The Combination of 13N-ammonia and 11C-methionine in Differentiation of Residual/Recurrent Pituitary Adenoma From the Pituitary Gland Remnant After Trans-sphenoidal Adenomectomy

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Abstract

Objective

To assess the usefulness of ^{13}N-ammonia and ^{11}C- Methionine (MET) PET/CT in the differentiation of residual/recurrent pituitary adenoma (RPA) from the pituitary gland remnant (PGR) after trans-sphenoidal adenomectomy.

Patients and Methods

Between June 2012 to December 2019, 19 patients [clinical/MRI suggestion of RPA (14 female and 5 male, mean age: 44.86 ± 15.58 years, range: 18–79 years)] with a history of trans-sphenoidal adenomectomy before PET/CT scans in our department were enrolled in this study. The maximum standard uptake value (SUVmax) of the target and gray matter was measured, and then the T/G ratio was calculated. First, the T/G ratios of RPA and PGR for each tracer were compared by Student *t*-test. Second, the T/G ratios of the two tracers were adopted as multiple variables for canonical discrimination analysis. According to the canonical discriminant function, every patient was classified into one group. A *P* value less than 0.05 was considered statistically significant.

Results

The T/G ratios of ^{13}N-ammonia were significantly higher in PGR than RPA (1.58±0.69 vs 0.63±1.37, P< 0.001), whereas the T/G ratios of ^{11}C-MET were significantly lower in PGR than RPA (0.78±0.35 vs 2.17±0.54, P < 0.001). By the canonical discriminant analysis, we calculated the predicted accuracy of RPA (100%), PGR (92.9%), and the overall predicted accuracy (96.43%).

Conclusions

The combination of ^{13}N-ammonia and ^{11}C-MET PET/CT is valuable in the differentiation of RPA from PGR after trans-sphenoidal adenomectomy.

Background

Accurate localization of residual/recurrent pituitary adenoma (RPA) and its differentiation from pituitary gland remnant (PGR) can promote targeted therapy, increasing the remission rate and maximizing the preservation of pituitary function. Postoperative magnetic resonance imaging (MRI), especially early reexamination, is difficult to interpret because of fluid, hemorrhage, and implanted material[1-3]. Besides, RPA is particularly more difficult to be detected by MRI due to its smaller size compared to primary tumor[3, 4]. Methionine (MET), a substrate for ^{11}C labeling to trace increased protein synthesis, has been a promising PET tracer for the diagnosis of pituitary adenomas with high sensitivity and relatively low uptake of normal brain tissue[5, 6]. According to the previous studies, ^{11}C-MET was superior to somatostatin receptor (SSTR) ligand tracer and ^{18}F-fluorodeoxyglucose (^{18}F-FDG) in the evaluation of pituitary adenomas[5, 7-9]. Our research team previously reported that ^{13}N-ammonia was useful in identifying pituitary tissue[10, 11]. The purpose of this study is to assess the usefulness of ^{13}N-ammonia and ^{11}C-MET PET/CT in the differentiation of RPA from the PGR after trans-sphenoidal adenomectomy retrospectively.

Patients And Methods

Patient

Between June 2012 to December 2019, 19 patients [clinical/MRI suggestion of RPA (14 female and 5 male, mean age: 44.86 ± 15.58 years, range: 18–79 years)] with a history of trans-sphenoidal adenomectomy before the PET/CT scans in our center were enrolled in this study. 3 of them were nonfunctional and 16 of them are secreting [9 patients produced adrenocorticotropic hormone (ACTH), 5 patients produced prolactin (PRL), 1 patient produced growth hormone (GH), and 1 patient produced follicle-stimulating hormone (FSH)]. All patients underwent both ^{13}N-ammonia and ^{11}C-MET PET/CT scans. This study was approved by the hospital ethics committee and the need for signed informed consent was waived.

PET/CT imaging

^{13}N-ammonia and ^{11}C-MET were produced in our department by commercially available systems for isotope generation (Ion Beam Applications, Cyclone-10, Belgium) with standard methods. The radiochemical purity was􏰀99%. PET/CT scans were performed with a Gemini GXL-16 scanner (Philips, Netherlands). Five minutes after intravenous injection of 7.4MBq (0.20mCi)/kg ^{13}N-ammonia or ^{11}C-MET, a 10-min serial PET/CT scan using a brain imaging protocol (matrix: 128 × 128 pixels; slice thickness: 1.5 mm; FOV: 180 mm) started. Images were attenuation-corrected with low-dose CT and reconstructed with the Line of Response RAMLA algorithm. ^{13}N-ammonia and ^{11}C-MET PET/CT were performed with an interval of at least 24 h.

Imaging analysis

(1)Visual analysis

The uptake of the targets was classified into 3 degrees visually compared to the surrounding normal brain tissue: low uptake, moderate uptake, and high uptake.

(2) Semi-quantitative analysis

For each patient, a region of interest (ROI) over the entire target was drawn on the trans-axial plane referred to MRI and computerized tomography (CT) images, and the maximum standardized uptake value (SUVmax) was measured. Then another referenced ROI (about 10 mm in diameter) was drawn on the normal gray matter of the left prefrontal cortex, gaining the target uptake/ gray matter uptake (T/G) ratio.

Statistical analysis

We performed the statistical analysis on SPSS 20.0 software (http://www.ibm.com). First, the T/G ratios of RPA and PGR were compared by Student *t*-test for each tracer. Second, the T/G ratios of the two tracers were adopted as multiple variables in the canonical discrimination analysis. By obtaining the canonical discriminant function, each patient can be successfully classified into one group according to the function result and finally, cross validation was done. A *P* value less than 0.05 was considered statistically significant.

Results

19 patients had histologic confirmation of RPA after repeat surgery. The PGR was identified in 14 patients and cannot be identified by any imaging modality in 5 patients. Of the 14 patients, 8 were determined as normal function, 6 were determined as hypopituitarism. The diameter of RPA ranged from 1.0 to 4.2 cm (mean ± SD, 1.83 ± 0.73 cm).

(1) Visual analysis

For the 19 patients with RPA, 14 (73.68%), 3(15.79%), 2(10.53%) patients were graded as low, moderate, and high uptake respectively on ^{13}N-ammonia PET images and 1 (5.26%), 18 (94.74%) patients were graded as low and high uptake respectively on ^{11}C-MET PET images.

For the 14 patients with PGR, 2 (14.29%), 12 (85.71%) patients were graded as moderate and high uptake respectively on ^{13}N-ammonia PET images and 8 (57.14%), 5 (35.71%), 1 (7.14%) patients were graded as low, moderate and high uptake respectively on ^{11}C-MET PET images.

(2) Semi-quantitative analysis

The T/G ratios of ^{13}N-ammonia were significantly higher in PGR than RPA (1.58±0.69 vs 0.63±1.37, $P <$ 0.001), however, the T/G ratios of ^{11}C-MET were significantly lower in PGR than RPA (0.78±0.35 vs 2.17±0.54, $P <$ 0.001) (Figs. 1, 2, 3). Canonical discriminant analysis with 14 patients whose PRA can be identified showed the optimal discriminant function was F (x, y) =-0.814x +1.820y -1.788, where x represented T/G ratio of ^{13}N-ammonia and y represented T/G ratio of ^{11}C-MET. The function result of RPA was 1.65 ± 1.03, which was significantly higher than that of PGR (-1.65 ± 0.97, $P <$ 0.001). The predicted accuracy of RPA (100%), PGR (92.9%), and the overall predicted accuracy (96.43%) were calculated, respectively. As a result, only 1 PGR was misdiagnosed as RPA (Table 1, Fig. 4).

Table 1 Predicted accuracy of the 2 groups by discriminant analysis

		Predicted Group Membership			
		Group	RPA	PGR	Total
Original	n (%)	RPA	14 (100)	0 (100)	14(100)
		PGR	1 (100)	13(100)	14(100)
Cross-validated	n (%)	RPA	14 (100)	0 (100)	14
		PGR	1 (100)	13(100)	14(100)

Discussion

For patients after trans-sphenoidal pituitary adenomectomy, postoperative follow-up by clinical and imaging methods remains necessary. Considering the morphological complexity of postoperative area, MRI is often unable to distinguish RPA from PGR [12, 13]. PET has been a complementary imaging modality for pituitary adenoma evaluation with different tracers[14]. Our results showed that ^{13}N-ammonia demonstrated higher uptake in the PGR than RPA. In contrast, ^{11}C-MET had higher uptake in the RPA than PGR. Given this, ^{13}N-ammonia PET played a better role in the identification of PGR, whereas the ^{11}C-MET PET seems more useful in the detection of RPA. By accurately locating RPA and PGR, ^{13}N-ammonia and ^{11}C-MET PET can guide the surgery and realize the maximal protection of the pituitary function.

^{13}N-ammonia is not only a good indicator of the blood flow of the pituitary gland, and it is also a potential tracer to indicate the glutamine synthesis metabolism, which has been elaborated already in our previous studies[15-17]. Pituitary tissue exhibited significantly high uptake of ^{13}N-ammonia due to the absence of blood-brain barrier (BBB), high regional cerebral blood flow (CBF), and high capillary permeability surface area product[17]. Besides, glutamine synthetase (GS) activity was confirmed in the anterior lobe of the pituitarium[18]. For displaying the position of pituitary tissue, the ability of ^{13}N-ammonia is comparable to MRI[11]. Surprisingly, ^{13}N-ammonia is also a promising imaging method to reflect the pituitary function. Hypopituitarism showed decreased ^{13}N-ammonia uptake and could be diagnosed in the early stage[10]. 6 patients were diagnosed with hypopituitarism in our study.

The usefulness of ^{11}C-MET PET/CT in identifying pituitary tumors has been reported in previous studies [8, 9, 13, 19]. Furthermore, B. N. T. Tang and Zize Feng reported a high positive rate of ^{11}C-MET PET/CT in recurrent adenomas regardless of the tumor size and the endocrine subgroups[6, 8], which contributed to the efficient management of tumors. RPA was characterized with high amino acid metabolism. The detection rate of ^{11}C-MET was very high in this investigation for RPA (18/19), even in non-functional adenomas. One patient showed low uptake of ^{11}C-MET because of extensive cystic degeneration within the tumor. Conversely, the PGR showed little uptake on ^{11}C-MET images. ^{18}F-FDG, as the most widely used PET radiotracer, was described to be unsatisfactory in the diagnosis of pituitary adenomas(especially recurrent cases) probably because FDG uptake is related to tumor malignancy or aggressiveness rather than hormonal production and secretion[20, 21]. Therefore, ^{11}C-MET is superior to ^{18}F-FDG in detecting RPA with high sensitivity and accuracy. Gender, age, and the menstrual cycle in women can influence the accumulation of ^{11}C-MET in the remaining pituitary tissue. Sometimes, the uptake can be confused and result in false positive results[22].To avoid this phenomenon, the comparison of MRI has been suggested to identify the residual pituitary tissue. In this study, we selected ^{13}N-ammonia to locate the pituitary gland. When ^{13}N-ammonia combined with ^{11}C-MET, the differential accuracy was 96.43%. To our knowledge,^{68}Ga 1,4,7,10-tetraazacyclododecane-N, N’, N”, N’”-tetraacetic acid-D-Phe1, Tyr3-octreotate (DOTATATE), a novel somatostatin analog, can also be applied in the recognition of remaining pituitary tissue. And the accumulation was only lower than the spleen, kidneys, and adrenal glands[23, 24]. Further study should make a comparison between ^{13}N-ammonia and ^{68}Ga- DOTATATE in detecting pituitary tissue.

Conclusions

The combination of ^{13}N-ammonia and ^{11}C-MET PET/CT is valuable in the differentiation of RPA from PGR after trans-sphenoidal adenomectomy.

Abbreviations

RPA：residual/recurrent pituitary adenoma

PGR：pituitary gland remnant

MRI：magnetic resonance imaging

MET：Methionine

SSTR：somatostatin receptor

^{18}F-FDG：^{18}F-fluorodeoxyglucose

GH：growth hormone

ACTH：produced adrenocorticotropic hormone

FSH：follicle-stimulating hormone

ROI：region of interest

CT：computerized tomography

SUVmax：maximum standardized uptake value

BBB：blood brain barrier

CBF：cerebral blood flow

GS：glutamine synthetase

DOTATATE：etraazacyclododecane-N, N’, N”, N’”-tetraacetic acid-D-Phe1, Tyr3-octreotate

Declarations

DISCLOSURE

No potential conflicts of interest relevant to this article exist.

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Figures

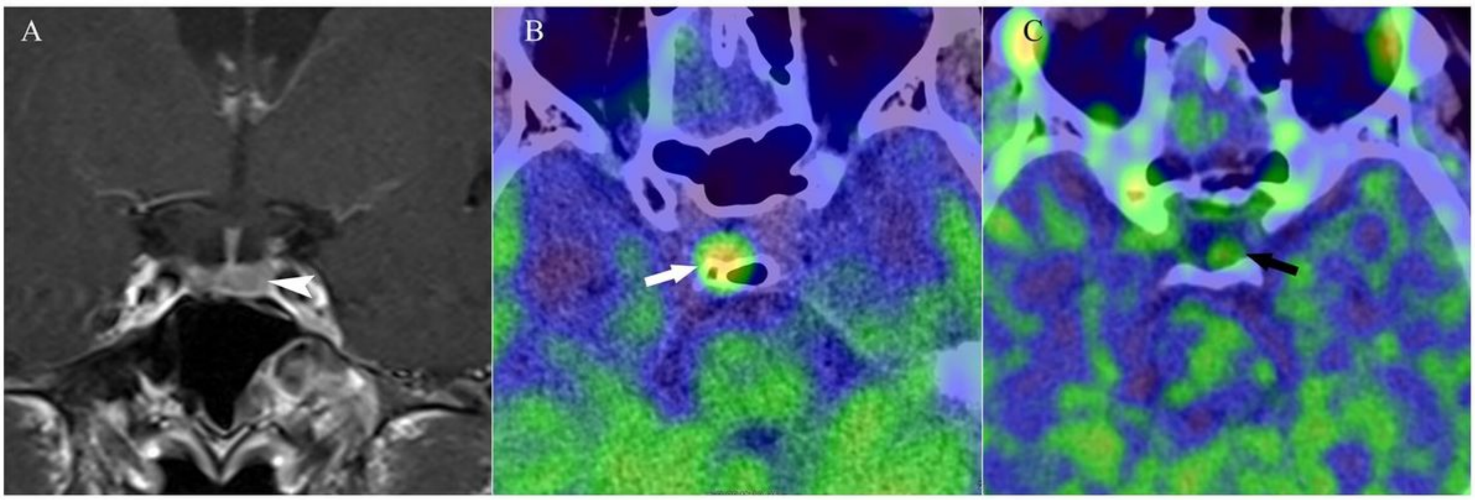

Figure 1

Images of a 20-year-old man with recurrent adrenocorticotropic hormone (ACTH)-secreting pituitary adenoma. T1-weighted contrast-enhanced coronal image showed an adenoma in the left part of the sella (A, arrow head). On 13N-ammonia PET/CT, a hypermetabolic region in the right part of the sella was observed, revealing the pituitary gland remnant with normal function (B, white arrow). On 11C-MET PET/CT, a moderate-metabolic region in the left part of the sella was observed, which was in agreement with the MRI result (C, black arrow).

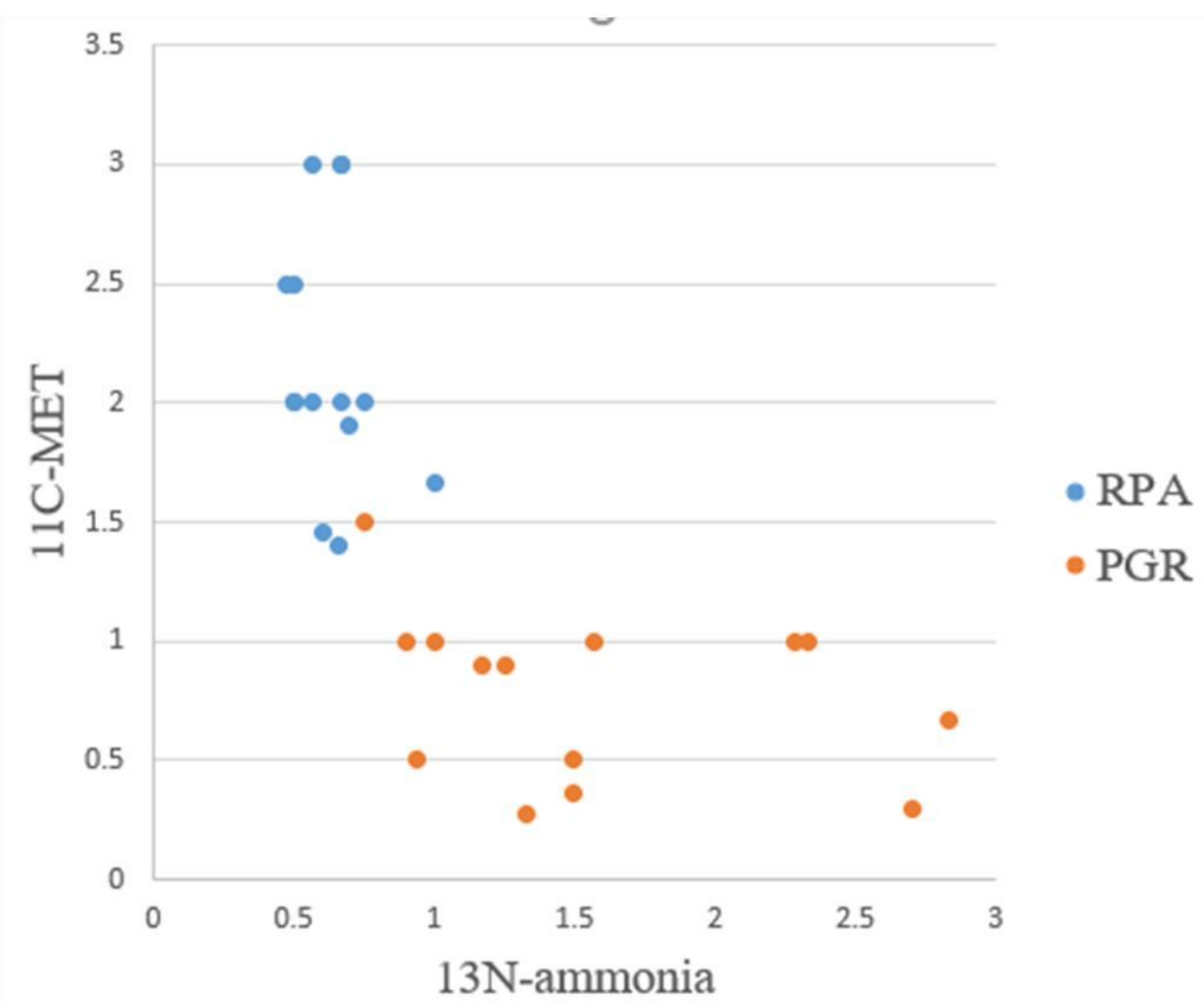

Figure 3

Distribution map of T/G ratios of 13N-ammonia and 11C-MET. As shown in this figure, there was a small overlap between RPA (blue spot) and PGR (red spot).

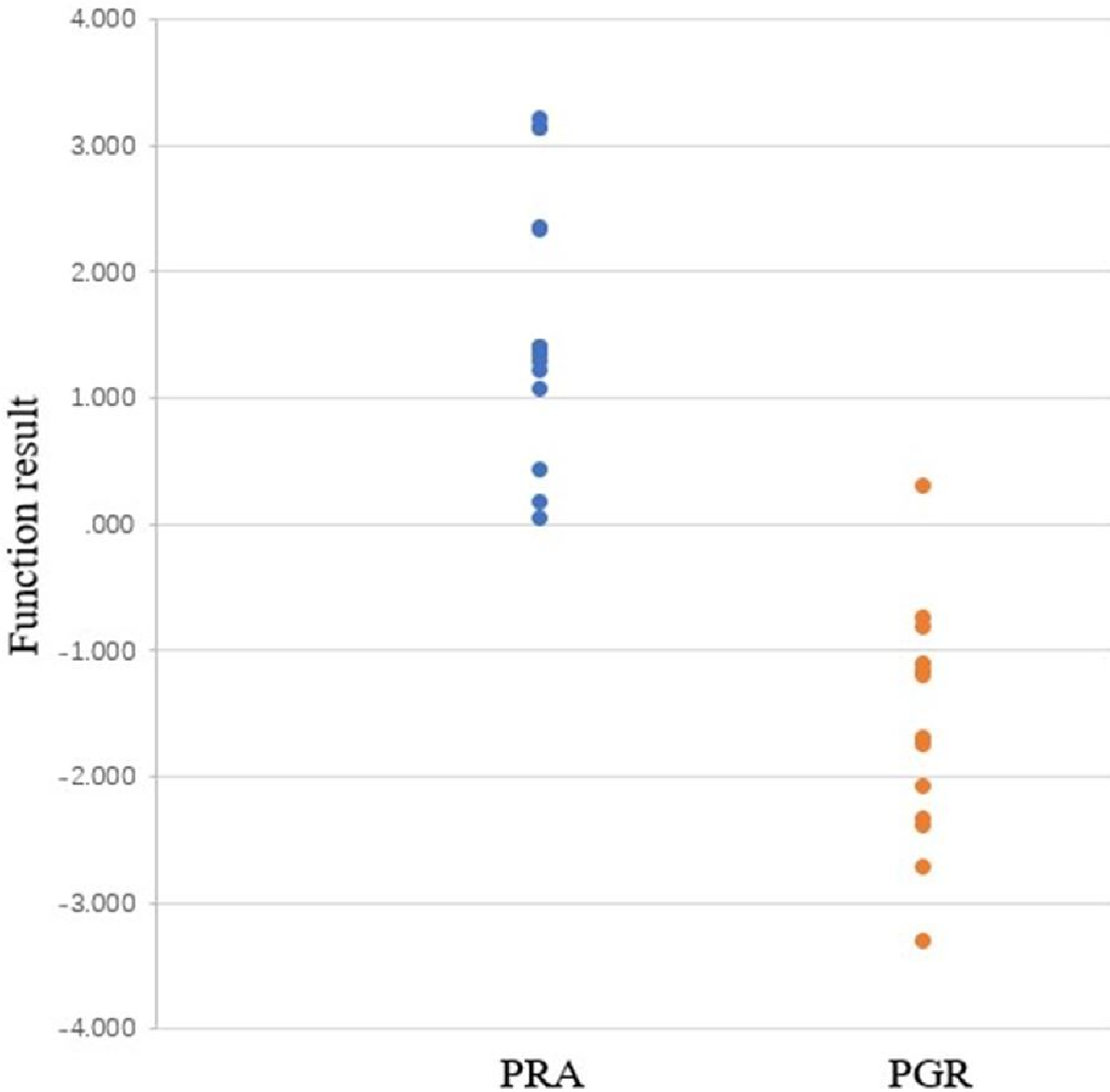

Figure 4

Discriminant function results of the two groups. The function results of RPA were obviously higher than that of PGR (1.65 ± 1.03 vs -1.65 ± 0.97). The combination of the two tracers could distinguish these two clinical entities effectively.