

Role of prolactin/adenoma maximum diameter and prolactin/adenoma volume in the differential diagnosis of prolactinomas and other types of pituitary adenomas

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Received October 25, 2016; Accepted September 28, 2017

DOI: 10.3892/ol.2017.7462

Abstract. The present study aimed to investigate the function of the prolactin/adenoma maximum diameter (PRL/MD) and the prolactin/adenoma volume (PRL/V) in the differential diagnosis of prolactinomas and other types of pituitary adenomas. A total of 118 patients with pituitary adenoma, hyperprolactinemia and a plasma PRL <250 $\mu\text{g/l}$ were enrolled. Clinical data from these patients were retrospectively analyzed. A receiver operating characteristic curve was plotted. The function of PRL, PRL/MD and PRL/V in the differential diagnosis of prolactinomas and other types of pituitary adenomas was compared. The results revealed that a PRL of 55.65 $\mu\text{g/l}$ was the most accurate [sensitivity (SE), 0.800; specificity (SP), 0.716; positive predictive value (PPV), 0.857; negative predictive value (NPV), 0.933; and Youden index (YI), 0.516]. The PRL/MD with the highest diagnostic value was 4.03 $\mu\text{g}/(\text{l} \times \text{mm})$ (SE, 0.800; SP, 0.898; PPV, 0.727; NVP, 0.929; and YI, 0.698). The PRL/V with the highest diagnostic value was 54.00 $\mu\text{g}/(\text{l} \times \text{cm}^3)$ (SE, 0.900; SP, 0.966; PPV, 0.900; NVP, 0.966; and YI, 0.866). The PRL/MD tended to be of higher diagnostic accuracy than PRL, but this difference was not statistically significant ($P=0.097$). The differentiation ability of PRL/V was significantly stronger than that of PRL ($P=0.028$). Thus, serum PRL, PRL/MD and PRL/V levels may be able to differentiate prolactinomas from other types of hyperprolactinemia-causing pituitary

adenomas prior to treatment. PRL/V may be better than the PRL level in achieving a differential diagnosis, and the optimal PRL/V ratio for differentiating prolactinomas from other types of hyperprolactinemia-causing pituitary adenomas was 54.00 $\mu\text{g}/(\text{l} \times \text{cm}^3)$.

Introduction

Hyperprolactinemia is most commonly caused by prolactinoma, but may also be caused by other types of pituitary adenomas, in addition to the pituitary stalk interruption effect, peritumoral pituitary compression and endocrine feedback (1,2). Pituitary adenoma-associated hyperprolactinemia is usually considered to be caused by prolactinoma, but other types of pituitary adenomas may also cause secondary hyperprolactinemia. For example, the incidence of non-functional pituitary large adenoma-associated secondary hyperprolactinemia is 34.8-41.2% (3-8). The presence of secondary hyperprolactinemia makes it difficult to differentiate prolactinoma from other types of pituitary adenomas (9-12). However, the treatment for prolactinoma differs greatly from that of other types of pituitary adenomas. Thus, it is of great importance to differentiate prolactinoma from other types of pituitary adenomas. Currently, clinical symptoms, imaging and pituitary hormone tests are used for this differential diagnosis, but the diagnostic accuracy of these techniques is limited (11,13-15).

Therefore, the present study was designed to identify a novel diagnostic approach for differentiating prolactinoma from other types of pituitary adenomas. The prolactin (PRL) level in prolactinomas is strongly associated with tumor size (16). As the tumor size increases, the synthesis and release of PRL is enhanced. However, the PRL levels of other types of pituitary adenomas depend more upon the location of the adenomas (17) and the increased size of the adenoma may not lead to a significant increase in PRL.

The present study proposed the use of the prolactin/adenoma maximum diameter (PRL/MD) and the prolactin/adenoma volume (PRL/V) as novel diagnostic tools for prolactinoma,

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Key words: pituitary adenoma, hyperprolactinemia, prolactin, prolactinomas, differential diagnosis

and the diagnostic value of these methods was investigated. Due to the fact that mis-differentiation occurs only in large adenomas, the present study primarily included large pituitary adenomas (diameter ≥ 10 mm). Meanwhile, the Hyperprolactinemia Treatment Guidelines of the European Endocrine Society demonstrate that a PRL >250 $\mu\text{g/l}$ is most likely caused by prolactinoma (15). Therefore, only patients with a PRL between the upper limit of the normal range and 250 $\mu\text{g/l}$ were included in the present study.

Patients and methods

Patients. Data from 516 patients with pituitary adenoma who had been admitted to the Department of Neurosurgery, Fuzhou General Hospital (Fuzhou, China) between December 2008 and December 2014 were retrospectively analyzed. A total of 178 of these were cases of large pituitary adenoma with hyperprolactinemia.

The inclusion criteria of the present study were as follows: i) Pituitary adenoma diagnosed by pathology and classified by immunohistochemistry (18,19); ii) having undergone ≥ 1 set of concurrent pituitary hormone tests and magnetic resonance imaging (MRI) prior to treatment; iii) a pituitary adenoma diameter >10 mm; and iv) a PRL between the upper limit of the normal range [PRL, 2.1–17.7 $\mu\text{g/l}$ (male), 2.8–29.2 $\mu\text{g/l}$ (female, not pregnant), 1.8–20.3 $\mu\text{g/l}$ (female, menopause) and 3.4–33.4 $\mu\text{g/l}$ (female, ovulatory phase)] and 250 $\mu\text{g/l}$. The exclusion criteria were as follows: i) The presence of other primary endocrine diseases, including hyperthyroidism and Cushing's syndrome; ii) pituitary hormone tests exhibiting growth hormone (GH; <10 $\mu\text{g/l}$), thyroid-stimulating hormone (TSH; 0.35–5.5 $\mu\text{IU/ml}$) or adrenocorticotrophic hormone (ACTH; 4.7–48.8 pg/ml) levels above the upper normal limit; iii) a history of glucocorticoid replacement therapy; and iv) recent treatment with drugs that affect pituitary hormone levels, including antipsychotic drugs, opioids, proton pump inhibitors, estrogen preparations and calcium antagonists. The surgical indications were as follows: i) A poor efficacy of medical therapy after 3–6 months of treatment; ii) the inability to tolerate medical therapy; iii) a lack of mental capacity to live with the tumor (determined by an interview with the patients or their family) or refusal of long-term medication; iv) the presence of tumor apoplexy, manifesting as severe headaches and a sharp decrease in vision; and v) experienced surgeons anticipating total tumor removal by surgery having fully taken into consideration the wishes of the patients (20).

Finally, there were 118 patients included in the present study. Patients were divided into two groups, with PRL(+), GH(-), ACTH(-), TSH(-), follicle-stimulating hormone (FSH) (-), and luteinizing hormone (LH)(-) patients (as assessed by immunohistochemistry) in group A (prolactinoma group, $n=30$) and all other patients in group B (other types of pituitary adenoma, $n=88$). The mean ages of the two groups were 35.27 (range, 19–64 years) in group A and 47.61 in group B (range, 20–74 years). The male:female ratio consisted of 7:23 in group A and 33:55 in group B. Prior written and informed consent was obtained from each patient and the study was approved by the Ethics Review Board of Fuzhou General Hospital.

Determination of tumor maximum diameter (MD) and tumor volume (V) by enhanced and plain MRI scanning. All patients underwent an enhanced and a plain MRI scan using a Siemens 3.0T MRI machine (Magnetom; Siemens AG, Munich, Germany). The scan sequences included at least axial and sagittal T1-weighted imaging, axial and coronal T2-weighted imaging, coronal fluid-attenuated inversion recovery and a three-dimensional enhanced scan. The imaging was measured at an INFINITT PACS workstation (PACS; INFINITT Healthcare Co., Ltd., Seoul, South Korea) by at least one neurosurgeon, one radiologist and one neurosurgery physician.

The tumor MD of all planes (including coronal, sagittal and axial) was measured, and the tumor was categorized as a micro pituitary adenoma (<10 mm), large pituitary adenoma ($10 \leq \text{MD} < 40$ mm) or macro pituitary adenoma (≥ 40 mm), as described previously (21). The maximum coronal length (a) and the sagittal width (b) were measured on enhanced T1-weighted imaging, and the maximum height (c) was measured at the middle sella turcica (middle cavernous) in the coronal section. The tumor V was calculated as follows: $V = a \times b \times c \times \pi/6$ (22).

Detection of hormone level by chemiluminescence. The levels of TSH, triiodothyronine (T3), thyroxine (T4), free triiodothyronine (FT3), free thyroxine (FT4), LH, FSH, PRL, ACTH, GH, estradiol, testosterone and cortisol were measured. A volume of 10 ml blood was collected from fasting outpatients (at 8:00 a.m.) and inpatients (at 7:00 a.m.), all of whom were in a resting state. Chemiluminescence was used to detect hormone levels using the ADVIA Centaur XP Immunoassay system (Siemens AG). The normal ranges of these hormones were: GH, <10 $\mu\text{g/l}$; ACTH, 4.7–48.8 pg/ml ; T3, 0.92–2.79 $\mu\text{g/l}$; T4, 58.1–140.6 $\mu\text{g/l}$; FT3, 3.5–6.5 pmol/l ; FT4, 11.5–22.7 pmol/l ; TSH, 0.35–5.5 $\mu\text{IU/ml}$; PRL, 2.1–17.7 $\mu\text{g/l}$ (male), 2.8–29.2 $\mu\text{g/l}$ (female, not pregnant), 1.8–20.3 $\mu\text{g/l}$ (female, menopause) and 3.4–33.4 $\mu\text{g/l}$ (female, ovulatory phase); FSH, 1.4–18.1 mIU/ml (male), 9.7–208 mIU/ml (female, pregnancy), 2.5–10.2 mIU/ml (female, follicular phase), 1.5–9.1 mIU/ml (female, luteal phase) and 23–116 mIU/ml (female, menopause); and LH, 1.5–9.3 mIU/ml (male), 1.9–12.5 mIU/ml (female, follicular phase), 8.7–76.3 mIU/ml (female, ovulatory phase), 0.5–16.9 mIU/ml (female, luteal phase) and 15.9–54 mIU/ml (female, menopause). For suspected prolactinoma patients with significantly low PRL levels, the PRL level was retested with a dilution of 1:100 to exclude the Hook effect (23,24). The PRL/MD ($\mu\text{g}/(1 \times \text{mm})$) was the ratio of PRL (μg) to MD (1 \times mm). The PRL/V ($\mu\text{g}/(1 \times \text{cm}^3)$) was the ratio of PRL (μg) to V (1 \times cm^3).

Statistical analysis. SPSS 19.0 statistical software (IBM Corp., Armonk, NY, US) was used for statistical analysis. Normally distributed data are expressed as the mean \pm standard deviation. The values of PRL, PRL/MD and PRL/V that were not normally distributed are expressed as the median (range). Categorical data were compared using the χ^2 test and quantitative data were compared using Student's t-test, analysis of variance followed by Tukey's test for post-hoc multiple comparisons and the rank sum test. The diagnostic sensitivity (SE), specificity (SP), positive predictive value (PPV) and negative predictive value (NPV), and the diagnostic accuracy of PRL, PRL/MD and PRL/V were recorded. Receiver

Table I. Clinical characteristics of all patients in the study.

Characteristic	Group A (n=30)	Group B (n=88)	P-value
Age, years ^a	35.27±11.31	47.61±12.65	<0.001
Gender (male:female), n	7:23	33:55	0.185
Hyperprolactinemia-related symptoms, n (%)	24 (80.00)	22 (25.00)	<0.001
Amenorrhea	17 (56.67)	14 (15.91)	
Lactation	20 (66.67)	9 (10.23)	
Decreased sexual function	0 (0.00)	7 (7.95)	
Fatigue	0 (0.00)	4 (4.55)	
Adenoma mass effects, n (%)	19 (63.33)	81 (92.05)	0.001
Headache, dizziness	14 (46.67)	51 (57.95)	
Visual impairment	8 (26.67)	57 (64.77)	
PRL level, $\mu\text{g/l}$			
Median (range) ^b	114.71 (31.74-238.16)	44.42 (18.03-220.59)	<0.001
18-50	4 (13.33)	55 (62.50)	
50-100	10 (33.33)	23 (26.14)	
100-150	4 (13.33)	8 (9.09)	
150-250	12 (40.00)	2 (2.27)	
Adenoma size ^a			
Maximum diameter, mm	15.81±4.93	29.00±10.97	<0.001
Volume, cm^3	1.58±2.20	8.21±8.53	<0.001
New indicators ^b			
PRL/MD, $\mu\text{g}/(\text{l} \times \text{mm})$	7.77 (1.73-17.01)	1.70 (0.45-11.59)	<0.001
PRL/V, $\mu\text{g}/(\text{l} \times \text{cm}^3)$	107.55 (5.29-360.99)	9.15 (0.68-117.50)	<0.001

Data presented as ^amean \pm standard deviation and ^bmean (range).

operating characteristic (ROC) curves were drawn to identify the cut-off point [corresponding to the maximum Youden index (YI)]. The area under the curve (AUC) was compared using Student's t-test. $P < 0.05$ was considered to indicate a statistically significant difference.

Results

Characteristics of patients. The 118 pituitary adenoma cases with PRL between the upper limit of the normal range and $250 \mu\text{g/l}$ were included, including 30 cases in group A (prolactinoma group) and 88 cases in group B (other pituitary adenoma group). There was no significant difference in gender ratio between the two groups, with 7:23 (male:female) in group A and 33:55 in group B. However, there was a significant difference in age between group A (mean, 35.27 ± 11.31 ; range, 19-64 years) and B (mean, 47.61 ± 12.65 ; range, 20-74 years) ($P < 0.05$). Immunohistochemistry revealed that all cases in group A were prolactin-type (confirmed prolactinoma cases). In group B, there were 4 cases of GH-type adenoma, 4 cases of ACTH-type adenoma, 1 case of TSH-type adenoma, 29 cases of null cell adenoma, 33 cases of gonadotrophic hormone (GnH)-type adenoma and 17 cases of plurihormonal-type adenoma (including 4 cases with tumors positive for ACTH + FSH + GH + PRL + TSH, 1 case positive for ACTH + PRL, 3 cases positive for ACTH + GH + PRL, 1 case positive for

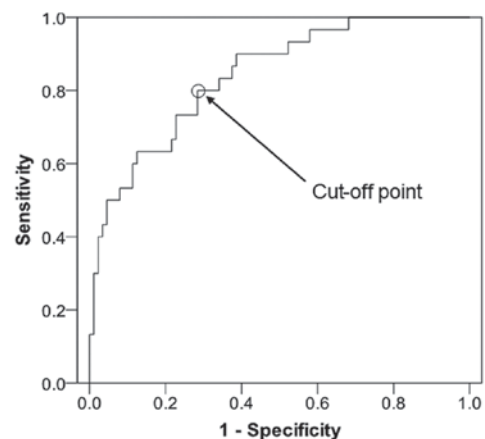


Figure 1. Receiver operating characteristic curve of PRL differentiation. PRL was used for differential diagnosis and immunohistochemistry results were used as the gold standard. Cut-off point, $55.65 \mu\text{g/l}$; AUC, 0.840; AUC standard error, 0.040; and 95% confidence interval, 0.761-0.919. AUC, area under the curve; PRL, prolactin.

ACTH + GH + LH + PRL + TSH, 2 cases positive for ACTH + FSH + GH + LH + PRL + TSH, 2 cases positive for FSH + PRL, 1 case positive for PRL + TSH, 1 case positive for GH + TSH, 1 case positive for ACTH + GH + LH + PRL and 1 case positive for ACTH + FSH + GH + PRL).

Table II. PRL differentiation of prolactinoma and other types of pituitary adenoma.

PLR, $\mu\text{g/l}$	Diagnosis	Group A, n	Group B, n	Total	SE	SP	PPV	NPV	YI
>55.65	Prolactinoma	24	4	28					
≤ 55.65	Other pituitary adenomas	6	84	90					
Total		30	88	118	0.800	0.716	0.857	0.933	0.516

SE, sensitivity; SP, specificity; PPV, positive predictive value; NPV, negative predictive value; YI, Youden index; PRL, prolactin.

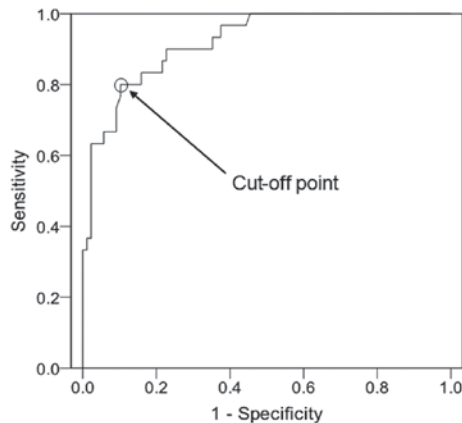


Figure 2. Receiver operating characteristic curve of PRL/MD differentiation. PRL/MD was used for differential diagnosis and immunohistochemistry results were used as gold standard. Cut-off point, $4.03 \mu\text{g}/(\text{l} \times \text{mm})$; AUC, 0.920; AUC standard error, 0.027; and 95% confidence interval, 0.868-0.972. AUC, area under the curve; PRL/MD, prolactin/adenoma maximum diameter.

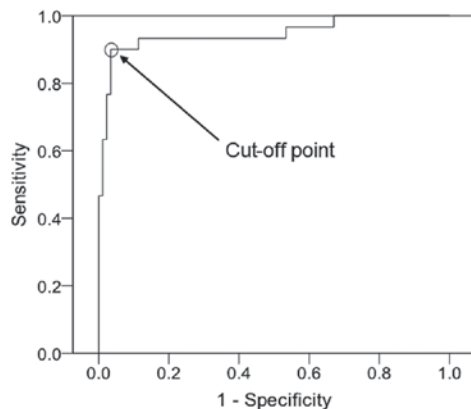


Figure 3. Receiver operating characteristic curve of PRL/V differentiation. PRL/V was used for differential diagnosis and immunohistochemistry results were used as gold standard. Cut-off point, $54.00 \mu\text{g}/(\text{l} \times \text{cm}^3)$; AUC, 0.947; AUC standard error, 0.028; and 95% confidence interval, 0.891-1.000. AUC, area under the curve; PRL/V, prolactin/adenoma volume.

There was a significant difference in the median PRL level between group A ($114.71 \mu\text{g/l}$; range, 31.74 - $238.16 \mu\text{g/l}$) and group B ($44.42 \mu\text{g/l}$; range, 18.03 - $220.59 \mu\text{g/l}$) ($P < 0.05$; Table I). In group B, the median PRL level in null cell-, GnH- and plurihormonal-type adenomas was 45.6 (range, 18.03 - 131.12) $\mu\text{g/l}$, 35.3 (range, 19.49 - 126.9) $\mu\text{g/l}$ and 51.17 (range, 21.97 - 220.59) $\mu\text{g/l}$, respectively. The PRL level in

plurihormonal-type adenoma was significantly higher than that in GnH-type adenoma ($P < 0.05$; data not shown). No significant difference was observed between null cell and plurihormonal-type adenomas or between null cell- and GnH-type adenomas ($P > 0.05$; data not shown). The maximum diameter was 15.81 ± 4.93 mm in group A and 29.00 ± 10.97 mm in group B, and the mean volume was $1.58 \pm 2.20 \text{ cm}^3$ in group A and $8.21 \pm 8.53 \text{ cm}^3$ in group B, with a significant difference (Table I). The mean PRL/MD was $7.77 \mu\text{g}/(\text{l} \times \text{mm})$ [range, 1.73 - $17.01 \mu\text{g}/(\text{l} \times \text{mm})$] in group A and $1.70 \mu\text{g}/(\text{l} \times \text{mm})$ [range, 0.45 - $11.59 \mu\text{g}/(\text{l} \times \text{mm})$] in group B, and the mean PRL/V was $107.55 \mu\text{g}/(\text{l} \times \text{cm}^3)$ [range, 5.29 - $360.99 \mu\text{g}/(\text{l} \times \text{cm}^3)$] in group A and $9.15 \mu\text{g}/(\text{l} \times \text{cm}^3)$ [range, 0.68 - $117.50 \mu\text{g}/(\text{l} \times \text{cm}^3)$] in group B, with a significant difference ($P < 0.001$). These results indicated that there were significant differences in the PRL level, PRL/MD and PRL/V between the two groups, which may aid in achieving a differential diagnosis.

Differential diagnosis using symptoms. To determine the differential diagnostic ability of clinical symptoms, hyperprolactinemia symptoms and pituitary adenoma mass effects, these factors were compared between the two groups. There were 24 cases (80.00%) in group A and 22 cases (25.00%) in group B with hyperprolactinemia symptoms, including amenorrhea, lactation, decreased sexual function and fatigue, with significant differences ($P < 0.001$). There were 19 cases (63.33%) in group A and 81 cases (92.05%) in group B with pituitary adenoma mass effects, including headache, dizziness and visual impairment, with significant differences ($P = 0.001$) (Table I). The differential diagnostic ability of hyperprolactinemia symptoms, including amenorrhea, lactation, decreased sexual function and fatigue, was further analyzed by ROC. The results revealed that the diagnostic SE was 0.800 and the SP was 0.750 (data not shown). These results indicated that hyperprolactinemia symptoms alone could not effectively differentiate prolactinomas from other types of pituitary adenomas.

Differential diagnostic potential of PRL. To determine the differential diagnostic potential of PRL, the PRL level was compared between the two groups. The ROC curve of PRL is presented in Fig. 1 [cut-off point, $55.65 \mu\text{g/l}$; AUC, 0.840; AUC standard error, 0.040; and 95% confidence interval (CI), 0.761-0.919]. The SE was 0.800, the SP was 0.716, the PPV was 0.857, the NPV was 0.933 and the YI was 0.516 (Table II). These results indicate that PRL has a high differential diagnostic capacity, however, a number of patients may have been misdiagnosed based upon the low YI.

Table III. PRL/MD differentiation of prolactinoma and other types of pituitary adenoma.

PLR/MD, $\mu\text{g}/(\text{l} \times \text{mm})$	Diagnosis	Group A, n	Group B, n	Total	SE	SP	PPV	NPV	YI
>4.03	Prolactinoma	24	9	33					
≤4.03	Other pituitary adenomas	6	79	85					
Total		30	88	118	0.800	0.898	0.727	0.929	0.698

SE, sensitivity; SP, specificity; PPV, positive predictive value; NPV, negative predictive value; YI, Youden index; PRL/MD, prolactin/adenoma maximum diameter.

Table IV. PRL/V differentiation of prolactinoma and other types of pituitary adenoma.

PRL/V, $\mu\text{g}/(\text{l} \times \text{cm}^3)$	Diagnosis	Group A, n	GroDup B, n	Total	SE	SP	PPV	NPV	YI
>54	Prolactinoma	27	3	30					
≤54	Other pituitary adenomas	3	85	88					
Total		30	88	118	0.900	0.966	0.900	0.966	0.866

SE, sensitivity; SP, specificity; PPV, positive predictive value; NPV, negative predictive value; YI, Youden index; PRL/V, prolactin/adenoma volume.

Table V. AUC comparison of receiver operating characteristic curve of PRL, PRL/MD and PRL/V.

Marker	AUC	Standard error	95% CI	P-value
PRL	0.840	0.040	0.761-0.919	-
PRL/MD	0.920	0.027	0.868-0.972	0.097 ^a
PRL/V	0.947	0.028	0.891-1.000	0.028 ^a

^aCompared with PRL. AUC, area under the curve; CI, confidence interval; PLR, prolactin; PLR/MD, PLR/adenoma maximum diameter; PLR/V, PLR/adenoma volume.

Differential diagnostic potential of PRL/MD. To determine the differential diagnostic potential of PRL/MD, PRL/MD was compared between the two groups. The ROC curve of PRL/MD is presented in Fig. 2 [cut-off point, 4.03 $\mu\text{g}/(\text{l} \times \text{mm})$; AUC, 0.920; AUC standard error, 0.027; and 95% CI, 0.868-0.972]. The SE was 0.898, the SP was 0.727, the PPV was 0.727, the NVP was 0.929 and the YI was 0.698 (Table III). These results suggest that, due to its higher YI, PRL/MD may be more effective than PRL in differentiating prolactinomas from other types of pituitary adenomas.

Differential diagnostic potential of PRL/V. To determine the differential diagnostic potential of PRL/V, PRL/V was compared between the two groups. Group A was considered as a positive case group and group B was considered as a negative case group. The ROC curve of PRL/V is presented in Fig. 3 [cut-off point, 54.00 $\mu\text{g}/(\text{l} \times \text{cm}^3)$; AUC, 0.947; AUC standard error, 0.028; and 95% CI, 0.891-1.000]. The SE was 0.900, the SP was 0.966, the PPV was 0.900, the NVP was 0.966 and the YI was 0.866 (Table IV). These findings

indicate that PRL/V may have the greatest differential diagnostic potential among these three indicators, due to the fact that its YI is the greatest.

Comparison of the differential diagnostic potential of PRL, PRL/MD and PRL/V. To compare the differential diagnostic potential of PRL, PRL/MD and PRL/V, an ROC curve and a Student's t-test were performed. The ROC curves of PRL, PRL/MD and PRL/V are presented in Figs. 1-3, and the AUC comparison is presented in Table V. PRL/MD tended to be more diagnostically accurate than PRL, but without a significant difference ($P=0.097$). PRL/V was of higher diagnostic accuracy compared with PRL, with significance ($P=0.028$). Therefore, PRL/V had a greater potential to differentially diagnose when compared with the PRL level. Furthermore, PRL/MD had a greater potential to differentially diagnose when compared with the PRL level, but without statistical significance.

Discussion

The present study is the first to propose the use of PRL/MD and PRL/V as diagnostic tools to distinguish prolactinoma from other types of pituitary adenomas. The optimal PRL differentiation level was 55.65 $\mu\text{g}/\text{l}$ with a YI of 0.516, the optimal PDL/MD differentiation ratio was 4.03 $\mu\text{g}/(\text{l} \times \text{mm})$ with a YI of 0.698, and the optimal PRL/V differentiation ratio was 54.00 $\mu\text{g}/(\text{l} \times \text{cm}^3)$ with a YI of 0.866. PRL/MD appeared to have a greater diagnostic accuracy than PRL, but with no statistical significance ($P=0.097$), while the greater diagnostic accuracy of the PRL/V compared with that of PRL was statistically significant ($P=0.028$). Therefore, for pituitary adenoma patients with PRL between the upper limit of the normal range and 250 $\mu\text{g}/\text{l}$, PRL/V may be a more efficient tool for differential diagnosis than PRL.

Patients with hyperprolactinemia symptoms were often believed to have prolactinoma with a high rate of misdiagnosis (25). In the present study, there were 24 cases (80.00%) in group A and 22 cases (25.00%) in group B with hyperprolactinemia symptoms, and 19 patients (63.33%) in group A and 81 cases (92.05%) in group B with pituitary adenoma mass effects. Although there were significant differences in clinical symptoms between groups A and B, the use of hyperprolactinemia symptoms in diagnosis led to a high rate of misdiagnosis (SE, 0.800; SP, 0.750).

The PRL level is frequently used for differential diagnosis. In cases where pituitary adenoma was present along with hyperprolactinemia (15), prolactinoma was clinically considered. PRL >500 $\mu\text{g/l}$ was considered to reflect the presence of large prolactinoma (26), and pituitary adenoma with PRL >250 $\mu\text{g/l}$ was considered to indicate likely prolactinoma (27). However, in clinical practice, the optimal PRL level for the differential diagnosis of prolactinoma and other types of pituitary adenoma is far from 250 $\mu\text{g/l}$. Kawaguchi *et al* (28) reported that the optimal PRL level for the differential diagnosis of prolactinoma and non-functioning adenomas was 38.6 $\mu\text{g/l}$, which is substantially lower than 100–200 ng/ml. Karavitaki *et al* (6) demonstrated that the PRL level of non-functional pituitary adenomas did not exceed 2,000 mIU/l (1 $\mu\text{g/l}$ =21.2 mIU/l), and 2,000 mIU/l was considered as the upper PRL limit of non-functional pituitary adenomas. However, Hong *et al* (14) revealed that 5/35 patients with non-functional pituitary adenoma exhibited hyperprolactinemia and a PRL level >100 $\mu\text{g/l}$. A total of 1.3–11.8% non-functional pituitary adenoma patients exhibited a PRL level >100 $\mu\text{g/l}$ (6,14,29). The Europe Endocrine Society recommended that pituitary adenomas with a PRL level >250 $\mu\text{g/l}$ should be diagnosed as prolactinoma (15). The PRL level of patients with secondary hyperprolactinemia caused by pituitary stalk compression was likely between 25–200 $\mu\text{g/l}$ (11,30). Therefore, the gray area (the upper limit of the normal range to 250 $\mu\text{g/l}$) may easily lead to a misdiagnosis. In the present study, the optimal PRL level for differential diagnosis was 55.65 $\mu\text{g/l}$, with an SE of 0.800 and an SP of 0.716. Therefore, a higher diagnostic accuracy is required.

The differentiation between prolactinoma and other types of pituitary adenomas is essential for making decisions regarding treatment. Dopamine agonists, which lead to tumor cell apoptosis and secondary necrosis, are the first line of treatment for prolactinomas (15,31,32). However, bromocriptine should be administered for ≥ 3 months for other types of pituitary adenomas in order to rule out prolactinoma (6). This is not only time-consuming, but may also aggravate adenoma fibrosis (33) and increase surgical risks. Additionally, unnecessary surgery for prolactinoma may increase the financial burden on the patient. In addition to treating prolactinoma, dopamine agonists may also reduce PRL levels in other types of pituitary adenomas with hyperprolactinemia and may relieve hyperprolactinemia symptoms. However, the effects of these drugs on the volume of adenoma remain unclear (9,15). Patients exhibiting GH, TSH or ACTH above the upper normal limits were excluded from the present study.

There are some limitations to the present study. Firstly, for a small portion of the patients, the PRL level, PRL/MD

and PRL/V were not able to accurately differentiate between disease types. Secondly, the sample size was small and data was collected from a single center. Therefore, multi-center and prospective clinical studies are required to further elucidate the role of PRL/MD and PRL/V in the differential diagnosis of adenoma.

In conclusion, serum PRL, PRL/MD and PRL/V were useful in the differential diagnosis of pituitary adenomas. For pituitary adenoma patients with a PRL level between the upper limit of the normal range and 250 $\mu\text{g/l}$, imaging combined with plasma hormone level detection may improve the accuracy of the differential diagnosis. PRL/V may be more accurate for the differential diagnosis than PRL, and the optimal PRL/V ratio in the differentiation of prolactinomas from other types of hyperprolactinemia-causing pituitary adenomas in this study was 54.00 $\mu\text{g}/(\text{l} \times \text{cm}^3)$.

Acknowledgements

The authors would like to thank Dr Qun Zhong (Department of Radiology, Fuzhou General Hospital, Fujian, China) for aiding in the preparation of the original manuscript. The present study was supported by Nanjing Military Region Fuzhou General Hospital Innovation (grant no. 2014CXTD07) and Nanjing Military Region Fuzhou General Hospital Young Talent (grant no. 2014Q32).

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