

Original Article

Identification of optimal value of magnetic resonance planimetry and the parkinsonism index for the diagnosis of Parkinson's disease and progressive supranuclear palsy



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Received 24 April 2023; revised 30 May 2023; accepted 10 July 2023; Available online 20 July 2023

المخلص

أهداف البحث: مرض باركنسون والشلل العصبي العُلوي التدرجي هما حالتان عصبية تتدهور وتتشابه في السمات السريرية والتصوير. هذا ينتج عنه صعوبة في تشخيص الشلل العصبي العُلوي التدرجي من مرض باركنسون. لذا، تهدف الدراسة إلى التحقق من القيمة الأمثل للقياس الخطي للرنين المغناطيسي ومؤشر باركنسون الذي يمكن أن يميز بين الشلل العصبي العُلوي التدرجي ومرض باركنسون.

طرق البحث: تضمنت الدراسة الاستيعابية مجموعة من 84 مريضاً، كان 27 مريضاً من كل من الشلل العصبي العُلوي التدرجي، ومرض باركنسون، والمراقبين الطبيعيين الذين خضعوا لفحص الرنين المغناطيسي للدماغ. تم قياس منطقة الجسم الثنائي، ومنطقة الدماغ الوسطى، ومنطقة الجسر، وعرض دماغ العصب القحفي الأوسط وعرض الدماغ القحفي العُلوي على صورة الرنين المغناطيسي للدماغ. تم حساب نسبة منطقة الجسر إلى الدماغ الوسطى، ونسبة عرض دماغ العصب القحفي الأوسط إلى عرض الدماغ القحفي العُلوي ومؤشر باركنسون على الرنين المغناطيسي.

النتائج: تم استخدام تحليل منحني الخصائص التشغيلية للمستقبل لتحديد القيمة التشخيصية لكل علامة حيوية. أظهر مؤشر باركنسون على الرنين المغناطيسي حساسية تبلغ 70.4 %، وتحديدية تبلغ 88.9 %، ودقة تشخيص تبلغ 79.6 % مع قيمة قطع مثلى تبلغ 24.3 للتمييز بين الشلل العصبي العُلوي التدرجي ومرض باركنسون. أظهرت نسبة منطقة الجسر إلى الدماغ الوسطى حساسية تبلغ 74.1

، وتحديدية تبلغ 77.8 %، ودقة تشخيص تبلغ 75.9 % مع قيمة قطع مثلى تبلغ 24.3 للتمييز بين الشلل العصبي العُلوي التدرجي ومرض باركنسون. أظهرت نسبة عرض دماغ العصب القحفي الأوسط إلى عرض الدماغ القحفي العُلوي حساسية تبلغ 66.7 %، وتحديدية تبلغ 77.8 %، ودقة تبلغ 72.2 % مع قيمة قطع مثلى تبلغ 4.65 للتمييز بين الشلل العصبي العُلوي التدرجي ومرض باركنسون.

الاستنتاجات: كشفت الدراسة أن مؤشر باركنسون على الرنين المغناطيسي ونسبة منطقة الجسر إلى الدماغ الوسطى هما علامات دقيقة للتمييز بين الشلل العصبي العُلوي التدرجي ومرض باركنسون وأيضاً يمكن أن تساعد القيم الأمثل المشتقة من دراستنا في التشخيص المبكر لمرض باركنسون.

الكلمات المفتاحية: مرض باركنسون؛ الشلل العصبي العُلوي التدرجي؛ مؤشر باركنسون؛ الرنين المغناطيسي للدماغ؛ القياس الخطي.

Abstract

Objectives: Parkinson's disease (PD) and progressive supranuclear palsy (PSP) are neurodegenerative conditions that have overlapping clinical and imaging features, thus making it difficult to distinguish and diagnose PSP from PD. Therefore, in this study, we aimed to investigate the optimal value of magnetic resonance planimetry and the parkinsonism index to differentiate between PSP and PD.

Methods: In this retrospective study, we recruited a total of 84 patients (27 patients with PSP, 27 patients with PD and 27 normal controls) who underwent MRI brain examinations. For each subject, we calculated the corpus callosum area, midbrain area, pons area, middle cerebellar peduncle (MCP) width and superior cerebellar peduncle (SCP) width on MRI brain images. We also calculated the pons to midbrain area (P/M) ratio, MCP/

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Peer review under responsibility of Taibah University.



SCP ratio and magnetic resonance parkinsonism index (MRPI).

Results: Receiver operating characteristic curve (ROC) analysis was used to identify the diagnostic value of each biomarker. MRPI had a sensitivity of 70.4%, a specificity of 88.9%, and a diagnostic accuracy of 79.6% with an optimum cut off of 24.3 for differentiating PSP from PD. P/M ratio had a sensitivity of 74.1%, a specificity of 77.8%, and a diagnostic accuracy of 75.9% with an optimal cutoff of 24.3 for differentiating PSP from PD. The MCP/SCP ratio had a sensitivity of 66.7%, a specificity of 77.8%, and an accuracy of 72.2% with an optimal cut off of 4.65 for differentiating PSP from PD.

Conclusions: The study revealed that MRPI and P/M ratio are accurate markers for differentiating PSP from PD. The optimal cut-off values derived from our study can help in the early diagnosis of PD.

Keywords: MRI brain; Parkinson's disease; Parkinsonism index; Progressive supra nuclear palsy

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Introduction

Parkinson's disease (PD) is a neurological condition that affects the motor system and causes coordination issues.¹ Progressive Supranuclear Palsy (PSP) is the second most frequent neurodegenerative condition after Parkinson's disease.² Although PSP has its own clinical manifestations, such as vertical gaze palsy, distinguishing PD from PSP can be difficult and lacks sensitivity, particularly in the initial stages of the disease.^{3–7}

Magnetic resonance imaging (MRI) plays a vital role in diagnosing various neurodegenerative diseases.⁷ Due to MRI's high spatial contrast resolution and multiplanar capabilities, it is possible to detect the *in vivo* presentation of a reduction in a substantial portion of structures in the central nervous system (CNS) with a regional distribution pattern; this is the typical finding of many movement disorders.^{8,9} PSP is associated with atrophy of the midbrain and superior cerebellar peduncle (SCP).¹⁰ In PD, however, all of these brain structures are spared.^{9,11} Mid-sagittal MRI can help us to appreciate midbrain atrophy and provides a direct comparison of other parts of the brainstem.¹²

Despite these suggestive characteristics, most clinical results are not clearly evident as there is considerable overlap between PD and PSP.¹³ Due to the lack of typical clinical findings, misdiagnosis is widespread in the early stages of many disorders. Several international studies have been conducted to investigate the accuracy of MRI planimetric measurements and the magnetic resonance parkinsonism index (MRPI) value. However, no previous study has determine the exact optimal cut-off value to differentiate

PSP from PD. Therefore, the main objective of this study was to investigate the optimum value of MRPI and planimetry value for discriminating PSP from PD.

Materials and Methods

This was a retrospective study. The data was collected retrospectively from patients who had undergone MRI of the brain between January 2016 and January 2022; due to the retrospective nature of this study, the need for informed consent was waived. This current study included 27 patients with PD, 27 patients with PSP, and 27 normal controls who had undergone MRI brain studies. The inclusion criteria were subjects with MRI brain images with clinically proven PSP and PD and healthy individuals who had undergone MRI brain studies for the evaluation of headache, but the MRI images reported by the radiologist showed no significant diagnostic abnormalities. Patients were excluded if they had any history of neurodegenerative disease or movement disorders, such as Alzheimer's disease, Huntington's disease, amyotrophic lateral sclerosis, frontotemporal dementia, and spinocerebellar ataxias. The demographic details of patients included age and gender; this information was collected from the hospital medical database.

MRI measurements

All patients had undergone MRI brain examination on a 1.5 T MRI system (Signa HDxt, GE Healthcare). The sequences included T1 weighted sagittal (TR: 340 ms, TE: 8.0 ms, slice thickness: 2 mm and spacing: 2 mm) and T2 weighted coronal (TR: 4480 ms, TE: 110 ms, slice thickness: 2 mm, spacing: 1 mm). The MRI brain images were retrieved from PACS (Picture Archiving and Communication System) and were loaded on a DICOM viewer in InstaRIS PACS Version 5.

The corpus callosum (CC) area, midbrain area, and pons area were measured at the mid-sagittal plane on sagittal T1-weighted MRI images (Figure 1). Using sagittal T1-weighted MR images, we measured the width of the middle cerebellar peduncle (MCP) (Figure 2). In addition, the width of the superior cerebellar peduncle (SCP) was measured on coronal T2-weighted MRI images (Figure 3). The average of the right and left side of the MCP and SCP widths was calculated. The ratio between the pons and midbrain areas, MCP and SCP widths (MCP/SCP), and MRPI, were calculated using the following formula, $MRPI = [\text{pons/midbrain}] \times [\text{MCP/SCP}]$.¹⁴ All measurements were performed manually using a free hand tool by two readers with more than ten years of experience in neuroradiology. The readers were blinded to the diagnosis and performed their measurements at different periods. These values were averaged to provide the final measurement. The method of MRI measurement validity has previously been proven to be excellent with respect to intra- and inter-observer variability.¹⁵

Statistical analysis

SPSS (Statistical Package for Social sciences) version 20.0 was used for statistical analysis. The mean and standard deviation of MRI planimetric measurements and

Parkinson's index for all three groups were calculated. One-way analysis of variance was used to compare the MRI planimetry and parkinsonism index value between the three groups. Receiver operating characteristic curve (ROC) analysis was used to calculate the sensitivity, specificity, accuracy, area under the curve (AUC), and optimum cut off value for P/M, MCP/SCP and MRPI value for differentiating PSP from PD. The Mann–Whitney U test was used for pairwise comparisons between groups (PD vs PSP, PD vs NC and PSP vs NC) and the p-value was determined by Bonferroni correction.

Results

Demographic details

A total of 81 patients were included; these were divided into three groups. Group 1 included 27 patients with PD; Group 2 included 27 patients with PSP, and Group 3 included 27 healthy controls. The demographic details of patients and healthy controls are shown in [Table 1](#).

MRI planimetric measurements and MRPI: group comparisons

One-way analysis of variance was used to compare the MRI planimetric measurements and the Parkinson's index across the three groups. The mean and standard deviation of MRI planimetric measurements and the Parkinson's index for all three groups were calculated and shown in [Table 2](#).

The mean measurements of the corpus callosum and pons did not show any significant difference in mean value ([Figure 5A](#), [Figure 6A](#), [Figure 7A](#)). The midbrain surface area measurements of PSP patients were significantly smaller with a mean of 0.99 cm² ([Figure 5A](#)) when compared to the mean measurements of patients with PD (1.40 cm²) ([Figure 6A](#)) and normal controls (1.99 cm²) ([Figure 7A](#)) ($p < 0.001$) ([Figure 4A](#)). The mean width of the MCP was slightly smaller and more significant in patients with PSP (1.08 cm) ([Figure 5B](#)) when compared to that of PD (1.19 cm) ([Figure 6B](#)) and NC (1.47 cm) ([Figure 7B](#)) ($p < 0.001$) ([Figure 4B](#)). Similarly, the mean

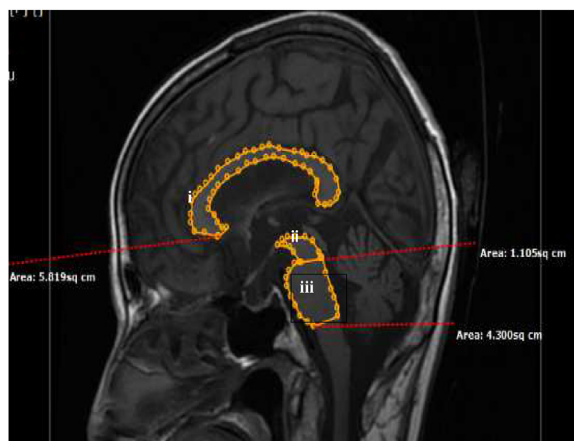


Figure 1: T1-weighted sagittal MRI image showing surface area measurements of the corpus callosum (i), midbrain (ii), and pons (iii).

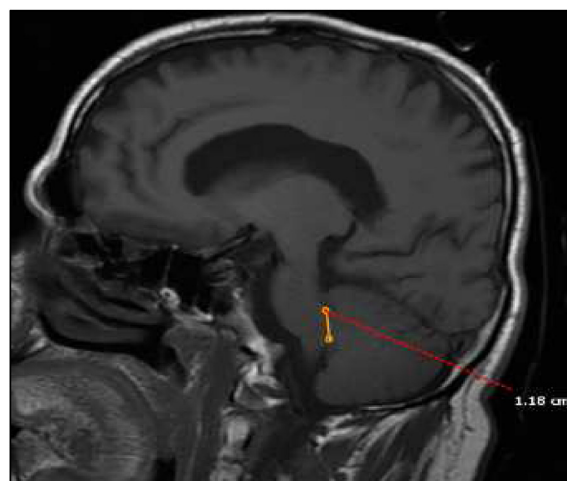


Figure 2: T1-weighted sagittal MRI image showing measurements of the middle cerebellar peduncle (MCP) width.

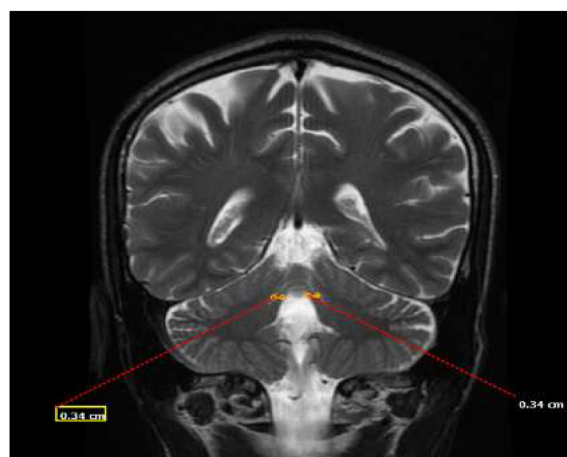


Figure 3: T2-weighted coronal MRI image showing measurements of the right and left superior cerebellar peduncle (SCP) width.

width of the SCP in patients with PSP was significantly smaller with a mean of 0.18 cm ([Figure 5C](#)) when compared to mean measurements of the SCP in patients with PD (mean 0.24 cm) ([Figure 6C](#)) and NC ([Figure 7C](#)) (mean 0.29 cm) ($p < 0.001$) ([Figure 4C](#)). The P/M ratio showed a significant difference ($p > 0.001$) and the mean value was comparably larger in patients with PSP ([Figure 4D](#)). The MCP/SCP ratio did not show statistically significance across the three groups. The MRPI in patients

Table 1: Demographic details of participants.

	PD	PSP	NC
No. of participants (n)	27	27	27
Mean age (years) at evaluation (Mean \pm SD)	68.11 \pm 9.22	67.51 \pm 8.12	67.88 \pm 9.16
Sex			
Male (n)	16	24	11
Female (n)	11	3	16

Table 2: MRI planimetric measurements and MRPI in PSP, PD and normal controls.

MRI measurements	PSP (mean \pm SD)	PD (mean \pm SD)	NC (mean \pm SD)	p value
Corpus Callosum (cm ²)	5.24 \pm 1.06	5.70 \pm 0.88	6.19 \pm 0.84	0.004
Midbrain (cm ²)	0.99 \pm 0.17	1.40 \pm 0.33	1.99 \pm 0.25	<0.001
Pons (cm ²)	4.74 \pm 0.50	5.09 \pm 1.02	5.23 \pm 0.48	0.005
MCP width (cm)	1.08 \pm 0.17	1.19 \pm 0.14	1.47 \pm 0.21	<0.001
SCP width (cm)	0.18 \pm 0.07	0.24 \pm 0.05	0.29 \pm 0.05	<0.001
Pons to midbrain ratio	4.90 \pm 1.07	3.77 \pm 0.89	2.66 \pm 0.39	<0.001
MCP to SCP ratio	6.79 \pm 2.62	5.36 \pm 1.91	5.02 \pm 1.24	0.003
MRPI	32.97 \pm 12.95	20.63 \pm 11.36	13.24 \pm 3.35	<0.001

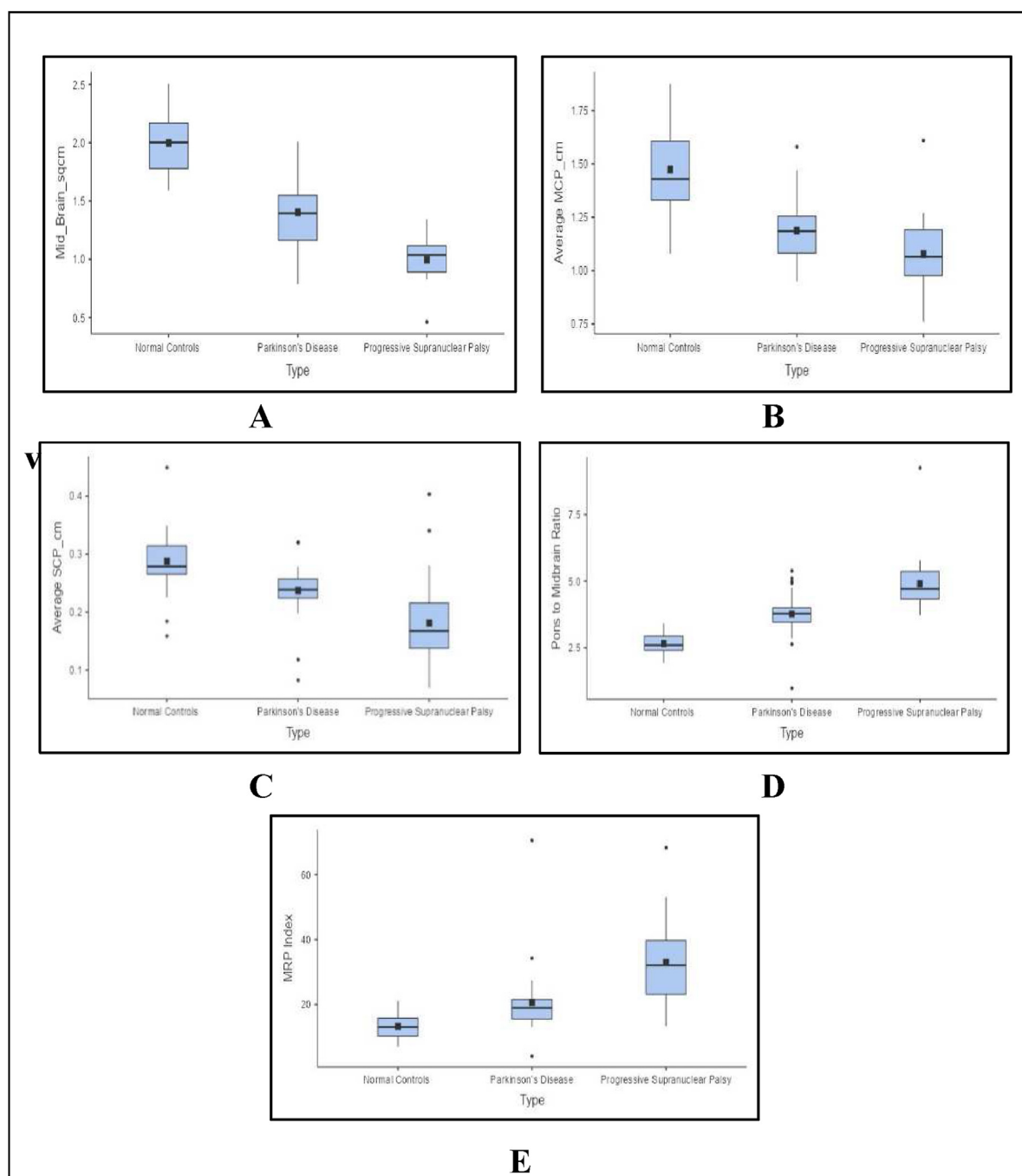


Figure 4: Box plots of MRI planimetric measurements. (A) Midbrain surface area, (B) MCP width, (C) SCP width, (D) Pons to midbrain ratio and (E) MRPI in PSP, PD and NC. Outliers (circles) are defined as cases when the interquartile ranges were more than 1.5 box lengths from the upper or lower box edge.

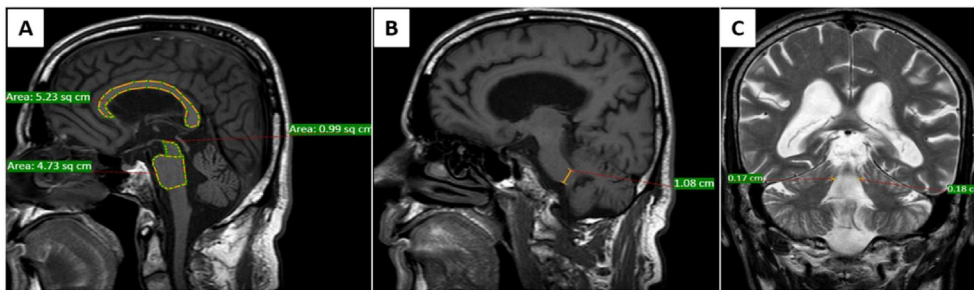


Figure 5: Sagittal T1-weighted MRI image of PSP showing the measurement of (A) corpus callosum area (5.23 cm^2), midbrain area (0.99 cm^2), pons area (4.73 cm^2), (B) MCP width (1.08 cm), (C) coronal T2-weighted MRI image of PSP showing the measurement of right SCP width (0.17 cm) and left SCP width (0.18 cm).

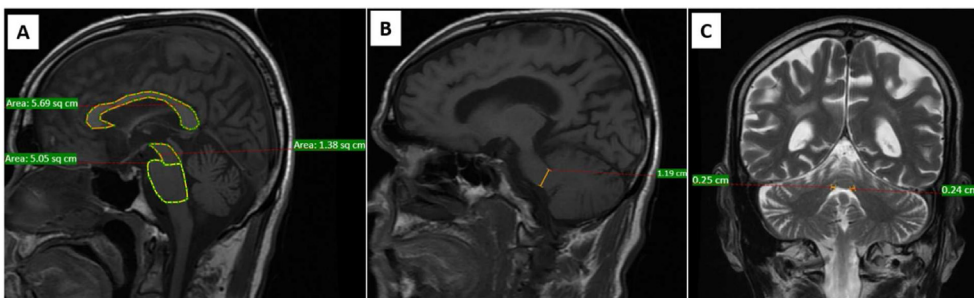


Figure 6: Sagittal T1-weighted MRI image of PD showing the measurement of (A) corpus callosum area (5.69 cm^2), midbrain area (1.38 cm^2), pons area (5.05 cm^2), (B) MCP width (1.19 cm), (C) coronal T2-weighted MRI image of PD showing the measurement of right SCP width (0.25 cm) and left SCP width (0.24 cm).

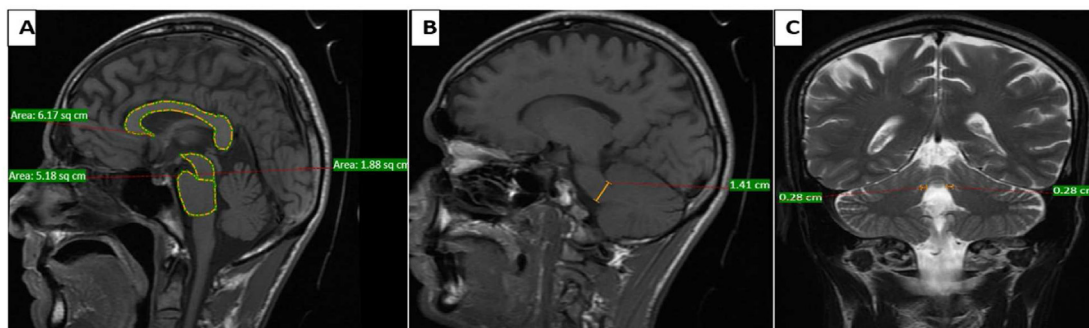


Figure 7: Sagittal T1-weighted MRI image of normal controls showing the measurement of (A) corpus callosum area (6.17 cm^2), midbrain area (1.88 cm^2), pons area (5.18 cm^2), (B) MCP width (1.41 cm), (C) coronal T2-weighted MRI image of normal controls showing the measurement of right SCP width (0.28 cm) and left SCP width (0.28 cm).

with PSP was significantly higher with a mean value of 32.97 compared to patients with PD with a mean value of 20.63 and normal controls with a mean value of 13.244 ($p < 0.001$) (Figure 4E). All measurements showed a minor overlap between the patients with PSP, PD and NC.

MRI planimetric measurements and MRPI: cut off value, sensitivity, specificity, diagnostic accuracy and area under the curve

ROC curve analysis was used to identify the cutoff value, sensitivity, specificity, and diagnostic accuracy of MRI planimetric measurement and MRPI for differentiating

patients with PSP, PD and NC compared with the other groups (Table 3).

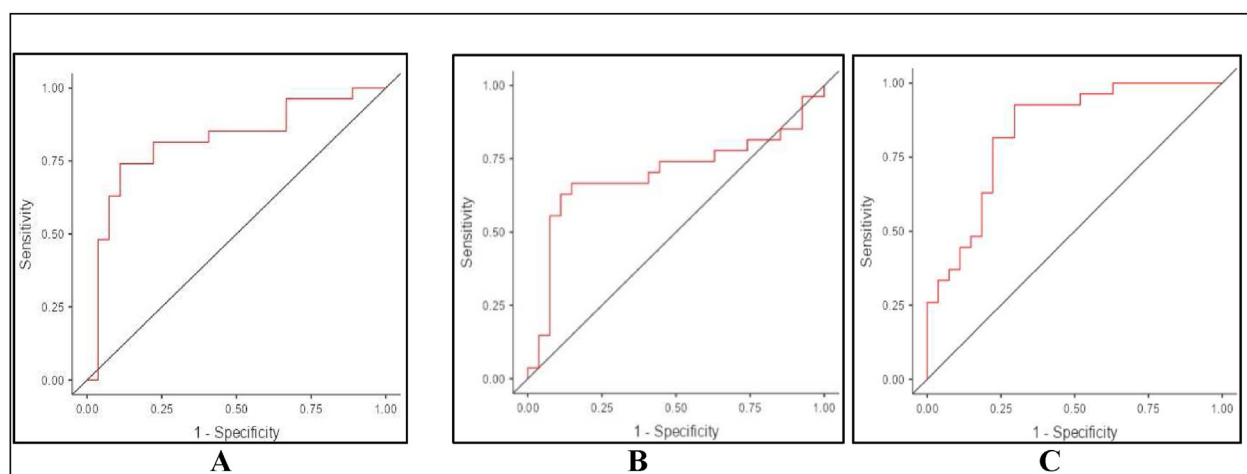
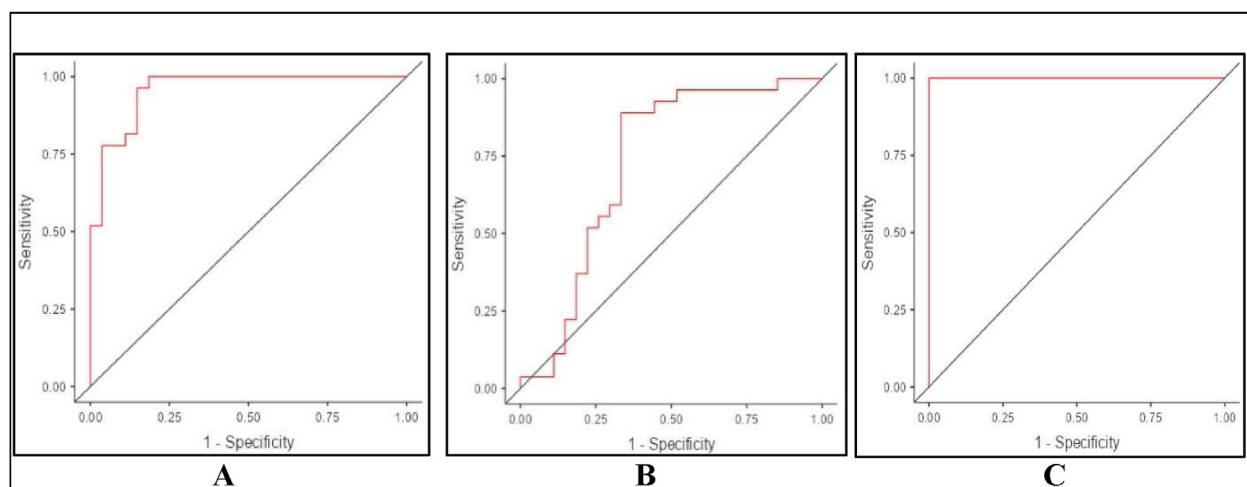
For the differentiation of PSP vs PD, MRPI had a cut off value of 24.3 (sensitivity: 70.4%, specificity: 88.9%, diagnostic accuracy: 79.6% and AUC: 82%), the MCP/SCP ratio had a cut off value of 4.65 (sensitivity: 66.7%, specificity: 77.8%, diagnostic accuracy: 72.2% and AUC: 69.8%), and the P/M ratio had a cut off value of 4.33 (sensitivity: 74.1%, specificity: 77.8%, diagnostic accuracy: 75.9% and AUC: 83.7%) (Figure 8A, B and C). For the differentiation of PSP vs NC, MRPI had a cut off value of 16.15 (sensitivity: 96.3%, specificity: 85.2%, diagnostic accuracy: 90.7% and AUC: 95.7%), the MCP/SCP ratio had a cut off value of 4.66

Table 3: ROC curve analysis of MRI planimetric measurements and MRPI for differentiating PSP vs PD vs normal controls.

	Cut off value	Sensitivity (%)	Specificity (%)	Diagnostic Accuracy (%)	Area under curve (%)
PSP vs PD					
MRPI	>24.3	70.4	88.9	79.6	82
MCP/SCP	>4.65	66.7	77.8	72.2	69.8
P/M	>4.33	74.1	77.8	75.9	83.7
PSP vs NC					
MRPI	>16.15	96.3	85.2	90.7	95.7
MCP/SCP	>4.66	77.8	66.7	72.2	72.8
P/M	>3.56	100	100	100	100
PD vs NC					
MRPI	>15.76	74.1	74.1	74.1	83.4
MCP/SCP	>4.92	55.6	44.4	50.0	54.2
P/M	>3.56	81.5	81.5	81.50	90.9

(sensitivity: 77.8%, specificity: 66.7%, diagnostic accuracy: 72.2% and AUC: 72.8%), and the P/M ratio had a cut off value of 3.56 with 100% sensitivity, specificity, diagnostic accuracy and AUC, respectively (Figure 9A, B and C). For the differentiation of PD vs NC, MRPI had a cut off value of 15.76 with 74.1% sensitivity, specificity and diagnostic

accuracy, respectively (AUC = 83.4%). The MCP/SCP ratio had a cut off value of 4.92 (sensitivity: 55.6%, specificity: 44.4%, diagnostic accuracy: 50% and AUC: 54.2%), while the P/M ratio had a cut off value of 3.56 with 81.5% sensitivity, specificity and diagnostic accuracy, respectively (AUC: 90.9%) (Figure 10A, B and C).

**Figure 8:** ROC curve for differentiating PSP vs PD: MRPI (A), MCP/SCP ratio (B), P/M ratio (C).**Figure 9:** ROC curve for differentiating PSP vs NC: MRPI (A), MCP/SCP ratio (B), P/M ratio (C).

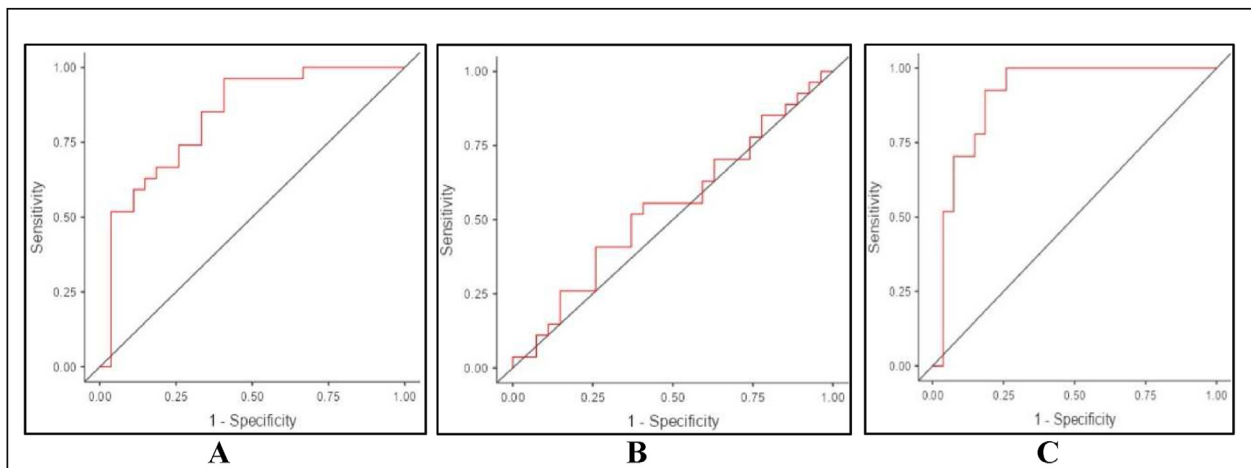


Figure 10: ROC curve for differentiating PD vs NC: MRPI (A), MCP/SCP ratio (B), P/M ratio (C).

Table 4: MRI planimetric measurements and MRPI pairwise comparison between groups.

	Corpus Callosum (cm ²)	Midbrain (cm ²)	Pons (cm ²)	MCP (cm)	SCP (cm)	MCP/SCP ratio	Pons/midbrain ratio	MRPI
PD vs PSP	0.007	<0.001	0.022	0.029	<0.001	<0.001	<0.001	<0.001
PD vs NC	0.017	<0.001	0.193	<0.001	<0.001	0.018	<0.001	<0.001
PSP vs NC	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

MRI planimetric measurements and MRPI: pair wise comparisons

The Mann–Whitney U test was used for pairwise comparisons (PD vs PSP, PD vs NC, and PSP vs NC) of MRI planimetric measurements and MRPI values. Mid brain surface area, SCP width, pons to midbrain ratio and MRPI showed statistical significance between all three groups in terms of pairwise comparisons. However, MCP was significantly different when compared between PD and NC and between PSP and NC but was not statistically significant when compared between PD vs PSP. The corpus callosum and pons were significantly different when compared between PSP and NC (Table 4).

Discussion

The measurements of neurological structures involving PSP and PD showed statistically significant differences, thus representing useful parameters for differential diagnosis. Importantly, increased atrophy was seen in the midbrain (PSP = 0.9971 cm²) (PD = 1.4034 cm²) and SCP (PSP = 0.1811 cm²) (PD = 0.2368 cm²), although there was some overlap in midbrain and SCP measurements in individuals with PSP and PD. A previous study conducted by Nizamani et al. showed that there was a difference between midbrain measurements; however there was no significant difference between SCP measurements due to overlapping of the individual values. This prevented the differentiation of PSP from other groups⁹

In our study, the P/M ratio was increased in patients with PSP with a mean value of 4.90 when compared to patients with PD with a mean value of 3.77. Similar results were obtained by Nizamani et al.⁹ and Longoni et al.¹⁶ Hussl et al.,¹⁰ Morelli et al.¹¹ and Moller et al.¹⁷ previously

calculated the midbrain to pons ratio (M/P ratio) instead of the P/M ratio, in which the mean value of PD was greater than the mean value of PSP. Heim et al. reported that MRPI and the M/P ratio provide good diagnostic accuracy for the differentiation of PSP from multiple system atrophy (MSA).¹⁸ Although the M/P ratio was determined, MRPI was calculated in previous studies by application of the same formula as in our study, thus leading to similar results.

The mean MRPI of PSP patients in the current study was significantly higher at 32.97 when compared to PD patients (20.62) and that of normal controls (13.244). This significant difference between PSP and PD value will play a crucial role in differentiating PSP patients from those with PD. Comparing the results of our study with those from other studies, all previous studies showed a significant difference in MRPI values between PSP and PD patients, thus facilitating differential diagnosis. Longoni et al.¹⁶ reported a mean of 20.7, Hussl et al.¹⁰ reported a mean of 18.63 and Quattrone et al.¹⁹ reported a mean of 24.56. The higher value obtained in our study might be due to the increased atrophy present in PSP patients when compared to other studies.

In the current study, when differentiation PSP from PD, the MRPI had a cut off value of 24.3 with a sensitivity of 70.4%, a specificity of 88.9% and a diagnostic accuracy 79.6%. Quattrone et al.¹⁹ reported higher sensitivity and specificity (100%) with a cut off of 13.55, whereas Constantinides et al.¹⁴ reported 91% and 95% sensitivity and specificity, respectively, with a cut off of 12.6 and an accuracy of 88.5%. Zangini et al.¹ reported a sensitivity and specificity of 87% and 93%, respectively, with a cut off of 10.67. Longoni et al.¹⁶ obtained a sensitivity of 70%, a specificity of 68%, and an accuracy of 40%. In the current study, the MRPI for differentiating PSP and NC showed a higher sensitivity of 96.3% and a specificity of

85.2% with a diagnostic accuracy of 90.65% and a cut-off of 16.15. Therefore, an MRPI value of more than 24.3 will yield a better diagnosis of PSP.

In the current study, the pons to mid brain ratio had a sensitivity of 74.1% and a specificity of 78% for differentiating PSP from PD with a cut-off of 4.33. We obtained 100% sensitivity, specificity, and diagnostic accuracy in discriminating PSP from NC with a cut-off value of 3.56. In a previous study, Zangini et al.¹ concluded that P/M was a better biomarker for the differential diagnosis of PSP from PD. Morelli et al.¹¹ found that P/M was not useful in distinguishing PSP from PD as these authors obtained lower specificity and diagnostic accuracy but obtained a higher sensitivity; this was due to the overlapping individual values. Hussl et al.¹⁰ also reported a lower specificity and diagnostic accuracy and a higher sensitivity although this did not yield any differential diagnosis when correlated clinically.

The ROC analysis of MCP/SCP in patients with PSP and PD obtained a sensitivity of 74.1%, a specificity of 77.8%, and a diagnostic accuracy of 83.7% with a cut-off of 4.65. When differentiating PSP from NC, the sensitivity, specificity, and diagnostic accuracy was 77.8%, 66.7% and 72.85%, respectively, with a cut off of 4.66. However, other studies did not report the sensitivity, specificity and diagnostic accuracy of the MCP/SCP ratio for differentiating PSP from PD.^{16,19} In the current study, there were statistically significant differences in midbrain surface area, P/M ratio, and MRPI ($p < 0.001$) between patients with PSP and PD. MCP was not significant. Similar results were obtained by Hussl et al.,¹⁰ Nizamani et al.,⁹ Longoni et al.,¹⁶ and Kim et al.²⁰

There are some limitations to this study that need to be considered. Firstly, the sample size was considerably small. Secondly, correlation with clinical details was not performed. Therefore, further prospective studies are needed with larger cohorts along with clinical and pathological confirmation.

Conclusion

We found that the optimal values of MRPI, MCP/SCP ratio and P/M ratio for discriminating PSP from PD were 24.3, 4.65 and 4.33, respectively. MRPI and P/M ratio had the highest accuracy for differentiating PSP from PD. The integration of MRPI and planimetry measurements will facilitate early diagnosis.

Source of funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of interest

The authors have no conflict of interest to declare.

Ethical approval

This study was approved by the Institutional Ethics Committee (IEC 419/2021) on 24th of July 2021. The study

was conducted by collecting patient data retrospectively and hence did not require consent from the patients.

Authors' contributions

NS, PK and P conceptualised and designed the study protocol. NS contributed to data collection. Data were analysed and findings were interpreted by NS, PK and P. A preliminary draft of the manuscript was prepared by NS. The manuscript was critically reviewed for its scientific content and relevance by PK and P. The final version of the manuscript was read and approved by all the authors prior to journal submission. All authors have met the recommended criteria by ICMJE for authorship and have contributed effectively to this manuscript. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

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How to cite this article: Shetty N, Koteshwar P, Priyanka. Identification of optimal value of magnetic resonance planimetry and the parkinsonism index for the diagnosis of Parkinson's disease and progressive supranuclear palsy. *J Taibah Univ Med Sc* **2023**;18(6):1577–1585.