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Clinical Characteristics and Associated Factors of Colonic Polyps in Acromegaly

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Key words
acromegaly, colonic polyps, growth hormone (GH), colonoscopy, insulin-like growth factor-1(IGF-1)

received 27.03.2022
revised 14.06.2022
accepted 13.07.2022
published online 08.09.2022

Bibliography
Exp Clin Endocrinol Diabetes 2022; 130: 714–722
DOI 10.1055/a-1913-7900
ISSN 0947-7349

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Supplementary Material is available under https://doi.org/10.1055/a-1913-7900

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ABSTRACT

Purpose To investigate the clinical characteristics and associated factors of colonic polyps in patients with acromegaly.

Methods Clinical characteristics and colonoscopy findings of 86 acromegaly patients who received treatment were retrospectively reviewed, and colonoscopy findings and the correlation with growth hormone (GH)-secreting pituitary adenoma (GHPA) volume and hormonal/metabolic levels were analyzed.

Results The prevalence of colonic polyps in acromegaly patients was 40.7 % and increased significantly with advanced age, especially in those ≥ 50 years. Multiple polyps (62.8 %) and colonic polyps in the left colon (54.2 %) were detected more frequently. Compared to acromegaly patients without polyps, those with polyps displayed higher insulin-like growth factor-1 × upper limit of normal (IGF-1 × ULN) levels ($P = 0.03$). IGF-1 levels and GHPA volumes in patients with polyps showed increasing trends, although the differences were not significant. GH levels were higher in patients with polyps of diameter ≤ 5 mm than those with polyps of diameter > 5 mm ($P = 0.031$). The univariate and multivariate logistic regression analysis revealed that GHPA volumes (OR: 1.09, 95 % CI: 1.01–1.20; $P = 0.039$) and IGF-1 × ULN Q2 levels (OR: 6.51, 95 % CI: 1.20–44.60; $P = 0.038$) were independent factors for predicting the risk of colonic polyp occurrence in acromegaly patients. A nomogram was prepared to evaluate the risk of colonic polyps in acromegaly patients.

Conclusion The acromegalic patients are a population with a high prevalence of colonic polyps. GHPA volumes and IGF-1 × ULN levels may be predictors of colonic polyp occurrence.

Introduction

Acromegaly is a chronic endocrine and metabolic disease accompanied by excessive secretion of growth hormone (GH) and insulin-like growth factor-1 (IGF-1) by GH-secreting pituitary adenoma (GHPA) [1, 2]. The increased mortality rate in acromegaly results from cardiovascular and cerebrovascular diseases, respiratory complications, and neoplastic complications such as colorectal cancer [3, 4].

Colonic polyps and diverticula are typical digestive complications in acromegaly. The significantly increased risk of colonic polyps in patients with acromegaly compared with the general population is well recognized [5]. The prevalence of colonic polyps in patients with acromegaly is reported over a wide range from 7 to 76 % [6–9], while there is still a lack of epidemiological data from China. Most colorectal cancers derive from an "adenomatous polyp-carcinoma sequence," and the process generally takes 10–15 years [10]. However, according to the current findings, the occurrence of colorectal cancer in patients with acromegaly remains controversial. A nationwide survey in Italy reported an overall standardized incidence ratio (SIR) for colorectal cancer of 1.67 (95 % CI: 1.07–2.58) [11, 12]. At the same time, some population-based studies did not identify any significant risk of colorectal cancer [13]. In patients with acromegaly, a better understanding of digestive diseases, especially colonic polyp developments, is critical for the early diagnosis of colorectal cancer and associated clinical intervention.

To gain insights into the clinical characteristics and the associated factors of colonic polyps in acromegaly, we collected and retrospectively analyzed the clinical data of 86 patients with acromegaly who underwent a colonoscopy diagnosis at our center. We also analyzed the prevalence, number, size, and site distribution of colonic polyps and other clinical indicators and identified the associated risk factors of colonic polyps in patients with acromegaly.

Materials and Methods

Patients

We retrospectively collected data of 181 patients with acromegaly followed at the Second Affiliated Army Medical University (Xinqiao Hospital) from August 2015 to July 2020. From these, we excluded 90 patients who did not undergo a colonoscopy due to personal reasons or had no endoscopic data and five patients who underwent a colonoscopy at other hospitals. Finally, 86 patients (44 males and 42 females) who underwent a colonoscopy at diagnosis were included in this study. Acromegaly was diagnosed according to the criteria available at the time of diagnosis as follows [14, 15]: 1) evidence of clinical signs and symptoms of the disease, 2) serum insulin-like growth factor I (IGF-I) levels beyond the normal range for age- and sex-matched control individuals, and elevated baseline growth hormone (GH) level, 3) maximally suppressed GH levels (GHnadir) during a 75-g oral glucose load test (OGTT) were > 1 μg/L, and 4) evidence of a pituitary tumor on imaging. No patient had a family history of colon cancer.

This study was approved by the Medical Ethics Committee of the Second Affiliated Hospital of Army Medical University (No. 2021–035–01) and registered in the Chinese Clinical Trial Registry (No. ChiCTR-1800017714). All the participants provided written informed consent.

Data collection

Clinical data, including age, sex, height, weight, body mass index (BMI), histological results, site distribution, size, and the number of polyps, were collected. Blood samples were obtained after overnight fasting. Glucose metabolic profiles were determined, including fasting blood glucose (FBG) and glycosylated hemoglobin A1c (HbA1c) levels. The automatic biochemical analyzer measured the creatinine (CREA) level, estimated the glomerular filtration rate (EGFR), and measured the levels of uric acid (UA), urea, cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C). GH and IGF-1 levels were quantified by chemiluminescent immunoassays. The outcome of the IGF-1 assay in each patient was represented by the IGF-1 index (IGF-1 × ULN): serum IGF-1/upper limit of IGF-I for that age [9]. Each patient consumed a 75-g glucose beverage in 5 min, and blood samples were collected before the start of the test (0 min) and 30, 60, 90, 120, and 180 min after glucose intake. GHnadir levels during OGTT corresponded to maximally suppressed GH lev-

els during the 180 min-OGTT. The pituitary was imaged with a 3T magnetic resonance imaging scanner with or without gadolinium-diethylenetriamine pentaacetic acid (1.0 mmol/kg). The anteroposterior diameter (AD), vertical diameter (VD), and transverse diameter (TD), as well as the Knosp classifications of the GHPA, were evaluated by two experienced radiologists using precision calipers. The GHPA volume was calculated using the formula for approximating the volume of an ellipsoid: π/6 × AD × VD × TD [16].

Experienced gastroenterologists performed colonoscopies in acromegalic patients after careful bowel preparation with a 2 L dose of polyethylene glycol electrolyte-based solution (Shenzhen Wanhe Pharmaceutical Co., Ltd., Shenzhen, China). All colonic polyps on colonoscopy were recorded and, if possible, removed for histological examination. Age was divided into four groups with a categorical variable as ≤ 39, 40–49, 50–59, and ≥ 60 years. The site distribution of polyps was defined as the right colon (the cecum, ascending colon, and hepatic flexure), the left colon (the splenic flexure, descending colon, sigmoid colon, and rectum), and the whole colon (both the right colon and the left colon) [10]. All colonic polyps detected at colonoscopy were grouped according to size (≤ 0.5, 0.6–0.9, and ≥ 1.0 cm) depending on endoscopic measurement by the diameter of open biopsy forceps [17]. The number of polyps was divided into a categorical variable (single or multiple (≥ 2)).

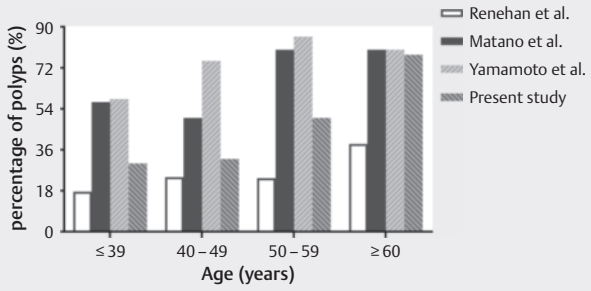
Statistical analysis

Analyses were conducted by R studio (version 1.3.1093). The Shapiro-Wilk W test verified the normality of the variable distribution; variable distribution was considered normal if $P \geq 0.05$. According to the distribution, variables were described either as means ± standard deviation or medians with interquartile ranges. For normally distributed variables, we used an independent samples *t*-test to compare variables between two groups, whereas one-way ANOVA, followed by Tukey's multiple comparison test, was used to compare variables among three or more groups. For non-normally distributed variables, the Mann-Whitney U test was used to compare variables between two groups, whereas the Kruskal-Wallis test, followed by pairwise comparisons using the best-worst scaling all-pairs test, was used for multiple subgroups. The relationships between variables were examined using Spearman's correlation analysis. Univariate and multivariate logistic regression analyses were performed to assess the associations of the variables with the diagnosis. A nomogram was created using the predictors from the multivariate analysis to relate the risk of polyp occurrence. The tests were considered statistically significant at $P < 0.05$.

Results

Clinical features of acromegalic patients with colonic polyps

A total of 86 acromegalic patients (mean age, 43.53 ± 11.78 years; sex, 48.8 % females) who underwent complete colonoscopy at our hospitals were included in this study. Of the 86 patients, 35 (18 females, 17 males) had one or more polyps, with a higher prevalence (40.7 %) than a general Asian population (17.6–23.9 %) of comparable age [17–20]. The prevalence of polyps increased with age, reaching a peak at ≥ 60 years. The prevalence rates of polyps in acromegalic patients aged ≤ 39, 40–49, 50–59, and ≥ 60 years were 30, 32, 50, and 77.8 %, respectively (▶ **Fig. 1**). Of the 35 patients, 13 (37.2 %) and 22 (62.8 %) had a single polyp and multiple polyps, respectively. The mean diameter of the polyps in most cases was ≤ 5 mm (71.4 %), and the maximum diameter was ≥ 10 mm. With respect to the distributions of colonic polyps at different sites, four (11.4 %) patients had polyps in the right colon, 19 (54.3 %) had polyps in the left colon, and 12 (34.3 %) had polyps in the whole colon. Colonic polyps were more frequently detected in the sigmoid colon and rectum. In addition, only five cases of colonic polyps were examined by biopsy, and all of them were histologically confirmed to be adenomas. Furthermore, 21 patients had hemorrhoids, and one had chronic colitis. No patient had colorectal carcinoma (▶ **Table 1**).



▶ **Fig. 1** Association between age (years) and prevalence of polyps (%). Age was parsed into a categorical variable with four groups: ≤ 39, 40–49, 50–59, and ≥ 60 years. Prevalence (%) of polyposis is presented according to Renehan et al. [30], Matano et al. [42], Yamamoto et al. [43], and this study.

At diagnosis, 79 (92 %) patients had pituitary macroadenoma, 3 (3 %) patients had pituitary microadenoma, and 4 (5 %) patients had no data on the pituitary tumor diameter. Hypertension and impaired glucose metabolism (diabetes mellitus and impaired glucose tolerance) were separately diagnosed in 24 (28 %) and 47 (55 %) patients (▶ **Table 1**).

Characteristics of colonic polyps associated with hormone levels

Patients with acromegaly and having colonic polyps were older and had higher insulin-like growth factor-1 × upper limit of normal (IGF-1 × ULN) levels than those without colonic polyps ($P = 0.005$ and $P = 0.03$, respectively, ▶ **Table 1**). No significant differences were found between acromegaly patients with or without colonic polyps regarding sex, BMI, FBG levels, dyslipidemia, hypertension, diabetes mellitus, GHPA volumes, Knosp classifications, UA levels, GH levels, GHnadir levels during OGTT, and IGF-1 levels (▶ **Table 1** and **Supplementary Table 1**). Although GH and GHnadir levels during OGTT were similar in acromegaly patients with or without colonic polyps, GHPA volumes and IGF-1 levels tended to be higher in those with polyps, but the differences between the two groups were not statistically significant (▶ **Table 1**). As shown in ▶ **Table 2**, with respect to the distribution of polyps at different sites, GH levels and GHnadir levels during OGTT in patients with polyps in the right colon were

▶ **Table 1** Clinical characteristics of the study patients with acromegaly.

	Total number of patients (n = 86)	Patients without polyps (n = 51)	Patients with polyps (n = 35)	*P*-value
Age (years)	43.53 ± 11.78	40.63 ± 11.58	47.77 ± 10.88	**0.005***
Sex, female, n (%)	42 (49)	24 (47)	18 (51)	0.858
BMI (Kg/m2)	26.1 ± 3.05	25.96 ± 3.05	26.31 ± 3.09	0.602
GHPA Volumes (cm^3)	2.47 (1.15, 6.44)	2.2 (1.17, 4.87)	3.19 (1.15, 7.31)	0.305
Basal GH levels (μg/L)	18.3 (8.08, 34.5)	17.8 (5.94, 29.8)	19.3 (9.7, 52.5)	0.153
GHnadir levels during OGTT (μg/L)	12.1 (5.24, 30.9)	12 (4.41, 25.2)	13 (6.54, 40.85)	0.18
Basal IGF-1 levels (ng/mL)	762.56 ± 259.66	733.73 ± 259.89	804.57 ± 2 57.24	0.215
IGF-1 × ULN	2.53 (1.94, 3.01)	2.22 (1.79, 2.88)	2.73 (2.1, 3.2)	**0.03***
FBG (mmol/L)	5.07 (4.4, 5.96)	4.95 (4.38, 5.82)	5.33 (4.54, 6.29)	0.34
Hemorrhoids, n (%)	21(24)	7(20)	14(27)	0.403
Hypertension, n (%)	24 (28)	15 (29)	9 (26)	0.896
Diabetes mellitus, n (%)				0.708
normal	25 (29)	14 (27)	11 (31)	
IGT	39 (45)	25 (49)	14 (40)	
DM	22 (26)	12 (24)	10 (29)	

Data are shown as mean ± standard deviation for variables of normal distribution and median with the interquartile range (25–75 %) for skewed variables. BMI: body mass index; GHPA Volumes: growth hormone (GH)-secreting pituitary adenoma volumes; GH: growth hormone; GHnadir levels during OGTT: the maximal suppression of GH levels during 180-OGTT; IGF-1: insulin-like growth factor-1; ULN: upper limit of normal; IGT: impaired glucose tolerance; DM: diabetes mellitus. *P* value for patients without polyps vs. patients with polyps, $^*P < 0.05$

higher than in those with polyps in the whole colon and the left colon. Interestingly, compared with polyp diameters > 5 mm, GH levels were significantly higher in patients with polyp diameters ≤ 5 mm ($P = 0.031$, ▶ **Table 2**). Apart from the BMI ($P = 0.013$), we did not identify relevant clinical indicators between the two groups with single polyps and multiple polyps (▶ **Table 2**). GHPA volumes, IGF-1 levels, and IGF-1 × ULN levels were similar among subjects with distribution at different sites, sizes, and the number of polyps.

In addition, hypertension and diabetes mellitus maybe have an association with the distribution of polyps at different sites (▶ **Table 2**). However, FBG and HbA1c levels did not differ with respect to the three different site of the distribution of polyps (**Supplementary Table 2**). Next, to investigate the effect of IGF-1 × ULN in acromegaly patients with polyps, we further divided the subjects into IGF-1 × ULN-quantile subgroups (Q1 to Q4) according to the IGF-1 × ULN level (**Supplementary Table 3**). Age, GH levels, and GHnadir levels during OGTT were significantly higher in acromegaly patients with the highest IGF-1 × ULN levels than those with the lowest IGF-1 × ULN levels in the first quantile ($P < 0.05$ for Q1 vs. Q4). Compared to patients with lower IGF-1 × ULN levels in the second quantile, UA levels were significantly higher in patients with the highest IGF-1 × ULN levels ($P < 0.05$ for Q2 vs. Q4). Notably, the IGF-1 × ULN-quartile subgroups differed with respect to acromegaly patients with or without colonic polyps, GHPA volumes groups, and IGF-1 levels ($P < 0.05$, **Supplementary Table 3**).

Prognostic model for colonic polyps in acromegaly patients

In univariate analysis of acromegaly patients, age, especially 60 years and older, and the IGF-1 × ULN level could predict polyp occurrence, as shown in Table 4. Furthermore, in multivariate analysis, these variables showed that GHPA volumes (OR: 1.09, 95 % CI: 1.01–1.20; $P = 0.039$) and IGF-1 × ULN Q2 levels (OR: 6.51, 95 % CI: 1.20–44.60; $P = 0.038$) were independently associated with polyp occurrence (▶ **Table 3**). IGF-1 × ULN Q3 and IGF-1 × ULN Q4 cloud also are independent risk predictors, although no significant difference was found. Thus, univariate and multivariate analyses revealed that GHPA volumes and IGF-1 × ULN levels could be independent risk factors for polyps in acromegaly patients. In addition, a nomogram for predicting acromegalic patients with polyp risk was constructed using the variables (▶ **Fig. 2**). According to the prognostic model, for evaluating the risk of colonic polyps, a woman with a GHPA volume of 3.0 cm^3 and an IGF-1 × ULN level of 3.5 was predicted to have an 85 % probability of polyps.

Discussion

Several population-based studies have indicated a 0.9 to 2.4 % incidence of colon cancer in patients with acromegaly [12, 21, 22]. However, the risk of colon cancer in acromegaly is still controversial. Colonoscopy screening for early detection can reduce mortality due to colorectal cancer by the removal of pre-existing adenomatous polyps. In this study, we ascertained a high prevalence of colonic polyps of 40.7 % in acromegalic patients. IGF-1 × ULN levels were higher in patients with polyps than in those without polyps. GHPA volumes and IGF-1 × ULN levels were independent risk factors for polyps.

Colonic polyps have a high prevalence in acromegaly patients; the overall prevalence of colonic polyps in this study was 40.7 %. The prevalence of colonic polyps in the acromegaly population is significantly higher than in the general Asian population. In the non-acromegaly population, the prevalence of polyps ranged from 17.6 to 23.9 % [17–20]. The prevalence of colonic polyps also varies in different acromegalic populations. One of the largest datasets from 14 centers across Europe indicated a 13 % prevalence of

▶ **Table 2** Clinical characteristics of acromegalic patients with polyps.

	The site distribution of polyps[a]			The size of polyps			The number of polyps		
	Right colon (n = 4)	**Left colon (n = 19)**	**Whole colon (n = 12)**	**≤ 5 mm (n = 25)**	**> 5 mm (n = 10)**	***P* value**	**Single polyp (n = 13)**	**Multiple polyps (n = 22)**	***P*-value**
Age (years)	49.25 ± 13	44.58 ± 10.47	52.33 ± 9.95	47 ± 11.43	49.7 ± 9.62	0.486	43.23 ± 11.73	50.45 ± 9.62	0.056
Sex (Female), n (%)	4 (100)	8 (42)	6 (50)	13 (52)	5 (50)	1	7 (54)	11 (50)	1
BMI (kg/m2)	27.09 ± 3.74	26.19 ± 3.56	26.24 ± 2.19	25.95 ± 3.42	27.2 ± 1.91	0.182	24.66 ± 3.25	27.28 ± 2.6	**0.013***
GHPA volumes (cm^3)	4.83 (3.55, 5.88)	3.48 (1.3, 12.63)	1.83 (0.96, 6.91)	3.48 (1.25, 6.75)	2.22 (0.54, 8.81)	0.615	3.59 (1.81, 7.46)	2.95 (1.05, 6.86)	0.366
Basal GH levels (μg/L)	127.5 (70.33, 189.5)	17 (13.05, 33.95)	11.95 (7.8, 33.08)	26.6 (14.5, 61.4)	9.7 (8.08, 19.1)	**0.031***	35.3 (14, 82)	16.45 (8.2, 27.57)	0.142
GHnadir levels during OGTT (μg/L)	73.9 (44.7, 111.1)	12.4 (8.59, 37.2)	8.75 (5.02, 24.25)	21.2 (8.76, 48)	8.7 (4.52, 12.32)	**0.05**	21.2 (10.3, 48)	11.25 (4.43, 28.23)	0.124
Basal IGF-1 (ng/mL)	731.75 ± 261.15	869 ± 267.81	726.83 ± 229.95	802.56 ± 271.42	809.6 ± 231.27	0.939	808.54 ± 247.11	802.23 ± 268.75	0.945
IGF-1 × ULN	2.92 (1.84, 3.93)	2.83 (2.22, 3.2)	2.59 (2.36, 2.97)	2.84 ± 1.05	2.94 ± 0.85	0.773	2.72 (2.08, 3.16)	2.78 (2.42, 3.22)	0.585
Hypertension, n (%)	1 (25)	1 (5)	7 (58)	6 (24)	3 (30)	0.694	1 (8)	8 (36)	0.109
DM, n (%)						0.33			0.455
normal	0 (0)	11 (58)	3 (25)	12 (48)	2 (20)		6 (46)	8 (36)	
IGT	0 (0)	6 (32)	4 (33)	6 (24)	4 (40)		2 (15)	8 (36)	
DM	4 (100)	2 (11)	5 (42)	7 (28)	4 (40)		5 (38)	6 (27)	

Data are shown as mean ± SD for variables of normal distribution and median with the interquartile range (25–75 %) for skewed variables. BMI: body mass index; GHPA volumes: growth hormone (GH)-secreting pituitary adenoma volumes; GH: growth hormone; GHnadir levels during OGTT: the maximal suppression of GH levels during 180-OGTT; IGF-1: insulin-like growth factor-1; ULN: upper limit of normal; DM: diabetes mellitus; IGT: impaired glucose tolerance; SD: standard deviation. a: Considering only four patients with polyps in the right colon may lead to unreliable statistical results, we only made statistical description in the site distribution of polyps subgroups. *: $P<0.05$.

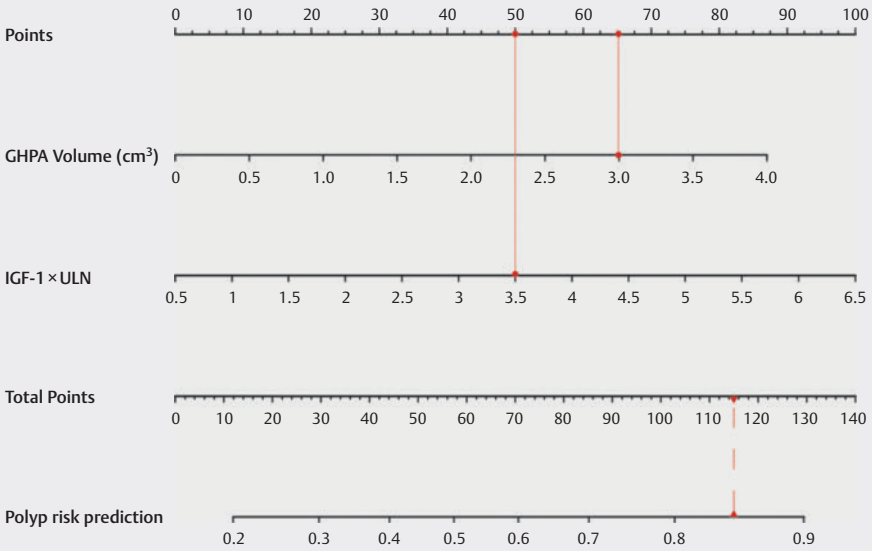
▶ **Table 3** Univariate and multivariable logistic regression analysis of associations between clinical and biochemical variables and polyps in patients with acromegaly.

	Univariate analysis		Multivariate analysis	
	OR (CI 95 %)	***P*-value**	**OR (CI 95 %)**	***P*-value**
Age	**1.06 (1.02, 1.11)**	**0.007**	1.05 (0.99, 1.12)	0.11
sex	1.19 (0.50, 2.84)	0.691	–	–
Height	0.02 (0.00, 2.03)	0.102	0.03 (0.00, 16.03)	0.286
Weights	0.98 (0.94, 1.02)	0.397	–	–
BMI	1.04 (0.90, 1.20)	0.597	–	–
GHPA volumes	1.06 (0.99, 1.15)	0.136	**1.09 (1.01, 1.20)**	**0.039**
Basal GH levels	1.00 (1.00, 1.01)	0.278	–	–
GHnadir levels during OGTT	1.00 (1.00, 1.01)	0.22	–	–
Basal IGF-1 levels	1.00 (1.00, 1.00)	0.216	–	–
IGF-1 × ULN	**1.65 (1.04, 2.75)**	**0.04**	1.47 (0.88, 2.55)	0.151
FBG	1.07 (0.86, 1.34)	0.548	–	–
TG	0.84 (0.50, 1.10)	0.394	–	–
TC	0.77 (0.49, 1.10)	0.21	–	–
HDL	1.96 (0.33, 12.46)	0.459	–	–
LDL	0.89 (0.47, 1.64)	0.71	–	–
UA	1.00 (1.00, 1.01)	0.702	–	–
Age groups		**0.011**		
≤ 39	1		1	
40–50	1.10 (0.34, 3.48)	0.873	–	–
50–60	2.33 (0.75, 7.53)	0.147	–	–
> 60	**8.17 (1.61, 62.58)**	**0.019**	–	–
IGF-1 × ULN quartile		**0.015**		
Q1	1		1	
Q2	**5.45 (1.34, 28.54)**	**0.026**	**6.51 (1.20, 44.60)**	**0.038**
Q3	**5.00 (1.24, 25.93)**	**0.033**	5.82 (0.71, 55.33)	0.106
Q4	**7.20 (1.80, 37.50)**	**0.009**	10.52 (0.42, 300.62)	0.152

OR, odd ratio; CI, confidence interval. BMI: body mass index; GHPA volumes: growth hormone (GH)-secreting pituitary adenoma volumes; GH: growth hormone; GHnadir levels during OGTT: the maximal suppression of GH levels during 180-OGTT; FBG: fasting blood glucose; IGF-1: insulin-like growth factor-1; ULN: upper limit of normal; OGTT: oral glucose tolerance test; TG: triglycerides; TC: total cholesterol; LDL: low-density lipoprotein cholesterol; HDL: high-density lipoprotein cholesterol; UA: uric acid; SD: standard deviation.

polyps in a fourth of acromegaly patients (820/3173) who had a colonoscopy [23]. Furthermore, the prevalence of polyps in patients with acromegaly was 32 % in an Italian single-center study [24]. In contrast, the French national registry data reported that the prevalence of colonic polyps ranged from 27 % to 55 % [22]. The different prevalence of colonic polyps in populations may be because of differences in genetic predisposition, environmental backgrounds, and lifestyle (including dietary habits). In our study, the prevalence of multiple polyps was 62.8 % compared to earlier reports by Bogazzi (50 %) [9] and Colao (72.1 %) [8]. A colonic polyp diameter > 10 mm is generally considered a high risk of colorectal carcinoma and is thought to take more than ten years to develop. A recent study reported a frequency of 15.2 % for polyps ≥ 10 mm, and five patients were detected with colorectal cancer [25]. However, in our study, the maximum diameter of colonic polyps was < 10 mm, and most colonic polyps were in their early stages ≤ 5 mm (71.4 %), which may explain why no colorectal cancer was detected.

We found a significant association between polyp occurrence and hormone levels. In detail, IGF-1 × ULN levels in patients with polyps were higher in than those without polyps, consistent with previous findings [22]. Although GH and GHnadir levels during OGTT were similar in patients with or without colonic polyps, IGF-1 levels and GHPA volumes tended to be higher in those with polyps. Nevertheless, few studies have consistently suggested that IGF-1 levels are significantly related to polyp prevalence [24, 26]. This study also indicated that GH and Ghnadir levels during OGTT were higher in patients with polyps with a diameter ≤ 5 mm in the right colon. However, limited by a small amount of data, our results need to be confirmed in a larger prospective study. As a result, we hypothesize that GH levels may play different roles in different stages of polyp development. The findings in patients with acromegaly suggest a higher prevalence of polyps in the left colon, similar to Battistone et al. [27]. In the general population, the site distribution of polyps was detected mainly in the left colon [17, 28], although several studies also observed polyps in the cecum and the ascending colon [29–31]. Additionally, the acromegaly patients



▶ **Fig. 2** Constructed colonic polyp incidence risk nomogram. The colonic polyp risk was constructed with the features, including GHPA volume and IGF-1 × ULN. GHPA volume: growth hormone (GH)-secreting pituitary adenoma volume; IGF-1: insulin-like growth factor-1; ULN: upper limit of normal. For example, a woman had a GHPA volume of 3.0 cm^3 and an IGF-1 × ULN level of 3.5. To use the nomogram, the points are located on each variable axis (GHPA volume axis and IGF-1 × ULN level axis) and draw the red line vertically up to the Points axis to determine the corresponding points for each variable. The point for GHPA volume points was 65, and the IGF-1 × ULN level was 50. The sum (115) of these points (GHPA volume points and IGF-1 × ULN level points) is located on the Total Points axis, and a red dotted line is drawn downward to the polyp risk prediction axis to determine the possibility of having polyps, which was approximately 85 % in this case.

with multiple polyps had higher BMI than those with single polyps. Compared to patients without polyps, those with polyps were older. Simultaneously, the prevalence of colonic polyps increased significantly with age ≥ 50 years (> 50 %). Bogazzi [9] and Parolin [24] also reported similar trends in polyp prevalence in ≥ 50 years old patients. Although the recent guidelines recommend the initiation of colonoscopy screening at 50 years of age for the average-risk non-acromegaly population [32, 33], this may be inadequate for patients with acromegaly. A few guidelines suggest that the initial colonoscopy should be performed at the age of 40 years for early detection of precancerous polyps in acromegaly [31, 34, 35]. We observed that several patients younger than 40 years had colonic polyps. Similarly, Terzolo et al. reported that younger acromegaly patients had a higher risk of colonic neoplasia than the age-matched controls [7]. Therefore, as per recent guidelines, colonoscopic surveillance should be performed at the time of diagnosis of acromegaly [36–39].

GHPA volumes may be a reliable predictor for polyp occurrence in acromegaly. According to univariate analysis and clinical parameters, the final diagnostic model was decided using age, height, GHPA volumes, and IGF-1 × ULN levels. To our knowledge, this is the first study to report that GHPA volume (OR: 1.09, 95 % CI: 1.01–1.20; $P = 0.039$) is an independent risk factor for colonic polyp occurrence. However, GHPA volumes did not differ significantly between patients with or without polyps. We speculate that the larger GHPA volumes indicate long-term and uncontrolled secretion of GH and IGF-1, contributing to the higher risk of polyp occurrence. Meanwhile, we found that the IGF-1 × ULN level (OR: 6.51, 95 % CI: 1.20–44.60; $P = 0.038$) is a predictor for polyp occurrence, similar to the results of Gonzalez [26]. Therefore, we established a polyp risk prediction model based on GHPA volumes and IGF-1 × ULN levels. For example, a man with a GHPA volume of 2.0 cm^3 and an IGF-1 × ULN level of 4.0 has an approximately 80 % probability of polyp occurrence.

In this study, standard intestinal preparation alone resulted in inadequate intestinal cleansing in most patients with acromegaly, seriously affecting the detection of colonoscopy (data not shown). Previous studies have suggested two consecutive bowel preparations or an increased dose of PEG solution for patients with acromegaly [40], with a significantly prolonged time required to reach the cecum during colonoscopy [41].

We acknowledge several limitations in our study. First, this study was conducted on a relatively small number of patients, with no control group. Second, this was a retrospective analysis, and it was not possible to avoid selectivity bias. Third, most polyps with a diameter > 5 mm were not examined by biopsy. Further long-term prospective studies involving patients with acromegaly may determine whether colonic polyps have a similar tendency to develop into colon cancer as in the general population.

In conclusion, we confirmed the high prevalence of colonic polyps in patients with acromegaly. Older age and multiple polyps, usually occurring in the left colon, were the clinical features of acromegaly patients with colonic polyps. In addition, GHPA volumes and IGF-1 × ULN levels might predict the occurrence of colonic polyp in the population with acromegaly.

Ethics Statement: This study was approved by the Medical Ethics Committee of The Second Affiliated Hospital of Army Medical University.

Informed consent: Informed consent was obtained from all individual participants included in the study.

Author Contributions

GLP, PH, and YLZ: data acquisition; RFS and LZ: analyzed MRI data; YYZ, JYB, and GLP: assessed colonoscopy data; GLP, XL, and RFS: statistical analysis of data and drafted the manuscript; LZ, MYL, YLZ and WXL: interpreted the data, contributed to the methods, and performed the laboratory analyses; ML, HTZ, and ZS: revised the manuscript; RFS and ML: obtained the study funding and supervised the study. All authors read and approved the manuscript for publication.

Funding

This work was supported by grants from the Clinical Research Project of Army Medical University (2019XLC2009 and 2018XLC3049) and the Chongqing Natural Science Foundation (Outstanding Youth Foundation, No. CSTC2020JCYJ-JQX0017).

Conflicts of Interest

The authors declare that they have no conflict of interest.

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