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Original Article

Clinical characteristics and prognostic factors of prolactinomas and growth hormone-secreting adenomas in premenopausal women in China

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Abstract: Pituitary adenomas, including prolactinomas and growth hormone (GH)-secreting adenomas, are common intracranial tumors in premenopausal women. Few studies have systematically documented the profile of these tumors in premenopausal women in China. Herein, we analyzed the clinical features and prognostic factors of 132 prolactinomas and 39 growth hormone-secreting adenomas treated by transsphenoidal surgery in Chinese premenopausal women. Patients with prolactinomas had smaller tumors (12 mm), higher preoperative prolactin levels (181.9 μg/L), and were younger (28 years) than those with GH-secreting adenomas or with other types of pituitary adenomas. The preoperative level of prolactin positively correlated with tumor size (r = 0.247, P = 0.005) and negatively correlated with age (r = -0.257, P = 0.003) in patients with prolactinomas. The diagnostic cut-off value for the preoperative level of prolactin was 112.2 μg/L with an area under the curve (AUC) of 0.854, a sensitivity of 78%, a specificity of 83%, a positive predictive value (PPV) of 73%, and a negative predictive value (NPV) of 86%. The postoperative remission rate of patients with prolactinomas was 60.7%. Tumor size, preoperative prolactin level, prolactin level on day 1 postsurgery, the postoperative prolactin reduction rate, and the tumor invasiveness were correlated with postoperative remission. However, the predictive factor of positive outcome was only low prolactin level on day 1 postsurgery [odds ratio (OR) = 0.931; 95% confidence interval (CI) = 0.883-0.981] in patients with prolactinomas, with a cut-off value of 20.49 μg/L (AUC: 0.950; sensitivity: 88%; specificity: 95%; PPV: 98%; NPV: 76%) based on logistic regression and receiver-operator characteristic (ROC) analysis. Patients with GH-secreting adenoma had a higher preoperative level of GH (14.3 μg/L), larger tumors (22.5 mm), and were older (41 years) than patients with prolactinoma or with other types of pituitary adenomas. The diagnostic cut-off value for the preoperative level of GH was 2.6 μg/L (AUC: 0.809; sensitivity: 77%; specificity: 83%; PPV: 36%; NPV: 97%), and the postoperative remission rate was 60.7%. Thus, we can conclude that the clinical characteristics and outcomes of prolactinomas and GH-secreting adenomas in premenopausal women were not precisely the same as those in patients with general pituitary adenoma. Prolactinoma should be suspected in premenopausal women with a prolactin level greater than 112.2 μg/L. A GH level greater than 2.6 μg/L is highly suggestive of GH-secreting adenomas. A prolactin level less than 20.49 μg/L on day 1 postsurgery is a strong independent predictor of remission in Chinese premenopausal women with prolactinoma.

Keywords: Prolactinomas, growth hormone-secreting adenomas, characteristics, prognostic, childbearing age

Introduction

In recent years, the incidence of pituitary adenomas has increased, ranging from 4.8% to 27% at autopsy in the general population [1]. Pituitary adenomas are characterized by excessive hormone production and enlargement of the pituitary gland. In 2004, the World Health Organization (WHO) established diagnostic criteria that classified pituitary adenomas as prolactinoma, adrenocorticotropin (ACTH)-secreting adenoma, growth hormone (GH)-secreting adenoma, nonfunctioning adenoma (NFA), thyroid-stimulating hormone (TSH)-secreting adenoma, gonadotropin-secreting adenoma, and plurihormonal-secreting adenoma, among whi-

ch prolactinoma, GH-secreting adenoma, and NFA are the most common.

Sex-related differences have been observed in the incidence of these tumors [2]. Prolactinoma occurs more often in women younger than 50 years of age, with a male-to-female morbidity ratio of 1:10 and an age of peak morbidity ranging from 25 to 34 years [3]. Sex-related differences in the incidence of ACTH-secreting adenoma have also been reported, with a male-to-female incidence ratio of 1:3 [4]. Therefore, a large portion of patients with pituitary adenomas are premenopausal women. However, few studies have systematically documented the profile of these tumors in premenopausal women in China. Herein, we analyzed the clinical data and outcomes of premenopausal women with these tumors who were treated by transsphenoidal surgery in our hospital to identify clinical characteristics, diagnostic criteria, and potential prognostic factors.

Materials and methods

Patient selection

The clinical data from 387 female patients aged 15 to 50 years who were diagnosed with pituitary adenoma between January 1, 2003, and March 31, 2012, at The Fifth People's Hospital of Shanghai affiliated with Fudan University were obtained. The data included the clinical characteristics, endocrine function, imaging findings, hormone levels, and pathological results. In these patients, 132 cases of prolactinoma and 39 cases of GH-secreting adenoma were identified for the current analysis. The diagnostic criteria for prolactinoma and GH-secreting adenoma were based on clinical manifestations, elevated serum hormone levels [including serum prolactin levels, serum GH levels after an oral glucose tolerance test (OGTT), and insulin-like growth factor-1 (IGF-1), respectively], magnetic resonance imaging (MRI) findings, and immunostaining. All the patients were operated on by the transsphenoidal route by the same experienced neurosurgeons (Shiqi Li at Hua Shan Hospital Affiliated with Fudan University). The rationales of performing surgery on patients with prolactinomas were as follows: (1) they expressed a personal preference for surgery instead of chronic medical treatment; (2) they experienced drug intolerance or resistance; (3) or they had macroadenomas, giant adenomas, or invasive tumors. The clinical outcomes were evaluated over a 6-month to 10-year follow-up period by contacting the patients by telephone, mail, or visit. The research involving human participants was approved by the Ethics Committee of Shanghai Fifth People's Hospital Affiliated with Fudan University. Written informed consent was also obtained from all participants.

Image findings

Based on the imaging findings, we defined microadenoma, macroadenoma, and giant adenoma as a tumor less than 10 mm, 10 to 40 mm, and greater than 40 mm in diameter, respectively. Invasive pituitary adenomas were classified as Hardy III or above. Local invasion (Hardy III) was defined as a tumor with a diameter greater than 20 mm, with invasion and damage of the sellar floor bone. Diffuse invasion (Hardy IV) was defined as a tumor with a diameter greater than 40 mm, with invasion and damage of the sellar floor bone. Giant invasive adenoma (Hardy V) was defined as a tumor with a diameter greater than 50 mm that had grown toward the sphenoid sinus and saddle, invading both sides of the cavernous sinus and damaging the upper clivus, or as a tumor with a diameter greater than 50 mm that had grown toward the postfovea, causing hydrocephalus due to blockage of the passage between the chambers of the third ventricle.

Immunohistochemistry

For each tumor, fragments were fixed in Bouin fixative and embedded in paraffin for immunocytochemistry. Functional pituitary adenomas were defined as those for which immunohistochemical analysis detected the presence of prolactin, GH, ACTH, TSH, and gonadotropin. The rate of prolactin reduction was equal to 1-postoperative prolactin level/preoperative prolactin level.

Oral glucose tolerance test

Among the patients who underwent the oral glucose tolerance test (OGTT), serum GH was measured at 30, 60, 90, and 120 minutes after orally administering 82.5 g of dextrose hydrate following an overnight fasting period.

Clinical follow-up

Tumor control was defined based on the imaging findings or clinical laboratory results. Re-

Table 1. General information and laboratory data of prolactinomas and other types of pituitary adenomas in premenopausal women

	Prolactinomas (n = 132)	GH-secreting adenomas (n = 39)	Other types of pituitary adenomas (n = 216)	*P* value
Age (years)*	28.00 (23.00-35.00)	41.00 (33.00-46.00)	37.00 (28.00-44.00)	< 0.001
Tumor size (mm)*	12.00 (10.00-18.70)	22.50 (16.00-28.73)	18.50 (11.00-25.00)	< 0.001
Pre-PRL (μg/L)*	181.90 (118.13-446.73)	22.87 (16.49-55.53)	47.22 (20.93-94.25)	< 0.001
Pre-GH (μg/L)*	0.40 (0.10-1.30)	14.30 (2.65-40.00)	0.80 (0.30-2.10)	< 0.001
Pre-E_2 (pg/mL)	25.81 (15.44-42.88)	21.83 (9.19-41.29)	34.61 (15.64-64.31)	0.345
Pre-LH (IU/L)	3.29 (1.39-6.50)	4.31 (1.18-7.61)	4.08 (1.55-6.74)	0.265
Pre-FSH (IU/L)*	4.98 (3.73-6.95)	4.78 (2.90-13.04)	5.7 (4.00-7.43)	0.001
Pre-ACTH (pg/mL)	23.70 (10.04-34.35)	23.00 (11.80-35.70)	29.50 (16.00-38.70)	0.830
Pre-F (nmol/L)*	264.60 (140.75-421.58)	356.00 (172.00-458.16)	376.44 (227.75-539.58)	0.004
Pre-TSH (mIU/L)	1.30 (0.78-2.30)	0.92 (0.62-1.65)	1.41 (0.75-2.13)	0.637
Pre-FT4 (pg/mL)	1.21 (1.10-1.38)	1.18 (0.95-1.31)	1.28 (1.08-1.60)	0.099

Date are presented as median (interquartile range). *P < 0.01. Abbreviations: Pre-PRL, preoperative prolactin; Pre-GH, preoperative growth hormone; Pre-E_2, preoperative estradiol; Pre-LH, preoperative luteinizing hormone; Pre-FSH, preoperative follicle-stimulating hormone; ACTH, pre-adrenocorticotropin; pre-F, preoperative cortisol; pre-TSH, preoperative thyroid-stimulating hormone; pre-FT4, preoperative free thyroxine.

mission was defined as no visible tumor occupying the preoperative location or the correction of serum hormone secretion at the end of the follow-up period. Residual tumor due to incomplete excision was defined as visible tumor at 1 to 3 days after surgery resulting in the incomplete correction of serum hormone secretion. Recurrence was defined as no visible tumor or the correction of hormone secretion after surgery, followed by the return of visible tumor or abnormal hormone secretion during the follow-up period.

Statistical analysis

The Epidata program (http://epidata.dk) was used for data entry, and the SPSS, version 17.0, software (IBM, Armonk, NY, USA) was used for the statistical analysis. All values were expressed as the median and 25th to 75th percentile. The one-way analysis of variance (ANOVA) test was used to assess the difference in variables among three groups, followed by the least significant difference (LSD) test for further comparisons between two groups. Two groups were compared using the Mann-Whitney U test. The Pearson chi-square test was used for categorical variables. Spearman correlation was used to evaluate the relationships between continuous variables. Binary logistic regression analysis was used to identify the independent predictors of remission. Receiver operating characteristic (ROC) curves were constructed to provide a graphical representation of the relationship between false-positive (specificity) and true-positive (sensitivity) detection rates for preoperative prolactin and GH levels for diagnosing pituitary adenomas, and prolactin level on day 1 postsurgery for the remission of prolactinomas. All tests for significance and resulting *P* values were two-sided, with a level of significance of 5%.

Results

Demographic and clinical characteristics

We identified 132 cases of prolactinoma and 39 cases of GH-secreting adenoma in premenopausal women. The most common clinical manifestations of prolactinomas included amenorrhea, paramenia, galactorrhea, and infertility, and the most common clinical manifestations of GH-secreting adenomas included enlargement of the hands and feet, abnormal facial features, amenorrhea, galactorrhea, headaches, and vision loss.

Among the patients with prolactinoma, 62% had macroadenomas, 36% had microadenomas, and 2% had giant adenomas, among which 47% had invasive tumors, and 60.6% were younger than 30 years of age. Patients with prolactinomas had the highest preoperative prolactin level, the lowest preoperative cor-

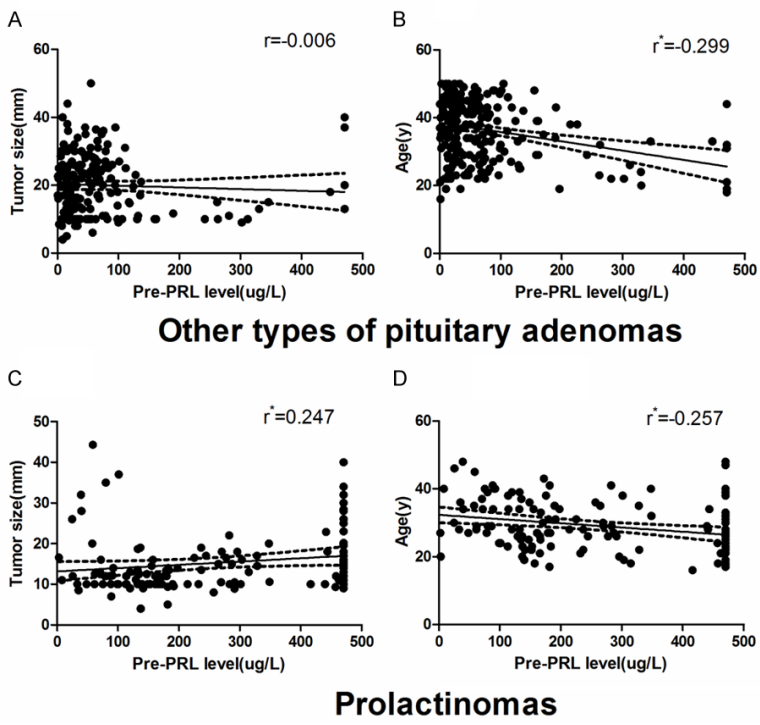

Figure 1. The correlation of pre-PRL with tumor size and age in premenopausal women with other types of pituitary adenomas (A and B) or with prolactinomas (C and D). *P < 0.01. Abbreviations: Pre-PRL, preoperative prolactin.

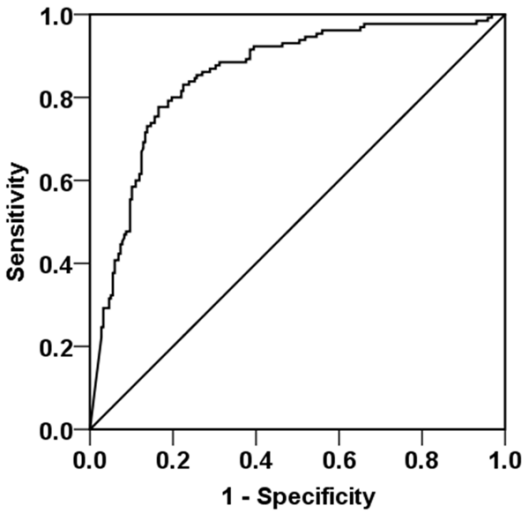

Figure 2. ROC curve for preoperative prolactin level to diagnose prolactinomas in premenopausal women.

tisol level, the smallest tumor size, and youngest age among prolactinomas, GH-secreting adenomas, and other types of pituitary adenomas. No significant differences were observed for levels of estradiol (E_2), luteinizing hormone (LH), adrenocorticotropic hormone (ACTH), thyroid-stimulating hormone (TSH), and free thyroxine (FT_4) (all, $P > 0.05$) (**Table 1**).

The preoperative prolactin level in patients with other types of pituitary adenomas was not correlated with tumor size (r = -0.006, P = 0.935), but it was negatively correlated with age (r = -0.299, $P < 0.001$). In addition, the preoperative prolactin level in patients with prolactinoma positively correlated with tumor size (r = 0.247, P = 0.005) and negatively correlated with age (r = -0.257, P = 0.003) (**Figure 1**).

Among the patients with GH-secreting adenoma, 87.5% had macroadenomas, 9.4% had microadenomas, and 3.1% had giant adenomas, among which 69.2% had invasive tumors, and 15.4% were younger than 30 years of age. Patients with GH-secreting adenoma had the highest preoperative GH level, the lowest preoperative PRL and FSH levels, the largest tumor size, and the oldest age among prolactinomas, GH-secreting adenomas, and other types of pituitary adenomas (**Table 1**).

The preoperative GH level was not correlated with tumor size (r = 0.323, P = 0.059 in GH-secreting adenomas and in other types of pituitary adenomas (r = 0.019, P = 0.760) or age (r = -0.179, P = 0.277 in GH-secreting adenomas and in other types of pituitary adenomas (r = 0.041, P = 0.468) for GH-secreting and other types of pituitary adenomas.

Diagnostic and prognostic factors for prolactinomas

In the immunohistochemical analysis, the prolactin-positive rate increased with the increasing prolactin level. The ROC was constructed for prolactin level. The ROC curve indicated that the area under the curve (AUC) for the prolactin level was 0.854 [P < *0.01*; 95% confidence

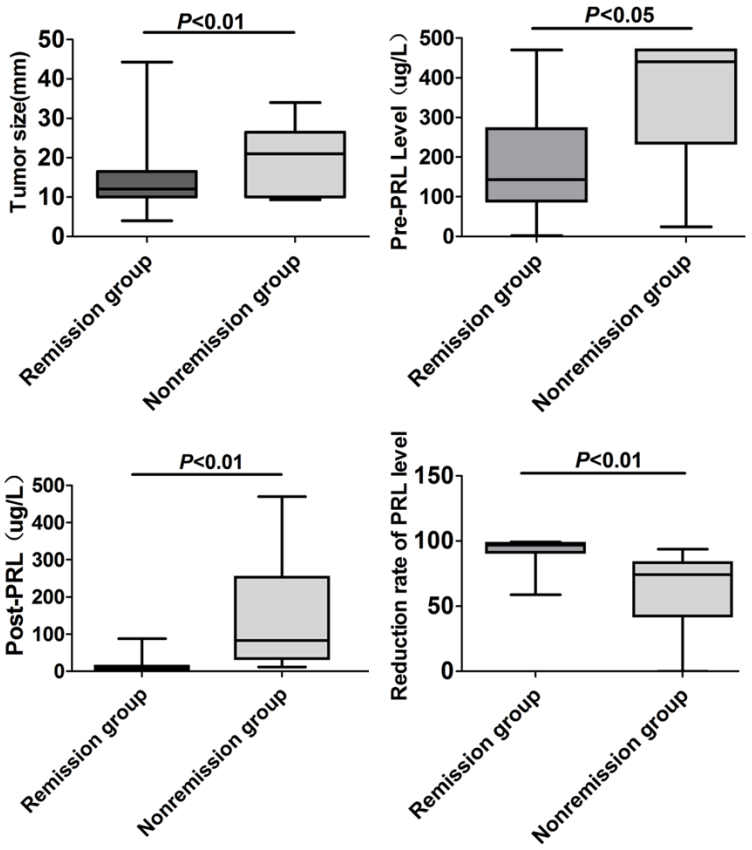

Figure 3. Differences of tumor size, pre-PRL level, post-PRL level, and reduction rate of PRL level between remission and non-remission groups in premenopausal women with prolactinomas, respectively. Abbreviations: Pre-PRL, preoperative prolactin; post-PRL, prolactin level on day 1 postsurgery; reduction rate of PRL level is equal to 1-post-PRL level/pre-PRL level.

interval (CI): 0.812-0.896; **Figure 2**] for patients with prolactinoma. The diagnostic cut-off value for prolactin was 112.2 μg/L with a sensitivity of 78%, a specificity of 83%, a positive predictive value (PPV) of 73%, and a negative predictive value (NPV) of 86%.

Among the 132 premenopausal women with prolactinomas, 84 completed the follow-up. During the follow-up period, remission occurred in 51 (60.7%) cases, and non-remission, which included residual and recurrence, occurred in 20 (23.9%) cases. Thirteen patients did not undergo imaging re-examination because of a return to normal menstruation and a lack of discomfort. Patients who experienced remission had a smaller tumor size (12 mm, P = 0.029), lower preoperative prolactin level (143.5 μg/L, P = 0.002), lower postoperative prolactin level (6.7 μg/L, P < 0.001), and a higher rate of prolactin reduction (98.8%, P < 0.001) than those who experienced non-remission (21 mm, 440.45 μg/L, 82.5 μg/L, and 69.9%, respectively; **Figure 3**). The Pearson chi-square test showed that the remission rate among the patients with prolactinoma with noninvasive tumor was 3.76 times higher than that of those with invasive tumor.

A multiple logistic regression analysis that included age, tumor size, preoperative prolactin level, tumor invasion, prolactin level on day 1 postsurgery, and the prolactin level reduction rate was performed (**Table 2**). A lower prolactin value on day 1 postsurgery was the only significant predictor of remission [odds ratio (OR) = 0.931 95% CI = 0.883-0.981; P = 0.008]. The ROC curve showed that the AUC for prolactin level on day 1 postsurgery was 0.950 (95% CI: 0.903-0.997; P < 0.001). The cut-off value of the postsurgery day 1 prolactin level was 20.49 μg/L (sensitivity: 88%; specificity: 95%; PPV: 98%; NPV: 76%; **Figure 4**) for the prediction of remission.

Diagnostic and prognostic factors in GH-secreting adenomas

Thirty-nine cases of GH-secreting adenomas in premenopausal women were confirmed by serum GH levels after OGTT, IGF-1, and immunohistochemical analysis. The minimum value of GH for those who underwent OGTT was 3.38 μg/L. The IGF-1 level was above the upper limit of the reference range used in our hospital, with an average value of 770.8 ng/L

Based on the preoperative GH level, GH-secreting adenomas were divided into three groups (< 2.5 μg/L, 2.5-5.0 μg/L, and > 5.0 μg/L). The incidence of GH-secreting adenomas as confirmed by the postoperative pathological diagnosis increased with the increase in

Table 2. Logistic regression analysis of prognostic factors in patients with prolactinomas

Variables	Estimated coefficients	SE	OR	95% CI	*P*
Age (years)	-0.037	0.062	0.963	0.853-1.088	0.547
Tumor size (mm)	-0.026	0.272	0.974	0.883-1.075	0.602
Pre-PRL (μg/L)	0.003	0.005	1.003	0.994-1.012	0.542
Tumor invasion	-0.438	1.047	0.645	0.083-5.025	0.676
Prolactin level reduction rate	0.009	0.022	1.009	0.966-1.054	0.686
Post-PRL (μg/L)*	-0.072	0.027	0.931	0.883-0.981	0.008

*P < 0.01; Abbreviations: Pre-PRL, preoperative prolactin; post-PRL, prolactin level on day 1 postsurgery; SE, standard error; OR, odds ratio; CI, confidence interval.

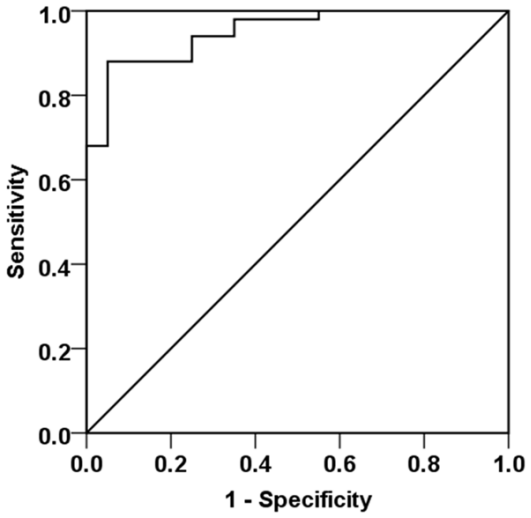

Figure 4. ROC curve for prolactin level on day 1 postsurgery to prognose remission of prolactinomas in premenopausal women.

preoperative GH level. The ROC curve indicated that the AUC for the preoperative GH level was 0.809 (*P* < 0.001, 95% *CI*: 0.719-0.899; **Figure 5**), and the diagnostic cut-off value of the preoperative GH level for GH-secreting adenomas was 2.6 μg/L with a sensitivity of 77%, a specificity of 83%, a PPV of 36%, and a NPV of 97%.

Among the 39 premenopausal women with GH-secreting adenomas, 16 completed the follow-up. During the follow-up period, nine (56%) patients had remission, and six (38%) patients had non-remission. One patient did not undergo imaging or anterior pituitary function analysis due to the complete removal of the tumor and normal postoperative endocrine function. No significant differences in age, preoperative GH level, or tumor size (*P* > 0.05, **Table 3**) were observed between the GH-secreting adenoma patients who experienced remission and those that did not have remission. However, the median GH level on day 1 postsurgery in the remission group was significantly lower (3.5 μg/L; *P* = 0.025) than that of the non-remission group (14.8 μg/L).

Discussion

Prolactinomas are the most common type of pituitary tumor, and have a morbidity rate of 100 in one million [5]. Although prolactinomas are usually treated medically with dopamine agonists [6, 7], patients are still referred to neurosurgeons for various reasons, such as a strong personal preference for surgery instead of chronic medical treatment, or drug intolerance or resistance. The current study aimed to provide information on clinical characteristics and better prognostic information for premenopausal women with prolactinomas treated by transsphenoidal surgery. Hyperprolactinemia interferes with the pulse secretion of gonadotropin-releasing hormone (GnRH), which reduces the secretion of follicle-stimulating hormone (FSH) and LH. Reductions in FSH and LH lead to disorders of the gonads, including amenorrhea and infertility in women [8]. Microadenomas are found almost exclusively in premenopausal women. In contrast, invasive macroadenomas are more common in men, which often results in erectile dysfunction, decreased libido, infertility, and mammary gland development [2, 5]. Among the 132 women with prolactinoma treated in our hospital, macroadenomas were more common than microadenomas. Prolactinomas were more common in female patients younger than 30 years of age, which is typically characterized by premature menopause, menstrual disorders, and infertility. Compared with patients with other types of pituitary adenomas, the patients with prolactinoma had smaller tumors and were younger.

In general, tumor size is positively correlated with the preoperative prolactin level, and an

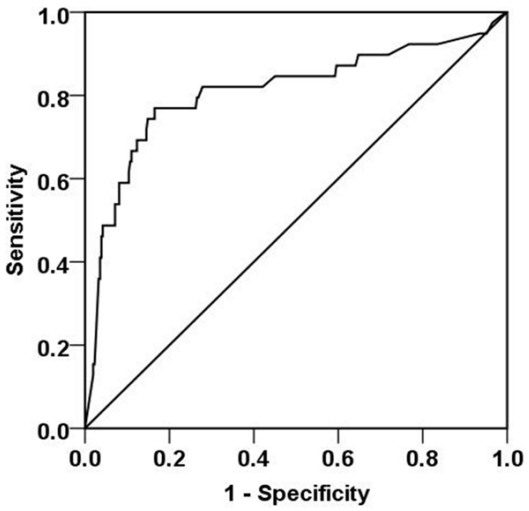

Figure 5. ROC curve for preoperative GH level to diagnose GH-secreting adenomas in premenopausal women.

increased level of prolactin was of significant predictive value for the diagnosis of prolactinomas. The prolactin level can increase to as high as 100 to 150 μg/L as a result of pituitary stalk oppression, or microadenomas, or taking special drugs. A prolactin level greater than 150 μg/L is a significant predictor of prolactinoma when combined with clinical and imaging data, and a level greater than 500 μg/L is sufficient for diagnosis in the absence of clinical and imaging data [6]. These findings are consistent with those from our analysis of premenopausal women with prolactinoma. We found that the prolactin level was higher in patients with prolactinoma than in patients with other types of pituitary adenomas. We also found that the preoperative prolactin level in patients with prolactinoma was positively correlated with tumor size, and negatively correlated with age. In addition, the incidence of prolactin-positive results in the immunohistochemical analysis increased with increasing levels of preoperative prolactin, and prolactinoma should be suspected in premenopausal women with a preoperative prolactin level greater than 112.2 μg/L.

Previous studies have shown that the factors that correlate with prolactinoma prognosis include age, tumor size, preoperative prolactin level, postoperative prolactin level, and resection range. However, results have been inconsistent. Logistic regression analysis by Losa et al [9] showed that the preoperative prolactin level was the only predictive factor of early surgical remission. Kreutzer et al [10] reported that the preoperative prolactin level, tumor size, and growth extension could predict remission. In agreement with Xin Qu et al [11], Raverot et al [12] illustrated that male sex was associated with an early negative surgical outcome by univariate analysis, whereas no significance was found with the multiple logistic regression analysis. In addition, Amar et al [13] showed that microadenomas and macroadenomas could be cured when the prolactin level was less than 10 μg/L within a week postsurgery. Recent evidence indicated that the remission rate reached 84% among patients with a prolactin level less than 20 μg/L, whereas the remission rate was 67% for patients with a prolactin level greater than 20 μg/L [14]. Therefore, when the postoperative prolactin level approaches the upper limit of the reference range, recurrence may be more likely to occur. In general, the postoperative prolactin level is considered to be a predictor of pituitary adenoma prognosis.

In the current study, univariate analysis showed that a negative surgical outcome was associated with a high preoperative prolactin level, large tumor size, high prolactin level on day 1 postsurgery, and low prolactin reduction rate. However, logistic regression analysis found that a lower prolactin value on day 1 postsurgery was the only significant predictor of remission. Furthermore, the ROC curve showed that a prolactin level less than 20.49 μg/L on day 1 postsurgery can prognose the remission of prolactinoma in premenopausal women.

Enlargement of hands and feet and face abnormalities are the most common clinical manifestations of GH-secreting adenomas. Joint pain, carpal tunnel syndrome, cacophony, and rough skin may also occur. Obstructive sleep apnea syndrome, hypertension, insulin resistance, type 2 diabetes, and heart disease can also develop in patients with GH-secreting adenomas. The risk of nodular goiter and intestinal polyps are increased in patients with GH-secreting adenoma, and patients who do not undergo treatment for GH-secreting adenomas have a lower 10-year survival rate [15]. Because acromegaly usually develops slowly, these characteristics are manifested over time, typically delaying the diagnosis for 7 to 10 years

Table 3. Differences of general information and laboratory data between remission and non-remission groups in premenopausal women with GH-secreting adenomas

	Remission group	Non-remission group	*P* value
Age (years)	45.00 (35.00-49.50)	35.00 (31.5-42.75)	0.111
Tumor size (mm)	16.00 (12.00-23.00)	22.00 (13.00-36.50)	0.370
Pre-GH (μg/L)	14.30 (2.50-38.00)	40.00 (8.87-42.50)	0.284
Post-GH (μg/L)$^{\Delta}$	3.50 (1.40-6.10)	14.80 (6.03-26.80)	0.025

Date are presented as median (interquartile range). $^{\Delta}P < 0.05$. Abbreviations: Pre-GH, preoperative growth hormone; post-GH, growth hormone level on day 1 postsurgery.

[16]. Most GH-secreting adenomas are macroadenomas (80%) [17]. The age of onset of acromegaly ranges from 20 to 50 years. After adjusting for age and sex, increased total IGF-1 level and GH level greater than 1 ng/mL in the OGTT are used to confirm the diagnosis of acromegaly [18].

Acromegalic manifestation occurred in 61.5% of 39 GH-secreting adenomas in premenopausal women. Macroadenomas occurred in 87.5% of GH-secreting adenomas, and 84.6% of these patients were older than 30 years of age. The patients with GH-secreting adenomas were older, had larger tumors, and had higher preoperative GH level than the patients with non-GH-secreting adenomas, but the preoperative GH level was not correlated with tumor size or age. After grouping the patients with GH-secreting adenomas based on GH level, we found that an increased preoperative level of GH was a predictor of GH-secreting adenomas, with a diagnostic cut-off value of greater than 2.6 μg/L, based on the ROC curve.

Transsphenoidal surgery is the first-line therapy for GH-secreting adenomas. The remission rate is 75% to 95% for microadenomas and 40% to 68% for macroadenomas [19]. In 2011, the American Association of Clinical Endocrinologists published guidelines for the treatment of acromegaly, [20] which stated that a GH level of less than 2.0 μg/L on day 1 postsurgery was associated with a long-term survival rate of 99%. In our current study, the postoperative remission rate among GH-secreting adenomas was 56%, and no significant difference in tumor size, age, or preoperative GH level was observed between patients who experienced remission and those who did not. We also found that the GH level on day 1 postsurgery was lower in patients who experienced remission. However, because the patients with GH-secreting adenomas who completed the follow-up examinations were relatively small in our study, the cut-off value for the GH level on day 1 postsurgery for predicting the response of GH-secreting adenoma patients could not be determined based on the ROC curve.

In conclusion, this is the first clinical study focusing specifically on prolactinomas and GH-secreting adenomas in premenopausal women. Our study indicated that the clinical characteristics and outcomes of premenopausal women with prolactinomas and GH-secreting adenomas were not precisely the same as patients with general pituitary adenomas. Moreover, our study demonstrated that prolactinoma should be suspected in premenopausal women with a prolactin level greater than 112.2 μg/L. A GH level greater than 2.6 μg/L is highly suggestive of GH-secreting adenomas. In addition, a prolactin level on day 1 of less than 20.49 μg/L is a strong predictor of remission in Chinese premenopausal women with prolactinoma. Our findings provide a clinical basis for improving the early diagnosis, treatment, and prognosis of pituitary adenomas in premenopausal women.

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Disclosure of conflict of interest

None.

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References

[1] Fainstein DP, Guitelman M, Artese R, Fiszledjer L, Chervin A, Vitale NM, Stalldecker G, De MV, Cornalo D, Alfieri A, Mallea Gil MS. Retro-

sprective multicentric study of pituitary incident alomas. Pituitary 2004; 7: 145-148.
[2] Lieva RR and Inzucchi SE. Diognosis and management of pituitary adenomas. Curr Opin Oncol 2011; 23: 53-60.
[3] Kars M, Souverein PC, Herings RM, Romijn JA, Vandenbroucke JP, de Boer A, Dekkers OM, Dekkers OM. Estimated age-and sex-specific incidence and prevalence of dopamine agonist-treated hyperprolactinemia. J Clin Endocrinol Metab 2009; 94: 2729-2734.
[4] Castinetti F, Morange I, Conte-Devolx B, Brue T. Cushing's disease. Orphanet J Rare Dis 2012; 7: 41.
[5] Mann WA. Treatment for prolactinomas and hyperprolactinaemia: a lifetime approach. Eur J Clin Invest 2011; 41: 334-342.
[6] Melmed S, Casanueva FF, Hoffman AR. Diagnosis and treatment of hyperprolactinemia: an endocrine society clinical practice guideline. J Clin Endocrinol Metab 2011; 96: 273-288.
[7] Glezer A, Bronstein MD. Prolactinoma. Arq Bras Endocrinol Metabol 2014; 58: 118-23.
[8] Faje A, Nachtigall L. Current treatment options for hyperprolactinemia. Expert Opin Pharmacother 2013; 14: 1611-1625.
[9] Losa M, Mortini P, Barzaghi R, Gioia L, Giovanelli M. Surgical treatment of prolactin-secreting pituitary adenomas: early results and long-term outcome. J Clin Endocrinol Metab 2002; 87: 3180-3186.
[10] Kreutzer J, Buslei R, Wallaschofski H, Hofmann B, Nimsky C, Fahlbusch R, Buchfelder M. Operative treatment of prolactinomas: indications and results in a current consecutive series of 212 patients. Eur J Endocrinol 2008; 158: 11-18.
[11] Qu X, Wang M, Wang G, Han T, Mou C, Han L, Jiang M, Qu Y, Zhang M, Pang Q, Xu G. Surgical outcomes and prognostic factors of transsphenoidal surgery for prolactinoma in men: a single-center experience with 87 consecutive cases. Eur J Endocrinol 2011; 164: 499-504.
[12] Raverot G, Wierinckx A, Dantony E , Auger C, Chapas G, Villeneuve L, Brue T, Figarella-Branger D, Roy P, Jouanneau E, Jan M, Lachuer J, Trouillas J. Hypopronos. Prognostic factors in prolactin pituitary tumors: clinical, histological, and molecular data from a series of 94 patients with a long postoperative follow-up. J Clin Endocrinol Metab 2010; 95: 1708-1716.
[13] Amar AP, Couldwell WT, Chen JC, Weiss MH. Predictive value of serum prolactin levels measured immediately after transsphenoidal surgery. J Neurosurg 2002; 97: 307-314.
[14] Massoud F, Serri O, Hardy J, Somma M, Beauregard H. Transsphenoidal adenomectomy for microprolactinomas: 10 to 20 years of follow-up. Surg Neurol 1996; 45: 341-346.
[15] Ezzat S, Gaspo R, Serri O, Ur E, Chik CL. A Canadian multicentre, open-label long-term study of pegvisomant treatment in refractory acromegaly. Clin Invest Med 2009; 32: E265.
[16] Melmed S. Medical progress: acromegaly. N Engl J Med 2006; 355: 2558-2573.
[17] Cook DM, Ezzat S, Katznelson L, Kleinberg DL, Laws ER Jr, Nippoldt TB, Swearingen B, Vance ML; AACE acromegaly guidelines task force. AACE medical guidelines for clinical practice for the diagnosis and treatment of acromegaly. Endocrine Pract 2004; 10: 213-225.
[18] Giustina A, Chanson P, Bronstein MD, Klibanski A, Lamberts S, Casanueva FF, Trainer P, Ghigo E, Ho K, Melmed S; Acromegaly Consensus Group. A consensus on criteria for cure of acromegaly. J Clin Endocrinol Metab 2010; 95: 3141-3148.
[19] Melmed S, Colao A, Barkan A, Molitch M, Grossman AB, Kleinberg D, Clemmons D, Chanson P, Laws E, Schlechte J, Vance ML, Ho K, Giustina A; Acromegaly Consensus Group. Guidelines for acromegaly management: an update. J Clin Endocrinol Metab 2009; 94: 1509-1517.
[20] Katznelson L, Atkinson JL, Cook DM, Ezzat SZ, Hamrahian AH, Miller KK; American association of clinical endocrinologists. 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.