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Acromegaly determination using discriminant analysis of the three-dimensional facial classification in Taiwanese

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Abstract

OBJECTIVES: The aim of this study was to assess the size, angles and positional characteristics of facial anthropometry between "acromegalic" patients and control subjects. We also identify possible facial soft tissue measurements for generating discriminant functions toward acromegaly determination in males and females for acromegaly early self-awareness.
MATERIAL AND METHODS: This is a cross-sectional study. Subjects participating in this study included 70 patients diagnosed with acromegaly (35 females and 35 males) and 140 gender-matched control individuals. Three-dimensional facial images were collected via a camera system. Thirteen landmarks were selected. Eleven measurements from the three categories were selected and applied, including five frontal widths, three lateral depths and three lateral angular measurements. Descriptive analyses were conducted using means and standard deviations for each measurement. Univariate and multivariate discriminant function analyses were applied in order to calculate the accuracy of acromegaly detection.
RESULTS: Patients with acromegaly exhibit soft-tissue facial enlargement and hypertrophy. Frontal widths as well as lateral depth and angle of facial changes were evident. The average accuracies of all functions for female patient detection ranged from 80.0–91.40%. The average accuracies of all functions for male patient detection were from 81.0–94.30%. The greatest anomaly observed was evidenced in the lateral angles, with greater enlargement of "nasofrontal" angles for females and greater "mentolabial" angles for males. Additionally, shapes of the lateral angles showed changes. The majority of the facial measurements proved dynamic

for acromegaly patients; however, it is problematic to detect the disease with progressive body anthropometric changes.

CONCLUSION: The discriminant functions of detection developed in this study could help patients, their families, medical practitioners and others to identify and track progressive facial change patterns before the possible patients go to the hospital, especially the lateral "angles" which can be calculated by relative point-to-point changes derived from 2D lateral imagery without the 3D anthropometric measurements. This study tries to provide a novel and easy method to detect acromegaly when the patients start to have awareness of abnormal appearance because of facial measurement changes, and it also suggests that undiagnosed patients be urged to go to the hospital as soon as possible for acromegaly early diagnosis.

Abbreviations:

3D	- three-dimensional
CT	- computed tomography
MRI	- magnetic resonance imaging
GH	- growth hormone
OGTT	- oral glucose tolerance test
IGF-I	- insulin like growth factor-1
zy	- zygion
g	- glabella
al	- alare
sn	- subnasale
ch	- cheillion
gn	- gnathion
tr	- trithion
prn	- pronasale
cm	- columella
ls	- labial superior
li	- labial interior
sm	- supramental
pg	- pogonion

INTRODUCTION

Acromegaly is a hormonal disorder that causes hard and soft body tissue to enlarge. It can affect the hands, feet, lips, ears, and organs such as the heart and kidneys. Acromegaly is a rare disease, which has long been known for its insidious signs and long delay from onset of symptoms to diagnosis (Etxabe *et al.* 1993; Holdaway *et al.* 1999; Daly *et al.* 2004; Melmed 2006). Delayed diagnosis with metabolic and neurological comorbidities showed that early detection is very important for acromegaly (Nabarro 1987; Molitch 1992; Pearce 2002). Since effective therapies can avoid disease progression in acromegaly patients, like many other diseases, treatment is heavily dependent upon how early the condition is detected (Bates *et al.* 1993; Freda 2000). Therefore, early recognition is considered key in achieving a high rate of treatment success and avoiding long-term comorbidities (Clemmons *et al.* 2003; Mestrón *et al.* 2004).

The gradual anthropometric changes have posed challenges for early stage acromegaly detection. Furthermore, most previous studies have shown that face, hands and feet are the easiest parts to detect; however, acromegaly facial change is the most important target in identification of this condition. Although efforts have been made to recognize acromegaly in its early stages, the delay from symptom onset to disease diagnosis has not changed in the last 24 years (Reid *et al.* 2010). In a previous study, the relationship between facial anthropometric change and related diseases could be used toward early detection of related disease (Nieuwlaat & Pieters 2004). However, the successful diagnosis rate of early stage acromegalic patients by physicians is still low at 20–40% (Schneider *et al.* 2011). It is important to diagnose the disease earlier by detecting facial anthropometric change.

In recent years, three-dimensional (3D) identification software has developed rapidly, offering potential application and advancement in detecting facial anthropometric changes (Loos *et al.* 2003; Swennen *et al.* 2005; Wagenmakers *et al.* 2015). 3D identification software has an acromegaly detection success rate of 90.9% for patients in the severe stage, but only 58.3% for patients in the mild stage (Schneider *et al.* 2011). Past research has focused upon the early identification of acromegaly by different detection tools, such as X-ray, CT, and MRI (Tariverdian *et al.* 1991; Dostálová *et al.* 2003; Gosau *et al.* 2009). Few studies focus on the easy and early detection indexes for acromegalic patients' self-awareness. It is difficult to detect acromegaly, as is evident in the fact that patients suffer its insidious signs over the course of a 7–10 year period until diagnosed (Molitch 1992; Fernandez *et al.* 2010). Schneider *et al.* (2011) also found a difference in detection accuracy between males and females. GH response to oral glucose tolerance test (OGTT) and the measurement of IGF-I both are gold standard for detecting whether or not somebody has acromegaly. However, long time late for diagnose with the gradual anthropometric changes before patients go to the hospital. This study tries to provide a new and easy method to detect the acromegaly when patients start to have awareness of abnormal appearance because of facial measurement changes, and it also suggests that patients be urged to go to the hospital as soon as possible for acromegaly early diagnosis.

Identification methods and tracking facial changes in the early stages of acromegaly by patients or family members could be important for promoting early disease diagnosis and treatment. This study hypothesizes that soft facial tissue measurement differences between acromegalic patients and control subjects are applicable in distinguishing between subjects "with" and "without" acromegaly in both sexes. The primary purpose of this study is to assess the size, angles, and positional characteristics of facial soft tissue measurements in order to evaluate the facial differences between the acromegalic patients and control subjects. The secondary purpose is to identify possible facial soft tissue measurements from which to generate discriminant functions for acromegaly detection in males and females. And significantly, this study could also provide a benchmark for such discriminant functions to be applied to specific population groups who suffer from the disease and start to have facial changes in the early stage.

MATERIAL AND METHODS

A group of patients with acromegaly was compared with a healthy control group. Eleven facial soft tissue measurements were collected. The study group consisted of 70 patients with acromegaly (35 females with ages ranging between 34 and 64 years with a mean age of 44.7 years; and 35 men aged between 28–67 years with a mean age of 43.5 years) who were admitted to the Chang Gung Memorial Hospital, Linkou, Taiwan between 2012 and 2014. All subjects participating in this cross-sectional study were Taiwanese and reside in Taiwan, R.O.C. All patients with acromegaly were diagnosed on the basis of relevant clinical features including a mean GH level >5 ng/mL, plasma IGF-I level greater than the average age/sex-matched levels, or a nadir GH >1 ng/mL after a 75 gm oral glucose tolerance test (OGTT). In gender-specific analyses, women had lower IGF-I levels [251±81 µg/liter (56–607 µg/liter) vs. 322±96 µg/liter (77–693 µg/liter), $p<0.02$] but there were no significant differences in spontaneous GH levels [1.45±0.2 g/liter (0.21–4.18 µg/liter) in women vs. 1.66±0.36 µg/liter (0.22–3.66 µg/liter), $p=0.26$] in men.

The control group comprised 140 healthy adults (70 women with ages ranging between 28–41 years with a mean age of 30.5 years and 70 men with ages ranging between 29–43 years with a mean age of 30.9 years). Controls were matched by gender to the acromegaly patient group at twice the sample size of those with the disease. Control subjects were volunteers from Chang Gung Memorial Hospitals. According to the check of clinical physicians' experts, we exclude the subjects as controls with major systemic diseases, such as clinical features and signs of acromegaly including facial abnormalities, extremities enlargement or previously operative history. The study was approved by the Institutional Review Board of the Chang Gung Memorial Hospital, Taiwan. Written informed consent of study participants was obtained.

3D Facial Stereo photographs and Image Acquisition

All examinations were conducted using standardized protocols, and trained staff gathered the data. Three-dimensional (3D) facial data was collected via a 3D camera system (LT3D FaceCam EXII). Participating subjects sat in front of a white background, and 3D facial stereo photographs were taken with the subject's head positioned in a cephalostand oriented on the Frankfort horizontal plane. The LT3D FaceCam EXII employed two devices in order to capture the subject's whole face at 180°. Capture devices consisted of (a) one camera and (b) two colored strip light projectors in order to generate facial stereo data. The resolution of this system is 0.3±0.08 mm that the human eye cannot distinguish the little changes in the facial measurements. All subjects were asked to maintain a natural facial expression,

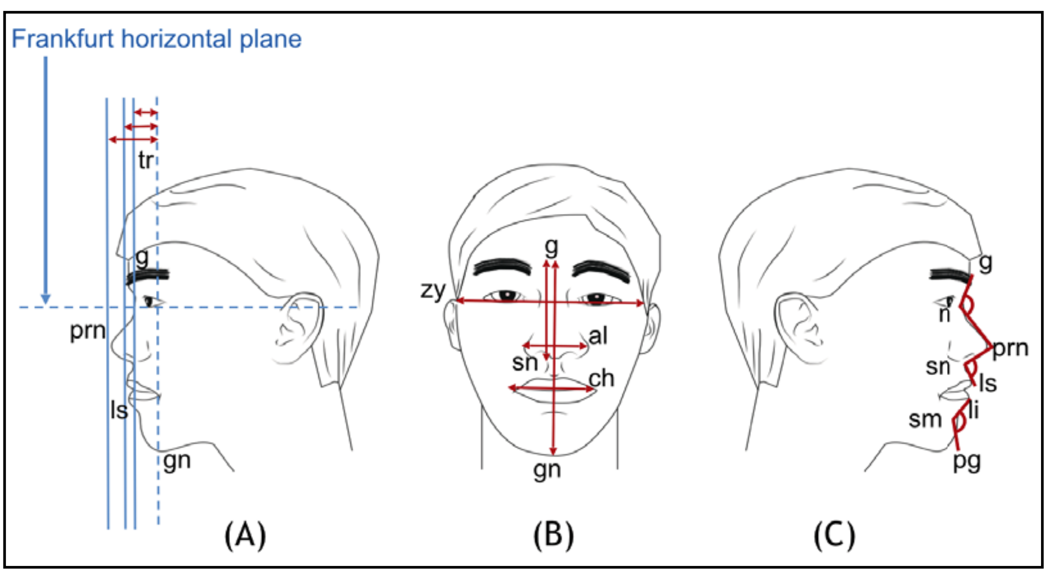

Figure 1 The depths of lateral view (A), the distances of frontal view (B) and the angular measurements of lateral view of the face (C). Soft tissue landmarks used in facial analysis. zy indicates zygion; g, glabella; al, alare; sn, subnasale; ch, cheillion; gn, gnathion; tr, trithion; prn, pronasale; cm, columella; ls, labial superior; li, labial interior; sm, supramental; and pg, pogonion. The depths that put a reference line cross the trithion (tr) landmark and the line is vertical with the Frankfort horizontal plane. Glabella (g-tr) depth indicates the width from glabella to trithion reference line; labial superior (ls-tr) depth indicates the depth from labial superior to trithion reference line; and pronasale (prn-tr) depth indicates the depth from pronasale to trithion reference line. The distances that collected from the front view of facial analysis. Facial width (zy-zy); special upper face height (g-sn); special face height (g-gn); nasal width (al-al); and mouth width (ch-ch). Angular measurements of the analysis. Nasofront angle (g-n-prn); nasolabial angle (prn-sn-ls); and mentolabial angle (li-sm-pg).

without smiling, and to remove any spectacles, while remaining in a seated posture.

Thirteen landmarks (Figure 1) were selected. Eleven variables from the three categories were selected and applied, including five frontal widths, three lateral depths and three lateral angular measurements (Bishara *et al.* 1995; Fernandez *et al.* 2010). All linear dimensions were measured from point-to-point (i.e., facial width *-zy-zy*). The angles measured were given in triple abbreviations (i.e., nasofrontal angle *-g-n-prn*). All measurements were collected and calculated by the one well-trained researcher. All measurements were taken on three separate occasions in order to assess any intra-observer error tendencies. To evaluate reproducibility of the reading, an intra-reliability test was performed. Twenty subjects were selected at random and their measurements were recorded at two different times, one week apart. A kappa test indicated significant agreement between both recorded measurements, with kappa = 0.816, $p<0.001$. Cronbach's alpha describes inter-item-consistency. Generally, a result >0.80 is deemed acceptable. The composite Cronbach's reliability was found to fluctuate between 0.89 and 0.97, resulting in a high reliability between individual measurements, thus indicating a minimal to negligible intraobserver-error.

Definitions of measurements

The depths that put a reference line cross the trithion (tr) landmark and the line is vertical with the Frankfort horizontal plane. Glabella (g-tr) depth indicates the width from glabella to trithion reference line; labial superior (ls-tr) depth indicates the depth from labial superior to trithion reference line; and pronasale (prn-tr) depth indicates the depth from pronasale to trithion reference line.

The distances that collected from the front view of facial analysis. Facial width (zy-zy); special upper face height (g-sn); special face height (g-gn); nasal width (al-al); and mouth width (ch-ch).

Angular measurements of the analysis. Nasofront angle (g-n-prn); nasolabial angle (prn-sn-ls); and mentolabial angle (li-sm-pg).

Statistical analysis

Independent t-tests were used to compare the mean measurement values between acromegalic and control samples from both sexes, where $p<0.05$ is considered

Tab. 1. Descriptive statistics and result of univariate discriminant analysis in acromegalic women (ACRO) and in controls (NORM).

Type	Facial Measurements	Mean (SD) Size		Mean Difference	Classification test on original samples (%)	
		ACRO (n=35)	NORM (n=70)		ACRO	NORM
Lateral view width (mm)	Glabella width (g-tr)	23.72(3.61)	19.50(4.52)	4.22***	68.60%	65.70%
	Superior width (ls-tr)	29.27(6.25)	27.10(4.85)	2.17	58.60%	45.70%
	Pronasale width (prn-tr)	36.29(4.98)	31.72(3.95)	4.57***	72.90%	62.90%
Frontal view distance (mm)	Facial width (zy-zy)	149.29(4.69)	142.71(3.62)	6.58***	84.30%	74.30%
	Special upper face height (g-sn)	63.87(6.14)	67.34(5.15)	–3.47***	74.30%	65.70%
	Special face height (g-gn)	133.79(7.72)	131.55(5.29)	2.24	57.10%	54.30%
	Nasal width (al-al)	39.03(5.87)	36.11(3.92)	2.92*	68.60%	62.90%
	Mouth width (ch-ch)	53.11(4.41)	51.14(4.67)	1.97*	61.40%	48.60%
Lateral view angle (degree)	Nasofront angle (g-n-prn)	113.48(9.14)	129.25(10.22)	–15.77***	75.70%	82.90%
	Nasolabial angle (cm-sn-ls)	99.72(8.21)	110.61(7.74)	–10.89***	72.90%	74.30%
	Mentolabial angle (li-sm-pg)	102.66(11.84)	119.81(7.34)	–17.15***	87.10%	74.30%

* Significantly different between acromegaly and normal samples at the level of $p<0.05$ and *** significantly different between acromegaly and normal samples at the level of $p<0.01$; the mean and SD of linear dimensions in mm, and the mean and SD of angle dimension in degree.

significant. Univariate and multivariate discriminant function analyses were performed with SPSS 20.0 (SPSS Inc., Chicago, IL, USA). Discriminant functions analysis is used to determine which continuous variables discriminate between two or more naturally occurring groups. The discriminant functions were constructed in two ways by using (a) each single variable, and (b) measurements for each dimensional group using univariate methods. All accuracies of discriminant functions were obtained by cross-validated classification.

RESULTS

The mean, standard deviation, and mean difference for female samples for all variables are presented in Table 1, and for male samples in Table 2. T-tests were used to compare the mean measurement values between acromegalic and control samples from both sexes. Table 1 illustrates the results from the measurements of females. Of the 11 variables, 9 demonstrated a statistically significant difference between the acromegalic and control samples ($p<0.05$). The exception was the aspect ratio of special face height (*g-gn*) and superior width (*ls-tr*).

Table 2 displays the results of male measurements. Of the 11 variables, 9 displayed a statistically significant difference between the acromegalic and control samples ($p<0.05$). The exception was the aspect ratio of special face height (*g-gn*) and nasal width (*al-al*). With the exception of special upper face height (*g-sn*), it is evident that acromegalic samples were larger than control samples in almost all variables of frontal distance and lateral width in both genders. In contrast, acromegalic samples were smaller than control samples in all variables of lateral angle in both sexes.

The efficiency of patient detection, for each parameter considered, was tested using univariate discriminant analysis. These results are reported in Table 1 (females) and Table 2 (males). Results for female control samples indicate that the range of resubstitution accuracies of all parameters was between 57.1–87.1% and for the acromegalic sample group between 45.7–82.9%. The average accuracies for female patient detection ranged from 54.3–82.83%, with the parameter showing the "highest" accuracy being the mentolabial angle (*li-sm-pg*) at 82.83% and the parameter with the "lowest" accuracy being the superior width (*ls-tr*) at 54.30%.

Tab. 2. Descriptive statistics and result of univariate discriminant analysis in acromegalic men (ACRO) and in controls (NORM).

Type	Facial Measurements	Mean (SD) Size		Mean Difference	Classification test on original samples (%)	
		ACRO (n=35)	NORM (n=70)		ACRO	NORM
Lateral view width (mm)	Glabella width (g-tr)	29.08 (4.58)	22.49 (2.87)	6.59***	85.70%	71.40%
	Superior width (ls-tr)	34.87 (6.51)	27.96 (2.51)	6.91***	92.90%	57.10%
	Pronasale width (prn-tr)	42.02 (4.66)	33.07 (3.55)	8.95***	87.10%	85.70%
Frontal view distance (mm)	Facial width (zy-zy)	155.84 (6.10)	151.11 (3.09)	4.73***	84.30%	62.90%
	Special upper face height (g-sn)	64.25 (7.3)	69.94 (1.60)	–5.69***	87.10%	62.90%
	Special face height (g-gn)	143.52 (9.36)	140.58 (4.33)	2.94	77.10%	48.60%
	Nasal width (al-al)	40.58 (6.42)	38.69 (2.52)	1.89	74.30%	54.30%
	Mouth width (ch-ch)	55.42 (4.92)	49.81 (4.04)	5.61*	87.10%	65.70%
Lateral view angle (degree)	Nasofront angle (g-n-prn)	106.27 (9.14)	124.41 (7.03)	–18.14***	85.70%	82.90%
	Nasolabial angle (cm-sn-ls)	98.70 (7.19)	103.40 (9.79)	–4.70***	58.60%	57.10%
	Mentolabial angle (li-sm-pg)	103.86 (9.29)	117.04 (9.57)	–13.18***	68.60%	74.30%

* Significantly different between acromegaly and normal samples at the level of $p<0.05$ and *** significantly different between acromegaly and normal samples at the level of $p<0.01$; the mean and SD of linear dimensions in mm, and the mean and SD of angle dimension in degree.

Male subject results produced an accuracy of control samples that ranged between 58.6–92.9% and acromegalic samples ranging between 48.6–85.7%. Univariate discriminant analysis was applied for each variable. The average accuracies for male patient detection was between 54.3–82.83%, where the parameter with the "highest" accuracy was the pronasal width (*prn-tr*) at 86.63% and the parameter with the "lowest" was the nasolabial angle (*cm-sn-ls*), at 58.10%.

Based upon the mean difference for all variables, multivariate discriminant analysis was used to select the parameters, which were the top two from the three categories, and to create the eight multivariate discriminant functions. Table 3 illustrates the multivariate discriminant analysis in the female acromegalic patient and control groups. When a direct discriminant procedure was run, only three of the eleven parameters remained, thus creating eight functions in total. The average accuracies of all functions for patient detection ranged from 80.0–91.40%, while functions no. 1 (*g-sn, g-tr, g-n-prn*) and no. 2 (*g-sn, g-tr, li-sm-pg*) displayed the highest percentage of accuracy for correct female patient detection at 91.4%. Function no. 8, obtained by associating different parameters, showed the lowest percentage of correct classification at 80%. Table 4 depicts the multivariate discriminant analysis concerning the male acromegalic patient and control groups. The average accuracies of all functions for male patient detection were from 81.0–94.30%, while function no. 1 (*g-sn, prn-tr, g-n-prn*) showed the highest percentage of

Tab. 3. Multivariate discriminant analysis in acromegalic women (ACRO) and in controls (NORM).

Function n. →	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Distance (zy-zy)	–	–	–	−0.18	−0.161	–	−0.157	−0.187
Distance (g-sn)	0.183	0.218	0.161	–	–	0.087	–	–
Depth (g-tr)	−0.258	−0.205	–	–	–	–	−0.012	0.113
Depth (prn-tr)	–	–	−0.088	0.44	0.016	−0.011	–	–
Angle (g-n-prn)	–	0.062	0.09	–	0.064	–	–	0.085
Angle (li-sm-pg)	0.061	–	–	0.091	–	0.074	0.083	–
Constant	−13.67	−17.76	−18.92	14.29	14.85	−10.58	13.59	14.20
Wilk's Lamda	0.365	0.396	0.438	0.407	0.528	0.506	0.413	0.502
Centroid of ACRO	−0.924	−0.864	−0.794	−0.846	−0.662	−0.693	−0.836	−0.698
Centroid of NORM	0.924	0.864	0.794	0.846	0.662	0.693	0.836	0.698
Accuracy (%)	91.4%	91.4%	87.6%	85.7%	83.8%	82.9%	82.9%	80.0%
Leave one out(%)	89.5%	89.5%	86.7%	84.8%	81.9%	81.0%	81.9%	80.0%

Tab. 4. Multivariate discriminant analysis in acromegalic men (ACRO) and in controls (NORM).

Function n. →	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Distance (g-sn)	0.184	0.174	−0.189	0.193	–	–	–	–
Distance (ch-ch)	–	–	–	–	0.09	0.062	0.106	0.057
Depth (g-tr)	–	−0.141	–	−0.209	–	0.112	0.185	–
Depth (prn-tr)	−0.175	–	0.261	–	0.089	–	–	0.236
Angle (g-n-prn)	0.069	0.086	–	–	0.088	−0.079	–	–
Angle (li-sm-pg)	–	–	0.001	0.048	–	–	−0.033	0.007
Constant	−14.35	−18.54	3.345	−13.42	3.528	2.104	−6.322	−12.27
Wilk's Lamda	0.228	0.268	0.276	0.313	0.38	0.364	0.466	0.448
Centroid of ACRO	−1.289	−1.158	−1.135	−1.037	−0.895	−0.927	−0.749	−0.778
Centroid of NORM	1.289	1.158	1.135	1.037	0.895	0.927	0.749	0.778
Accuracy (%)	94.3%	92.4%	92.4%	89.5%	88.6%	88.6%	84.8%	81.0%
Leave one out(%)	94.3%	91.4%	91.4%	89.5%	87.6%	88.6%	83.8%	80.0%

correct male patient detection at 94.3%. Function no. 8, obtained by associating different parameters, showed the lowest percentage of correct classification at 81%. Tables 3 and 4 list the key measures. Wilks' lambda (X) denotes the ratio of the within-groups sum of squares to the total sum of squares. Its value ranges from 0 to 1.0; the smaller it is, the more it contributes to the discriminant function (i.e., values of near zero denote high discrimination between groups). In this analysis, about 36–52% of the variance for females and 22–46% for males are not explained by group differences, which indicates that there is much variability between groups and little variability within the groups in both genders. Tables 3 and 4 also provide information on the discriminant function coefficients. The larger the standardized coefficient, the greater the contribution of the respective variable to the discrimination. The group centroids denote the dimension along which the groups differ. Applied the multivariate discriminant functions to test the normal controls, the false-positive rate is as lowest as 7.4% in women, and 6.5% in men, respectively. Using the multivariate discriminant functions to test the acromegaly samples, the false-negative rate is as lowest as 8.9% in women, and 5.8% in men, respectively.

DISCUSSION

Significantly, this paper is the first to investigate "easy" and "early" detection indexes for acromegaly self-awareness by analyzing facial measurement differences between patient and control samples through building up the discriminant functions. This study discovered that the majority of facial measurements, regardless of gender, showed a significant difference between acromegalic patients and control samples.

Enlargements of hard and soft tissue in facial measurements could be important signs for detecting acromegaly (Formby *et al.* 1994; Dostálová *et al.* 2003; Schneider *et al.* 2011; Ribeiro-Oliveira *et al.* 2012). According to study results, a great number of the acromegalic patients' linear measurements presented smaller angles than those of the control samples for both sexes. Facial measurements of males were larger than that of females with acromegaly, as well as in the control samples (Burton *et al.* 1993). With regard to the females, of the 11 variables, nine showed a statistically significant difference between the acromegaly and control samples, especially in the categories of frontal width and angles. The exceptions were the aspect ratio of special face height (*g-gn*) and superior width (*ls-tr*). In the male group, visible exceptions were the aspect ratio of special face height (*g-gn*) and nasal width (*al-al*), especially in the categories of lateral depths and angles. In line with previous studies on facial changes in acromegaly, also discovered was a similar enlargement trend for acromegaly; however, occurring in different parts between females and males. Dostalova *et al.* (2003) concluded that patients with acromegaly exhibited an enlargement of all parts of the neurocranial and orofacial bones except in the maxilla. The greatest anomaly was seen in the mandible, with greater enlargement of the ascending ramus than of the body of the mandible. The shape of this bone was altered too. In particular, special upper face height (*g-sn*) in males and females was due to rises in the nose caused by the phenomenon of reduced size. Wagenmakers *et al.* (2015) also found that compared to the control, the patients in remission of acromegaly had a wider face at the level of the zygoma and a longer maxilla.

With regard to both genders, the facial measurements with statistically significant differences also displayed a higher accuracy for acromegaly detection. Results, with respect to females, ranged from 54.3–82.83%, while mentolabial angle (*li-sm-pg*) evidenced the highest accuracy rate. In the males, results ranged from 58.1-86.63%, with pronasal width (*prn-tr*) having the highest accuracy rate. The large range of detection could come from the mild, moderate, or severe facial features of acromegaly by the overall impression, which made detections for acromegaly difficult, especially in the mild stage (Formby *et al.* 1994). Reid *et al.* (2006) found that features of 324 patients diagnosed with acromegaly did not change for the last 25 years. The author showed that the delay in diagnosis was long, at an average of 5.3±4 years from symptom onset, with no change over time. This conclusion was reached because the time of true disease onset was unknown, but likely preceded symptom onset by many years. On diagnosis, 96% of early and late stage groups had facial feature changes and/or hand/foot enlargement. However, it was still very problematic to detect acromegaly especially since only 15.2% of the acromegalic cases mentioned that facial changes were noted by patients or others. Also noteworthy is that 23.1% of cases had concurrent changes in the face and hands/feet noted by patients or others when they presented complaints that led to the diagnosis of acromegaly. Despite the fact that changes in facial and cephalometric features are widespread, these may be attributed to aging or weight change factors and may lead to false positive diagnoses. The breadth and heterogeneity of the signs and symptoms, which a variety of patients present, could contribute to detection delays (Molitch 1992; Reid *et al.* 2010). According to this study's findings, as well as related research, difficulties were found in the detection of acromegaly in its early stage when factoring in only a single sign or symptom.

The measurements with the highest detection accuracy belonged to the lateral category, and they showed obvious changes in the lateral side of the face. The inherent difficulties of observing lateral views could cause patients to ignore or miss facial changes in the early stage and might contribute to the long delay period for acromegaly detection. Miller *et al.* (2011) compared the computers' and clinicians' early diagnoses of acromegaly, which evidenced that the lowest detection accuracy for physicians was 16%, with an average of 26%, whilst the computers' detection accuracy was 86%. The computers showed high and stable detection accuracy greater than that of the physicians, especially in the junior physicians group. Sixty percent of acromegalic patients have visited primary care facilities prior to diagnosis, but were still under-diagnosed (Reid *et al.* 2010). This is due to the fact that patients could not detect, or otherwise ignore, the disease without obvious signs or symptoms and hence contributed to the long diagnosis delay period.

Compared to the accuracies of three categories from the univariate discriminant analysis, the lateral angles displayed the highest accuracy between all three categories. The lateral angles, calculated from the two prominent variables, made a larger difference than the other two categories. Furthermore, the angles could be calculated by the relative point-to-point from the 2D lateral image without the real dimensional measurements (Bishara *et al.* 1995).

Multivariate discriminant analysis revealed that the discriminant functions derived from three variables of three categories could predict the best resubstitution accuracy of 91.4% in females and of 94.3% in males for acromegaly detection in this study. Schneider *et al.* (2011) showed that mild to severe stage acromegaly classification accuracy by software was 58.3–90.9%, by medical experts was 38.9–93.9%, and by general internists was 20.8–78.8%. Miller *et al.* (2011) showed that the accuracy of the computer model was 86%, while the average of the 10 physicians was 26% and in general, classification accuracy by computers/software is higher than that of the physicians. However, the acromegaly medical experts had the highest classification accuracy for acromegaly detection. This demonstrates the importance of experience, as well as reliable assistance for junior physicians using computers/software in detecting acromegaly.

Using fewer variables to create higher accuracy for acromegaly detection demonstrates the advantage/s gained from this study. Discriminant functions with the highest acromegaly detection accuracy rates included three variables (*g-sn, g-tr, g-n-prn*) for females, and (*g-sn, g-tr, li-sm-pg*) for males. The average accuracy of the multivariate discriminant analysis was higher than the univariate discriminant analysis. Comparing both sexes, variables for the multivariate discriminant analysis were similar, such as special upper face height (*g-sn*) and glabella width (*g-tr*). These results demonstrated the importance of special upper face height (*g-sn*) and glabella width (*g-tr*) with regard to acromegaly detection. Moreover, the variables were different, such as nasofrontal angle (*g-n-prn*) regarding females and mentolabial angle (*li-sm-pg*) regarding males. These differences in variables with regard to acromegaly detection in both sexes may derive from the natural facial growth patterns between females and males. Males displayed higher detection accuracy than females in both univariate and multivariate discriminant analysis. This study's results were similar to those of Schneider *et al.* (2011), exhibiting acromegaly detection accuracy at 82.1% for males and 62.1% for females. Results may be affected by facial change sensitivity differences between both sexes, where females' self-detection changes more than that of males. The extent of facial change in males was greater than in females, thus facilitating higher male patient acromegaly detection.

The multivariate discriminant analysis findings indicated that the discriminant functions can be applied to a special set of circumstances when acromegaly detection must be obtained using only facial measurements; for example, when no other dimensions may be useful, present, or adequately collected in acromegaly detection (i.e., feet, hands, body, etc.). Therefore, the results of this study may be an important supplement for acromegaly detection in the Taiwan populace, especially in the area of facial measurements. This study has also demonstrated the need for different discriminant functions concerning disparate population groups.

CONCLUSIONS

In summary, patients with acromegaly exhibited both facial soft-tissue enlargement and hypertrophy. Facial changes were discovered in the frontal widths as well as in the lateral depths and angles. The greatest anomaly observed lay in the lateral angles, with greater enlargement of nasofrontal angles in females and of mentolabial angles in males; additionally, the shape of the lateral angles was found to be altered. The majority of the facial measurements displayed changes regarding the patients with acromegaly. However, it is challenging to detect the disease given the progressive nature of body changes within the condition over time.

The discriminant functions developed and applied throughout this study could help patients or others to detect and track progressive facial change patterns. However, in self-detection, lateral angles are particularly difficult to observe. Thus, point-to-point change calculations from 2D lateral imagery without 3D measurements could be utilized, cost effectively, and applied for accurate detection by the patients, their families, medical practitioners and others. The results of this research could be an assistant tool for the patients to sense the acromegaly and urge them to go to hospital for medical diagnosis.

LIMITATION AND FUTURE STUDY

This study chose the normal controls who had no acromegaly based on the lack of facial abnormalities and major systemic diseases according to the physicians' experts of clinical specialties. But IGF-I ans GH measurements would be helpful in detecting acromegaly. Since no acromegalic changes can be detected in the earliest years, it should be one of the limitations. Since acromegaly causes subtle changes in appearance particularly in the earliest years of the disease, some patients may be recognized as healthy. For this reason, it would be better to carry out endocrinological awareness to exclude acromegaly in the future study.

Facial appearance may vary from one ethnic population to another one. Therefore, the data obtained from a special population (Taiwanese) could not be generalized. A limitation could be that the standard cut-off measurements would not be possible for all ethnic populations. It will be an important issue to compare the acromegaly facial measurements for different ethnic populations in the future study.

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Competing interests

The authors declare that they have no conflict of interest.

Authors' contributions

All authors have contributed significantly to this work and contributed to the paper in the equal parts: MH Wang had the idea for the project and developed the framework, performed and designed the experiments, and participated in literature research and writing of the manuscript. JD Lin gave orientation regarding materials. CN Chang gave orientation regarding materials. WK Chiou mentored the study and performed the statistical analysis and carried out proofreading. All authors read and approved the final manuscript and are in agreement with the content of the manuscript.

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