, a clinical pathway for screening and subsequent referral to the nearest, most accessible endocrinologist and endocrine center was formulated.

There is also a minority of patients who did not have any information regarding tumour status; it cannot be derived from the registry if the tumour status was undocumented or if MRI/CT imaging was not done. Hypertension, diabetes, hypothyroidism and dyslipidemia were the most commonly reported symptoms of acromegaly among patients in Malaysia, which concurs with published reports and other Asian acromegaly registry studies.[10,20-22] Interestingly, two patients with microadenoma had hypopituitarism, which is usually associated with macroadenomas. There have been previous reports on cases of microadenomas with resultant hypopituitarism.[23,24] Although, patients with acromegaly frequently have multinodular non-toxic goiters, some present with less common thyroid presentations such as toxic multinodular goiter (10 patients) and thyroid carcinoma (4 patients). A recent meta-analysis concerning different cancer types in acromegaly reported a significant increase in the prevalence of thyroid cancers.[25]

In the past, endocrinology practice in Malaysia was confined to a limited number of certain public hospitals which hampered the screening of these patients, ultimately resulting in delayed diagnosis and management. With the increasing number of endocrinologists, more cases are expected to be detected and referred for complete assessment and long-term care.

From this study, only around 67% of patients had IGF-1 results. IGF-1 assay only became available in Malaysia in 1993 and was previously only available at the Institute of Medical Research with a long turnaround time. Currently, selected public hospitals also offer IGF-1 assays which should increase the availability of this test.

Surgery is the treatment of choice for most patients (76.3%), especially for those with macroadenomas. As per guidelines[17], transsphenoidal surgical removal of adenomas is the preferred technique for most patients. Clinical practice in Malaysia concurred with practice in other Asian countries such as Japan, Korea, China and Taiwan.[20-22,26]

In terms of medical treatment, guidelines recommend the use of somatostatin analogues first and consider dopamine agonists in milder cases.[17-19] However, dopamine agonists are given more often used than somatostatin analogues in practice due to its ease of administration, wide accessibility and affordability. In Malaysia, the use of somatostatin analogues is restricted and tightly regulated. It is mainly reserved as second-line treatment when surgery or dopamine agonists have failed to control the disease. Although the GH receptor antagonist, pegvisomant is currently the most effective treatment for acromegaly,[27] it is currently unavailable in Malaysia.

The use of radiotherapy is low in Malaysian patients because it is usually reserved for residual or recurrent tumours with high surgical risk or if the patient refuses surgery.[17] Data from the registry shows that additional radiotherapy was given only if with persistent disease after primary treatment. However, it has posed a greater risk of hypopituitarism and an uncertain long-term complication rate.[21] Although radiotherapy has taken a back seat with the development of effective and safer medical therapies such as somatostatin analogues or pegvisomant, radiotherapy still plays a role in salvage therapy.[17-19,28-30]

Regardless of the treatment modality, a high proportion of patients continue to have persistent disease. A recent study looking at acromegaly in Central and Eastern Europe, Israel and Kazakhstan also showed that there could be improvements in disease control.[31] Chronic exposure to elevated levels of GH and IGF-1 prior to diagnosis and optimal treatment of disease are suggested to play an important role in disease persistence.[32] However, with the limitation in the registry data, we are unable to suggest any correlation of patient characteristics to disease persistence.

One limitation of this study was that only 12 hospitals were invited to participate in this registry and therefore, may not accurately capture the full picture of all patients with acromegaly in Malaysia. However, these are the main endocrine centers in the public sector. A few patients were seen privately but most patients were referred to these public endocrine centers for long-term follow-up. Data may be incomplete since only those submitted by clinicians would be included in the registry.

Data presented were collected before the Malaysia Consensus Statement for the Diagnosis and Management of Acromegaly was launched in 2019.[17] Since the consensus was launched, there have been huge initiatives to standardise diagnosis and management of acromegaly in Malaysia, including efforts to increase awareness of the disease among primary care physicians. These efforts have also reached out to other healthcare professionals, patients and caregivers. A patient support group was established for patients with acromegaly. A future study is currently underway to assess the impact of the consensus and these initiatives.

CONCLUSION

This registry data provided the first epidemiological snapshot of patients with acromegaly in Malaysia serving as an initial step for further population-based studies. This study serves as baseline of the clinical practice of diagnostics, treatment and management of patients with acromegaly. With the establishment of the consensus statement, we hope that future initiatives would help improve patient care.

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Statement of Authorship
The authors certified fulfillment of ICMJE authorship criteria.

CRediT Author Statement
MBLB: Conceptualization; Methodology, Investigation, Resources, Data curation, Writing – review and editing, Supervision, Project administration; **AMK:** Conceptualization, Resources, Writing – review and editing, Visualization, Project administration, Funding acquisition; **FHST:** Investigation, Writing – original draft preparation, Writing – review and editing, Visualization, Supervision; **NAA:** Investigation, Resources, Writing – review and editing; **NMA:** Investigation, Writing – original draft preparation, Writing – review and editing; **NAK:** Conceptualization, Methodology, Formal analysis, Investigation, Resources, Writing – original draft preparation, Writing – review and editing, Supervision; **SRV:** Writing – original draft preparation, Writing – review and editing; Visualization; **BS:** Conceptualization, Project administration, Funding acquisition; **ZH:** Conceptualization, Methodology, Validation, Investigation, Resources, Writing – original draft preparation, Writing – review and editing, Visualization, Supervision, Project administration, Funding acquisition.

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References
1. Melmed S. Acromegaly pathogenesis and treatment. J Clin Invest. 2009;119:3(11):3189-202. PMID: 19884662. PMCID: PMC2769196. https://doi.org/10.1172/JCI39375.
2. Burton T, Le Nestour E, Neary M, Ludlam W. Incidence and prevalence of acromegaly in a large US health plan database. Pituitary. 2016;19(3):262-7. PMID: 26792654. PMCID: PMC4858553. https://doi.org/10.1007/s11102-015-0701-2.
3. Broder M, Chang E, Cherepanov D, Neary M, Ludlam W. Incidence and prevalence of acromegaly in the United States: A claims-based analysis. Endocr Pract. 2016;22(11):1327-35. PMID: 27540880. https://doi.org/10.4158/EP161397.OR.
4. Dal J, Feldt-Rasmussen U, Andersen M, et al. Acromegaly incidence, prevalence, complications and long-term prognosis: A nationwide cohort study. Eur J Endocrinol. 2016;175(3):181-90. PMID: 27280374. https:/doi.org/10.1530/EJE-16-0117.
5. Gatto F, Trifirò G, Lapi F, et al. Epidemiology of acromegaly in Italy: Analysis from a large longitudinal primary care database. Endocrine. 2018;61(3):533-41. PMID: 29797214. https://doi.org/10.1007/s12020-018-1630-4.
6. Kwon O, Song YD, Seong YK, Lee EJ; for the Rare Disease Study Group, Science and Research Committee, Korean Endocrine Society. Nationwide survey of acromegaly in South Korea. Clin Endocrinol (Oxf). 2013;78(4):577-585. PMID: 22909047. https://doi.org/10.1111/cen.12020.
7. Gadelha MR, Kasuki L, Lim DST, Fleseriu M. Systemic complications of acromegaly and the impact of the current treatment landscape: An update. Endocr Rev. 2019;40(1):268-332. PMID: 30184064. https://doi.org/10.1210/er.2018-00115.
8. Colao A, Grasso LFS, Giustina A, et al. Acromegaly. Nat Rev Dis Primers. 2019;5(1):20. PMID: 30899019. https://doi.org/10.1038/s41572-019-0071-6.
9. Tirosh A, Shimon I. Complications of acromegaly: Thyroid and colon. Pituitary. 2017;20(1):70-5. PMID: 27631334. https://doi.org/10.1007/s11102-016-0744-z.
10. Pivonello R, Auriemma RS, Grasso LF, et al. Complications of acromegaly: Cardiovascular, respiratory and metabolic comorbidities. Pituitary. 2017;20(1):46-62. PMID: 28224405. https://doi.org/10.1007/s11102-017-0797-7.
11. Dineen R, Stewart PM, Sherlock M. Acromegaly. QJM 2017;110(7):411–20. PMID: 26873451. https://doi.org/10.1093/qjmed/hcw004.
12. Nabarro JD. Acromegaly. Clin Endocrinol (Oxf) 1987;26(4):481–512. PMID: 3308190. https://doi.org/10.1111/j.1365-2265.1987.tb00805.x.
13. Ezzat S, Forster MJ, Berchtold P, Redelmeier DA, Boerlin V, Harris AG. Acromegaly. Clinical and biochemical features in 500 patients. Medicine (Baltimore). 1994;73(5):233–40. PMID: 7934807.
14. Chanson P, Salenave S. Acromegaly. Orphanet J Rare Dis. 2008;3:17. PMID: 18578866. PMCID: PMC2459162. https://doi.org/10.1186/1750-1172-3-17.
15. Esposito D, Ragnarsson O, Johannsson G, Olsson DS. Prolonged diagnostic delay in acromegaly is associated with increased morbidity and mortality. Eur J Endocrinol. 2020;182(6):523-31. PMID: 32213651. https://doi.org/10.1530/EJE-20-0019.
16. Kreitschmann-Andermahr I, Buchfelder M, Kleist B, et al. Predictors of quality of life in 165 patients with acromegaly: Results from a single-center study. Endocr Pract. 2017;23(1):79-88. PMID: 27749131. https://doi.org/10.4158/EP161373.OR.
17. Hussein Z, Bidin M, Alias A, et al. Malaysian consensus statement for the diagnosis and management of acromegaly. J ASEAN Fed Endocr Soc. 2019;34(1):8-14. PMID: 33442131. PMCID: PMC7784186. https://doi.org/10.15605/jafes.034.01.03.
18. Katznelson L, Laws ER Jr, Melmed S, et al. Acromegaly: An endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2014;99(11):3933-51. PMID: 25356808. https://doi.org/10.1210/jc.2014-2700.
19. Katznelson L, Atkinson JL, Cook DM, et al. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the diagnosis and treatment of acromegaly--2011 update. Endocr Pract. 2011;17(Suppl 4):1-44. PMID: 21846616. https://doi.org/10.4158/ep.17.s4.1.
20. Matsubayashi K, Kawakami K. Prevalence, incidences, comorbidities, and treatment patterns among Japanese patients with acromegaly: A descriptive study using a nationwide claims database. Endocr J. 2020;67(10):997-1006. PMID: 32522909. https://doi.org/10.1507/endocrj.EJ20-0129.
21. Yun SJ, Lee, JK, Park SY, Chin SO. Descriptive epidemiology and survival analysis of acromegaly in Korea. J Korean Med Sci. 2021;36(23):e159. PMID: 34128596. PMCID: PMC8203854. https://doi.org/10.3346/jkms.2021.36.e159.
22. Guo X, Wang K, Yu S, Gao L, et al. Patient characteristics, diagnostic delays, treatment patterns, treatment outcomes, comorbidities, and treatment costs of acromegaly in China: A nationwide study. Front Endocrinol (Lausanne). 2020;11:610519. PMID: 33335513. PMCID: PMC7736552. https://doi.org/10.3389/fendo.2020.610519.
23. Yuen K, Cook D, Sahasranam P, et al. Prevalence of GH and other anterior pituitary hormone deficiencies in adults with nonsecreting pituitary microadenomas and normal serum IGF-1 levels. Clin Endocrinol (Oxf). 2008;69(2):292-8. PMID: 18221393. PMCID: PMC2953553. https://doi.org/10.1111/j.1365-2265.2008.03201.x.
24. Manappallil RG, Veethil PP, Babu H, Khan SR. Pituitary microadenoma with hypopituitarism presenting as hyponatremia. BMJ Case Reports. 2021;14(8):e244426. PMID: 34380688. PMCID: PMC8359447 (available on 2023-08-11). https://doi.org/10.1136/bcr-2021-244426.
25. Dal J, Leisner M, Hermansen K, et al. Cancer incidences in patients with acromegaly: A cohort study and meta-analysis of the literature. J Clin Endocrinol Metab. 2018;103(6):2182-8. PMID: 29590449. https://doi.org/10.1210/jc.2017-02457.
26. Tseng F, Huang T, Lin J, Chen S, et al. A registry of acromegaly patients and one year following up in Taiwan. J Formos Med Assoc. 2019;118(10):1430-7. PMID: 30612883. https://doi.org/10.1016/j.jfma.2018.12.017.
27. van der Lely AJ, Hutson RK, Trainer PJ, et al. Long-term treatment of acromegaly with pegvisomant, a growth hormone receptor antagonist. Lancet. 2001;358(9295):1754-9. PMID: 11734231. https://doi.org/10.1016/s0140-6736(01)06844-1.

28. Hannon MJ, Barkan AL, Drake WM. The role of radiotherapy in acromegaly. Neuroendocrinology. 2016;103(1):42-9. PMID: 26088716. https://doi.org/10.1159/000435776.
29. Melmed S, Bronstein MD, Chanson P, et al. A consensus statement on acromegaly therapeutic outcomes. Nat Rev Endocrinol. 2018;14(9): 552-61. PMID: 30050156. PMCID: PMC7136157. https://doi.org/10.1038/s41574-018-0058-5.
30. Frara S, Maffezzoni F, Mazziotti G, Giustina A. The modern criteria for medical management of acromegaly. Prog Mol Biol Transl Sci. 2016;138:63–83. PMID: 26940387. https://doi.org/10.1016/bs.pmbts.2015.10.015.
31. Bolanowski M, Adnan Z, Doknic M, et al. Acromegaly: Clinical care in Central and Eastern Europe, Israel and Kazakhstan. Front Endocrinol (Lausanne). 2022;13:816426. PMID: 35273565. PMCID: PMC8902495. https://doi.org/10.3389/fendo.2022.816426.
32. Christofides E. Clinical importance of achieving biochemical control with medical therapy in adult patients with acromegaly. Patient Prefer Adherence. 2016;10:1217-25. PMID: 27471378. PMCID: PMC4948729. https://doi.org/10.2147/PPA.S102302.