

The relation between Parkinson's disease and cardiac sympathetic innervation: role of ¹²³I-MIBG Scintigraphy

Abstract

Background: Cardiac ¹²³I metaiodobenzylguanidine (¹²³I-MIBG) scintigraphy is used for early detection of Parkinson's disease (PD) and distinguishing it from Multiple System Atrophy (MSA). This study aimed to evaluate the role of ¹²³I MIBG in the differential diagnosis of parkinsonian syndromes and to assess the relationships between myocardial MIBG uptake and age, and disease severity.

Methods: This case-control study evaluated 124 participants (62 participants with PD, 32 participants had other neurological disease and 30 participants were negative served as controls) referred to the Nuclear Medicine Department, Dokkyo Medical University, Japan, who underwent ¹²³I MIBG myocardial scintigraphy. A Receiver Operating Characteristic (ROC) test was performed to determine the best cut-off value for MIBG early and MIBG delayed as well as Heart washout rate and H/M.

Results: There was no significant difference (relationship) between the variables (MIBG.early, MIBG.delayed, Heart washout rate, H/M washout rate values) and Modified Hoehn and Yahr (H.Y.). MIBG early (2.12) AUC 0.684 with sensitivity 90%, specificity 60%, accuracy 69.5% and MIBG delayed (1.98) AUC 0.753 with sensitivity 90%, specificity 68%, accuracy 75% as diagnostic tool for distinguishing between Parkinson's participants and controls. Heart washout rate (22.1) AUC 0.817 with sensitivity 90%, specificity 70%, accuracy 84% and H/M washout rate (18.6) AUC 0.837 with sensitivity 90%, specificity 80%, accuracy 87% as diagnostic tool for distinguishing between Parkinson's participants and controls. MIBG early (2.39) AUC 0.813 with sensitivity 87.5%, specificity 71%, accuracy 76.6% and MIBG delayed (2.31) AUC 0.878 with sensitivity 96.9%, specificity 71%, accuracy 79.8% as diagnostic tool for distinguishing between Parkinson's participants and other neurological diseases. Heart washout rate (25.57) AUC 0.812 with sensitivity 82.3%, specificity 68.7%, accuracy 77.7% and H/M washout rate (28.35) AUC 0.873 with sensitivity 82.3%, specificity 84.4%, accuracy 83% as diagnostic tool for distinguishing between Parkinson's participants and other neurological diseases.

Conclusions: MIBG early and MIBG delayed as well as Heart washout rate and H/M washout rate are diagnostic tool to distinguish Parkinson's participants and controls also, in distinguish Parkinson's participants and other neurological diseases. Incorporating these parameters could enhance the accuracy of PD diagnosis, particularly in clinical scenarios where concurrent cardiac disease may confound the diagnosis.

Keywords: Parkinson's disease, ¹²³I MIBG scintigraphy, multiple system atrophy, progressive supranuclear palsy, heart-to-mediastinum, washout rates, sympathetic nervous system

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Abbreviations: ¹²³I MIBG, ¹²³I metaiodobenzylguanidine; APS, atypical parkinsonian syndromes; CBS, corticobasal syndrome; GBS, Guillain-Barré syndrome; H/M, heart to mediastinum ratio; H-Y Grade, Hoehn and Yahr scale; MIBG, metaiodobenzylguanidine; MND, motor neuron disease; MRI, magnetic resonance imaging; MSA, multiple system atrophy; MSA-P, multiple system atrophy-parkinsonian type; PD, Parkinson's disease; PET, positron emission tomography; PSP, progressive supranuclear palsy; SCA, spinocerebellar ataxia; SND, sensory neuron disease; SD, standard deviation; SPECT, single-photon emission computed tomography; SPSS, statistical package for social science; WR, washout rate; REM, rapid eye movement; RBD, REM sleep behavior disorder; HF, high-frequency; MF, mid-frequency; DLB, dementia with Lewy bodies.

Introduction

Parkinson's disease (PD) is a chronic, progressive neurodegenerative disorder clinically characterized by bradykinesia, rigidity, resting tremor, and postural instability with gait impairment.¹ PD typically affects individuals over 50 years of age, with its prevalence increasing significantly with advancing age, particularly up to 80 years. In addition to motor symptoms, PD is frequently accompanied by autonomic dysfunctions, including gastrointestinal disturbances, sudomotor abnormalities, bladder dysfunction, and orthostatic hypotension, which can significantly impact participants' quality of life.²

Differentiating PD from atypical parkinsonian syndromes (APS), such as multiple system atrophy (MSA), progressive supranuclear palsy (PSP), and corticobasal syndrome (CBS), poses a considerable

clinical challenge. MSA is characterized by a combination of autonomic failure, parkinsonism, and cerebellar signs.³ PSP presents with postural instability, early falls, and vertical gaze palsy, while CBS is defined by asymmetrical parkinsonism accompanied by limb dystonia, myoclonus, apraxia, and alien limb phenomena.⁴ Despite their distinct clinical features, overlapping manifestations often complicate diagnosis, even for experienced neurologists and movement disorder specialists.⁵

To enhance diagnostic accuracy, several biomarkers have been investigated, including central dopaminergic depletion assessed via positron emission tomography (PET) or single-photon emission computed tomography (SPECT), peripheral noradrenergic depletion evaluated by ¹²³Imetaiodobenzylguanidine (MIBG) myocardial scintigraphy, α -synuclein biomarkers in cerebrospinal fluid, and structural changes in the substantia nigra using ultrasound or magnetic resonance imaging (MRI).⁶

Iodine-123 meta-iodobenzylguanidine (¹²³I]MIBG), an analogue of norepinephrine, is a tracer for functioning of sympathetic neurons.⁶ ¹²³I]MIBG scintigraphy has emerged as a valuable tool for assessing cardiac sympathetic innervation and autonomic dysfunction. Initially developed to evaluate cardiac conditions such as coronary artery disease, cardiomyopathies, and heart failure, it has recently been applied to neurodegenerative diseases, including PD, to differentiate it from other parkinsonian syndromes.⁷

This study aimed to evaluate the role of ¹²³I MIBG in the differential diagnosis of parkinsonian syndromes and to assess the relationships between myocardial MIBG uptake and age, and disease severity.

Participants and methods

A total of 124 participants who met the inclusion criteria were enrolled in the study. All participants underwent I-MIBG scintigraphy in the Nuclear Medicine Department, Dokkyo Medical University. This case control study comprised 62 participants with PD, 32 participants had other neurological disease and 30 participants were negative served as controls. The other neurological disease group consisted of 12 participants with Multiple System Atrophy (MSA), 4 participants with Progressive Supranuclear Palsy (PSP), 4 participants with SCA, 4 participants had MSA-P, 2 participants with GBS, 2 participants with MND, 2 participants with SND, and 2 participants with cerebral infarction.

All PD participants were diagnosed according to the current MDS criteria, meeting either clinically possible or clinically confirmed definitions for PD.⁸

The diagnosis of PPS participants was established based on relevant consensus guidelines and confirmed by neurology specialists.⁹

Exclusion criteria included: (1) iodine allergies; (2) presence of other neurological disorders that could potentially influence the results, such as Alzheimer's Disease (AD), recent cerebrovascular events within six months, and psychiatric disorders such as depression or mania; (3) organic heart diseases such as heart failure, cardiac insufficiency, coronary artery disease, and malignant arrhythmias; (4) salivary gland diseases such as parotid dysfunction, infection, parotid ductal stones, or other autoimmune diseases that could cause salivary gland dysfunction such as Sjögren's syndrome; (5) abnormal thyroid function tests indicated by abnormal levels of T3, T4, or TSH (T3: 1.3–3.1 nmol/L; T4: 66–181 nmol/L; TSH: 0.27–4.2 mIU/L).

In accordance with previous research,¹⁰ to minimize potential interference with MIBG uptake, all medications such as tricyclic antidepressants, reserpine, decongestants, and calcium channel blockers were discontinued 72 h prior to the examination. These drugs may affect MIBG uptake by inhibiting sodium-dependent uptake systems, interfering with vesicular transport, depleting vesicular storage content, or via calcium ion-related mechanisms. However, participants continued their regular anti-Parkinsonian medications including levodopa, except for MAO-B inhibitors. The patient data involved in this study were derived from previous examination results and clinical records. Informed consent was obtained from each patient. The study strictly adhered to the Declaration of Helsinki and the relevant regulations of the hospital's ethics committee during data collection and analysis.

Clinical evaluation

All participants underwent comprehensive clinical evaluations and examinations by neurology specialists, including routine laboratory tests and brain MRI scans, which were used to rule out other diseases. Collected clinical data included gender, age, and disease duration. For the 124 participants, additional data were gathered, including Hoehn and Yahr (H-Y) staging and scores from the Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS).

I23I-MIBG imaging

We performed ¹²³I-MIBG imaging within 2 weeks after the participants became clinically stable. A dose of 111 MBq of ¹²³I-MIBG (FUJIFILM RI Pharma Co., Ltd, Tokyo, Japan) was administered intravenously with 20 ml saline while the participants were resting in the supine position after an overnight fast. All images were acquired using a 256 x 256 matrix and a dual-head rotating gamma camera equipped with a low energy, high-resolution parallel-hole collimator (eCAM; Siemens Medical Systems, Chicago, IL, USA). Photopeak energy was centered at 159 keV with a 15–20% energy window. Preset time of 5 min was used for image acquisition. Anterior planar imaging was carried out at 15–30 min (early images) and 180–240 min (delayed images) following ¹²³I-MIBG injection. The planar ¹²³I-MIBG images were analysed with a region-of-interest (ROI) technique to obtain quantitative parameters for tracer distribution. Relative organ uptake was determined by setting the region of interest (ROI) on the anterior view. The heart ROI for calculating the Heart-to-Mediastinum (H/M) ratio includes both the left ventricular cavity and the surrounding myocardium (whole cardiac silhouette) was drawn, and a rectangular 9x9 pixel ROI was set on the mediastinum area. The heart to mediastinum ratio (H/M) was calculated by dividing the average counts of the cardiac silhouette ROI by that of the average counts of mediastinum ROI according to the standard method described previously.^{11,12} The ¹²³I-MIBG count densities of the heart (H) and the mediastinum (M) were calculated from the 30- and 240-min images. The heart-to-mediastinum (H/M) ratios of ¹²³I-MIBG uptake at 30 min (early H/M) and 240 min (delayed H/M) were calculated as previously reported. The washout rate (WR) from the myocardium was calculated as $[(H-M) \text{ at } 30 \text{ min} - (H-M) \text{ at } 240 \text{ min}] \times 100 / (H-M) \text{ at } 30 \text{ min} (\%)$. WR was also calculated using half-time correction. According to our database, a delayed H/M ratio of 1.6 or higher and washout 30% or lower are considered normal (Figures 1-3).

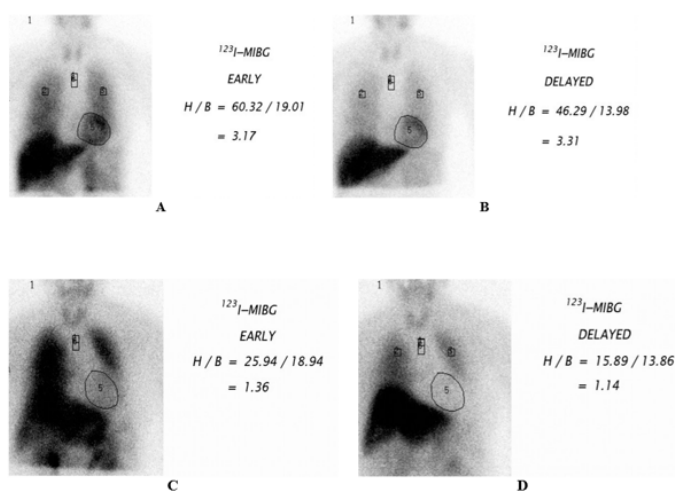


Figure 1 Anterior planar cardiac imaging of ^{123}I -MIBG scintigraphy in normal control (A: Early image and B: Delayed image) and in patient with Parkinson's disease "PD" H-Y stage III (C: Early image and D: Delayed image). Regions of interest enclosing ^{123}I -MIBG uptake were placed in heart "H" and mediastinum background "B". The MIBG uptake of the myocardium in Parkinson's disease "PD" was found to be significantly lower (early H/M ratio of 1.36 and a late H/M ratio of 1.14) than in normal control, both of early and delayed images (early H/M ratio of 3.17 and a late H/M ratio of 3.31).

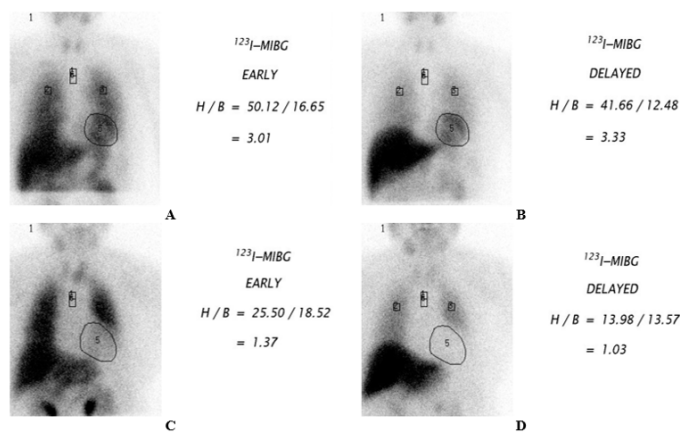


Figure 2 Anterior planar cardiac imaging of ^{123}I -MIBG scintigraphy in normal control (A: Early image and B: Delayed image) and in patient with Parkinson's disease "PD" H-Y stage II (C: Early image and D: Delayed image). Regions of interest enclosing ^{123}I -MIBG uptake were placed in heart "H" and mediastinum background "B". The MIBG uptake of the myocardium in Parkinson's disease "PD" was found to be significantly lower (early H/M ratio of 1.37 and a late H/M ratio of 1.03) than in normal control, both of early and delayed images (early H/M ratio of 3.01 and a late H/M ratio of 3.33).

Data collection and echocardiography

The following data at baseline were collected from medical records: age, gender, hypertension, diabetes mellitus, dyslipidaemia, orthostatic hypotension, constipation, dysuria, Hoehn–Yahr stage, and medications. Hypertension was defined as systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, or treatment with antihypertensive drugs. A sample of venous blood was obtained from the study subjects within 3 days of the day when ^{123}I -MIBG imaging was performed. Diabetes mellitus was defined as fasting plasma glucose ≥ 126 mg/dl, plasma glucose ≥ 200 mg/dl at 2 h postprandial.

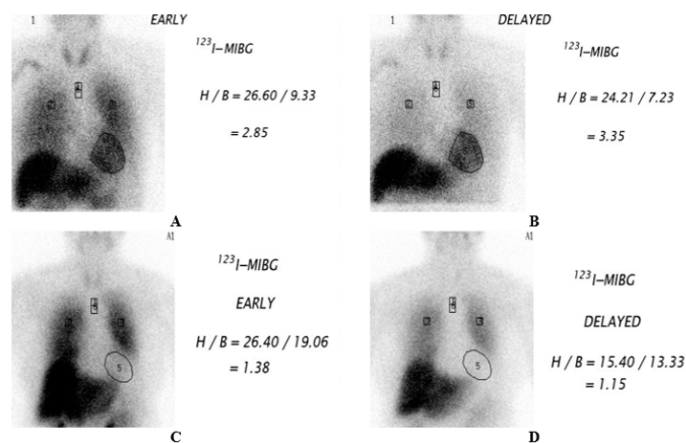


Figure 3 Anterior planar cardiac imaging of ^{123}I -MIBG scintigraphy in normal control (A: Early image and B: Delayed image) and in patient with Parkinson's disease "PD" H-Y stage IV (C: Early image and D: Delayed image). Regions of interest enclosing ^{123}I -MIBG uptake were placed in heart "H" and mediastinum background "B". The MIBG uptake of the myocardium in Parkinson's disease "PD" was found to be significantly lower (early H/M ratio of 1.38 and a late H/M ratio of 1.15) than in normal control, both of early and delayed images (early H/M ratio of 2.85 and a late H/M ratio of 3.35).

The glomerular filtration rate (GFR) was estimated from the modification of diet in renal disease formula.¹³ We performed conventional M-mode and two-dimensional echocardiographic studies using standard techniques within 3 days of the day when ^{123}I -MIBG imaging was performed. Data were gathered from the participants' medical records in our hospital PACS.

Sample size calculations

The sample size for this study was calculated using the OpenEpi online calculator (version 3), with a statistical power of 80% and a significance level (α) of 0.05. Based on the findings of Matsubara et al.,¹⁴ which reported a delayed H/M ratio sensitivity of 80.0% (95% CI: 61.4%–92.3%) and specificity of 92.3% (95% CI: 74.9%–99.1%), the minimum required sample size was estimated at 112 participants. To account for potential dropouts, this was increased to 124 participants, who were then divided into three groups to ensure adequate representation of disease-positive, disease-negative, and control cases.

Statistical analysis

The studied variables were tested for normality using Shapiro-Wilks test. They were expressed in: Number (No), percentage (%), mean (\bar{x}), range and standard deviation (SD). Results were collected, tabulated and statistically analyzed by an IBM compatible personal computer with SPSS statistical package version 27 (SPSS Inc. Released 2020). IBM SPSS statistics for windows, version 27.0, Armonk, NY: IBM Corp.). One way ANOVA (F) test with post hoc test (Bonferroni test) is a test of significance used for comparison of quantitative variables between more than two groups of normally distributed data, while Kruskal Wallis test was used for not normally distributed data. Chi-square test (χ^2) was used to study association among qualitative variables. Correlation test (r-test) was used to test association between quantitative data. Receiver operator characteristic (ROC) curve with respective points of maximal accuracy for sensitivity and specificity were generated. Area under the ROC curve (AUROC) Measures the accuracy of the test. Statistical significance was defined as $P < 0.05$ and < 0.001 was considered statistically highly significant.

Results

This case control study comprised 62 participants with PD, 32 participants had other neurological disease and 30 participants were

negative served as controls. Age was with a mean (\pm SD) value of 67.69 ± 10.03 , range 43-86 years. There were 65 (52.42%) males and 59 (47.58%) females (Table 1).

Table 1 Age and sex distribution among the study groups

	Control (n=30)	Parkinsonism (n=62)	Other neurological diseases (n=32)	Test of significance	P value
Age (years)					
Mean \pm SD	66.50 \pm 10.89	67.77 \pm 10.21	68.81 \pm 8.99	F = 0.41	0.67
Range	45 - 83	43 - 86	54 - 81		
Sex (n %)					
Male	20 (66.7%)	28 (45.25%)	17 (53.1%)	$\chi^2 = 3.76$	0.15
Female	10 (33.3%)	34 (54.8%)	15 (46.9%)		

F= ANOVA test, χ^2 = chi square test

Table 1 shows that P value > 0.05, F and Chi-square X2 tests are low degrees which means very weak/no correlation (relationship) between the variables (age, sex) and the study groups (Control, Parkinsonism, Other neurological diseases) i.e the age and sex categorical distribution are not significantly different between the three study groups.

Regarding clinical disease duration, mean disease duration was 4 years (range 1-12 years). Regarding clinical examination, there were 62 (50%) participants had Parkinsonism, 32 (25.81%) participants had other neurological disease (25.81%, 17 men and 15 women, mean age (\pm SD) 68.81 ± 8.99 , range 54-81 years), 12 (9.68%) participants had MSA, 4 (3.23%) participants had PSP, 4 (3.23%) participants had SCA, 4 (3.23%) participants had MSA-P, 2 (1.61%) participants had GBS, 2 (1.61%) participants had MND, 2 (1.61%) participants had SND, and 2 (1.61%) participants had cerebral infarction). Thirty subjects, who underwent 123 I-MIBG scintigraphy and their results was negative served as controls.

An age and sex-matched group of 30 persons (24.19%, 20 men and 10 women, mean age (\pm SD) 66.50 ± 10.89 , range 45-83 years) who underwent 123 I-MIBG scintigraphy and their results was negative served as the control group. They had no neurological disease and none of them were being treated with drugs or had history of cardiac disease or of a disease that might affect the cardiac autonomic nervous system.

Age was correlated with early and delayed H/M ratio in Parkinson's participants as well as Heart and H/M washout rate (Fig. 4, 5). Figures 4 shows that P value > 0.05, "r" values are negative low degrees which means very weak/no negative correlation (relationship) between the variables (MIBG.early, MIBG.delayed,) and age in Parkinson's participants. While Figure 5 shows that P value > 0.05, "r" values are positive low degrees which means very weak/no positive correlation (relationship) between the variables (MIBG.early, MIBG.delayed, Heart washout rate, H/M washout rate values) and age in Parkinson's participants.

According to Modified Hoehn and Yahr (H.Y.) Scale in Parkinsonism Participants grade III Parkinsonism Participants was the most grade included in our study while grade I and II Parkinsonism Participants were the least grade included in our study (Table 2).

Table 2 Modified Hoehn and Yahr (H.Y.) scale in studied Parkinsonism participants

Modified Hoehn and Yahr (H.Y.) Scale	Study Parkinsonism Patients (N = 62)	%
Grade I	12	19.4
Grade II	12	19.4
Grade III	24	38.7
Grade IV	14	22.6

Table 2 shows that according to Modified Hoehn and Yahr (H.Y.) Scale, grade III Parkinsonism Patients was the most grade included in our study while grade I and II Parkinsonism Patients were the least grade included in our study.

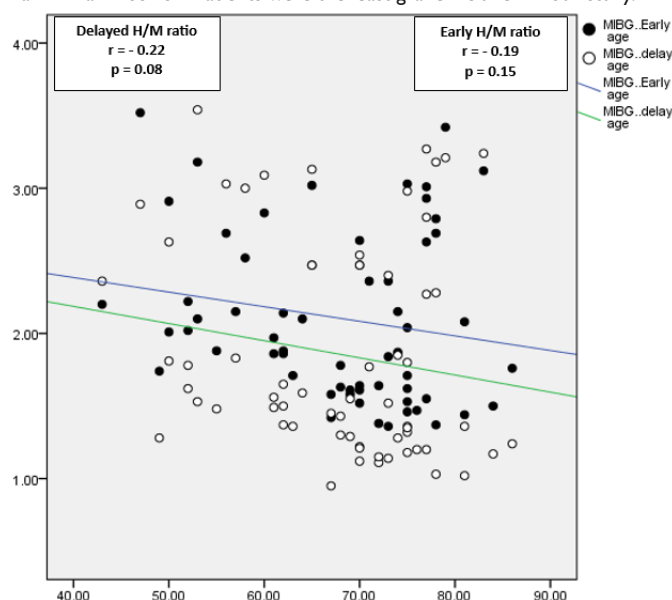


Figure 4 Correlation between early and delayed H/M ratio and age in Parkinson's participants.

Table 3, Figures 6 and 7 shows that P value for MIBG.early is less than 0.05 which is typically considered to be statistically significant in differentiation between the studied groups (Control, Parkinsonism and Other neurological diseases), P value for MIBG.delayed is less than 0.05 which is typically considered to be statistically significant in differentiation between the studied groups, P2 value for Heart washout rate% is 0.48 which is typically considered to be statistically non-significant in differentiation between the study groups (control group and other neurological diseases) nevertheless it is statistically significant in differentiation between the study groups (Parkinsonism and other groups), P2 value for H.M. washout rate% is 0.96 which is typically considered to be statistically non-significant in differentiation between the study groups (control group and other neurological diseases), nevertheless it is statistically significant in differentiation between the study groups (Parkinsonism and other groups).

Table 3 Imaging findings among study groups

	Control (n=30)	Parkinsonism (n=62)	Other neurological diseases (n=32)	P value
MIBG.early				
Mean±SD	2.42 ± 0.37	2.11 ± 0.58	2.76 ± 0.41	<0.001**
Range	1.41 - 2.85	1.36 - 3.52	2.10 - 3.62	P1=0.005* P2=0.005* P3=0.008*
MIBG.delayed				
Mean±SD	2.61 ± 0.56	1.86 ± 0.74	3.01 ± 0.43	<0.001**
Range	1.17 - 3.59	0.95 - 3.54	2.17 - 3.61	P1=<0.001** P2=0.004* P3=<0.001**
Heart washout rate%				
Mean±SD	22.79 ± 10.03	35.92 ± 10.35	23.23 ± 8.69	<0.001**
Range	8.72 - 47.69	11.3 - 54.71	8.57 - 41.11	P1=<0.001** P2=0.48 P3=<0.001**
H/M washout rate%				
Mean±SD	22.26 ± 19.06	52.01 ± 23.83	18.92 ± 13.23	<0.001**
Range	1.68 - 73.08	1.80 - 108.94	1.55 - 42.20	P1=<0.001** P2=0.96 P3=<0.001**
Imaging Conclusion (n "%")				
Negative	27 (90%)	10 (16.1%)	32 (100%)	<0.001**
Positive	3 (10%)	52 (83.9%)	0 (0.00)	P1=<0.001** P2=0.06 P3= <0.001**

**Highly significant difference, * significant difference
 P1= comparison between Parkinsonism group and other neurological diseases
 P2= comparison between control group and other neurological diseases
 P3= comparison between control group and Parkinsonism

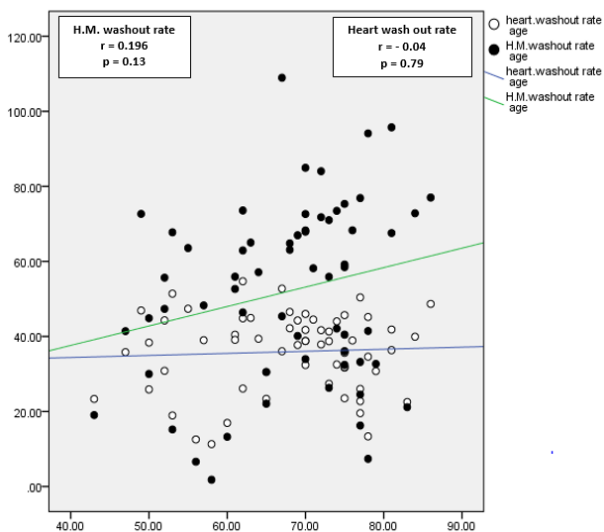


Figure 5 Correlation between Heart and H/M washout rate and age in Parkinson's participants

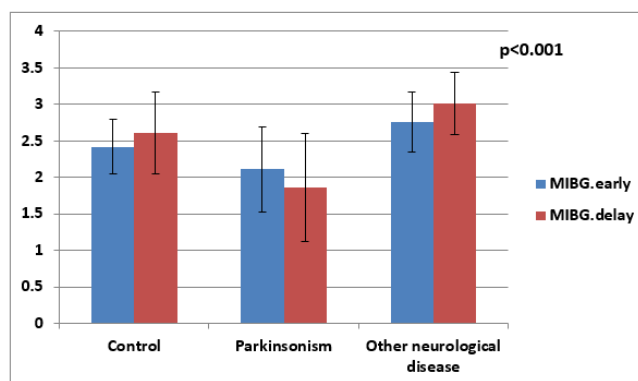


Figure 6 Error bar (mean± SD) of early and delayed MIBG among studied groups.

**Highly significant difference, * significant difference
 P1= comparison between Parkinsonism group and other neurological diseases
 P2= comparison between control group and other neurological diseases
 P3= comparison between control group and Parkinsonism

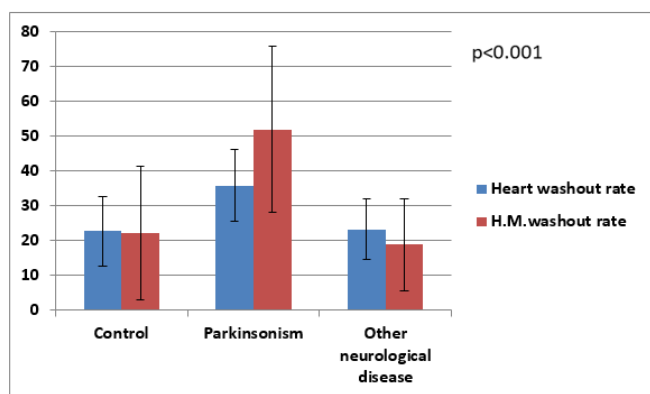


Figure 7 Error bar (mean± SD) of Heart and H/M washout rate among studied groups.

Imaging findings among different Modified Hoehn and Yahr (H.Y.) Scale Stages in Parkinson's participants was observed. Table 4 shows that P value > 0.05 which means no significant difference (relationship) between the variables (MIBG.early, MIBG.delayed,

Heart washout rate, H/M washout rate values) and Modified Hoehn and Yahr (H.Y.) Scale Stages in Parkinson's Participants (Table 4). Figures 8 shows that P value > 0.05 and "r" values are negative low degrees which means very weak/no negative correlation (relationship) between the variables (MIBG.early and MIBG.delayed values) and Modified Hoehn and Yahr (H.Y.) Scale Stages In Parkinson's Participants. Figures 9 shows that P value > 0.05 and "r" values are low positive degrees which means very weak/no positive correlation (relationship) between the variables (Heart washout rate and H/M washout rate values) and Modified Hoehn and Yahr (H.Y.) Scale Stages In Parkinson's Participants (Figure 8 & 9).

A Receiver Operating Characteristic (ROC) test was performed to determine the best cut-off value for MIBG early and MIBG delayed as well as Heart washout rate and H/M washout rate as diagnostic tool to distinguish Parkinson's participants and controls. Figure 10, Tables 5 & 6: A Receiver Operating Characteristic (ROC) curve to determine the best cut-off value of MIBG early (2.12) AUC 0.684 with sensitivity 90%, specificity 60%, accuracy 69.5% and MIBG delayed (1.98) AUC 0.753 with sensitivity 90%, specificity 68%, accuracy 75% as diagnostic tool for distinguishing between Parkinson's patients and controls.

Table 4 Imaging findings among different modified Hoehn and Yahr (H.Y.) scale stages in Parkinson's participants.

	Modified Hoehn and Yahr (H.Y.) Scale in Parkinson's patients (n=62)				P value
	Stage I (n=12)	Stage II (n=12)	Stage III (n= 24)	Stage IV (n=14)	
MIBG.early					
Mean±SD	2.31±0.63	2.09±0.56	2.04±0.61	2.06±0.48	0.51
Range	1.58 - 3.52	1.37 - 3.03	1.36 - 3.42	1.38 - 3.01	
MIBG.delayed					
Mean±SD	2.06±0.72	1.92±0.80	1.80±0.82	1.73±0.58	0.69
Range	1.11 - 3.24	1.03 - 3.09	0.95 - 3.54	1.15 - 3.27	
Heart washout rate					
Mean±SD	34.72±7.79	33.90±13.09	35.44±11.04	39.49±8.41	0.39
Range	22.53 - 48.67	11.30 - 54.71	12.55 - 52.73	19.54 - 50.41	
H/M washout rate					
Mean±SD	48.88±22.23	48.32±28.41	53.85±26.53	54.68±16.83	0.90
Range	19.05 - 84.04	1.80 - 94.12	6.61 - 108.94	16.26 - 76.88	

Table 4 shows that P value > 0.05 which means no significant difference (relationship) between the variables (MIBG.early, MIBG.delayed, Heart washout rate, H.M. washout rate values) and Modified Hoehn and Yahr (H.Y.) Scale Stages in Parkinson's Patients.

Table 5 Area under the curve for MIBG early and MIBG delayed as diagnostic tool to distinguish Parkinson's patients and controls.

	AUC	P value	95% Confidence Interval	
			Lower Bound	Upper Bound
MIBG early	0.684	0.004	0.568	0.800
MIBG delayed	0.753	0.000	0.644	0.861

Table 6 Validity and accuracy for MIBG early and MIBG delayed as diagnostic tool to distinguish Parkinson's patients and controls.

	Cut off point	Sensitivity (%)	Specificity (%)	False positive rate (%)	False negative rate (%)	Accuracy (%)
MIBG early	2.12	90	60	40	10	69.5
MIBG delayed	1.98	90	68	32	10	75

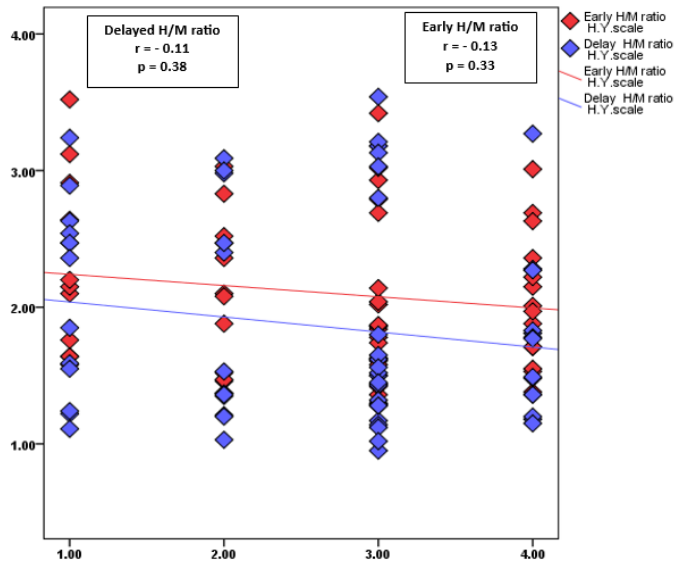


Figure 8 Correlation between early and delayed H/M ratio and H.Y. scale in Parkinson's participants.

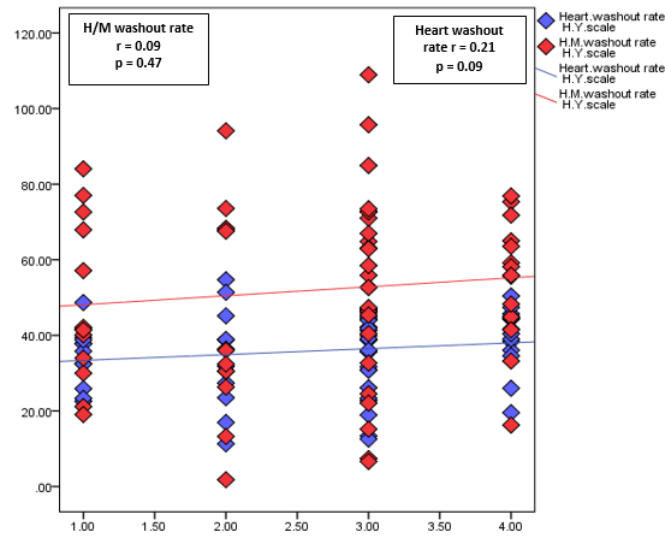


Figure 9 Correlation between heart washout rate and H/M washout rate and H.Y. scale in Parkinson's participants.

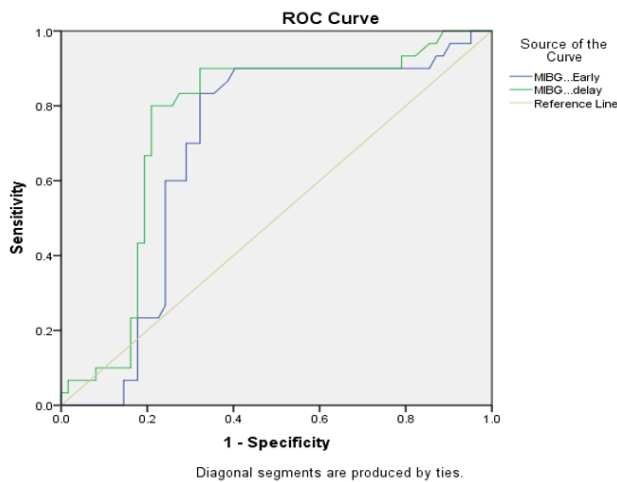


Figure 10 ROC curve showing MIBG early and MIBG delayed as diagnostic tool to distinguish Parkinson's participants and controls.

Figure 11, Tables 7 & 8 portrayed A Receiver Operating Characteristic (ROC) curve to determine the best cut-off value of Heart washout rate (22.1) AUC 0.817 with sensitivity 90%, specificity 70%, accuracy 84% and H/M washout rate (18.6) AUC 0.837 with sensitivity 90%, specificity 80%, accuracy 87% as diagnostic tool for distinguishing between Parkinson's participants and controls (Figure 11, Table 7 & 8).

Figure 11 ROC curve showing Heart washout rate and H/M washout rate as diagnostic tool to distinguish Parkinson's participants and controls.

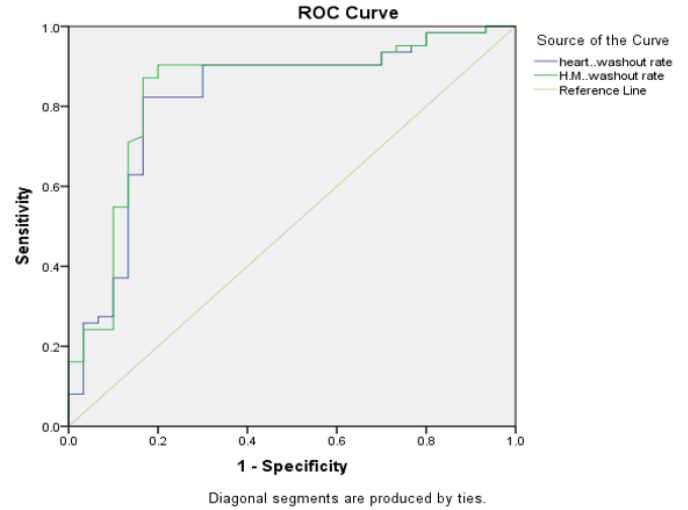


Table 7 Area under the curve for Heart washout rate and H.M. washout rate as diagnostic tool to distinguish Parkinson's patients and controls

	Area under the curve (AUC)	P value	95% Confidence Interval	
			Lower Bound	Upper Bound
Heart washout rate	0.817	<0.001	0.716	0.917
H.M. washout rate	0.837	<0.001	0.741	0.933

A Receiver Operating Characteristic (ROC) test was performed to determine the best cut-off value for MIBG early and MIBG delayed as well as Heart washout rate and H/M washout rate as diagnostic tool to distinguish Parkinson's participants and other neurological diseases. Figure 12, Tables 9 & 10: A Receiver Operating Characteristic (ROC) curve to determine the best cut-off value of MIBG early (2.39) AUC 0.813 with sensitivity 87.5%, specificity 71%, accuracy 76.6% and MIBG delayed (2.31) AUC 0.878 with sensitivity 96.9%, specificity 71%, accuracy 79.8% as diagnostic tool for distinguishing between Parkinson's patients and other neurological diseases.

Table 8 validity and accuracy of Heart washout rate and H.M. washout rate as diagnostic tool to distinguish Parkinson's patients and controls

	Cut off point	Sensitivity (%)	Specificity (%)	False positive rate (%)	False negative rate (%)	Accuracy (%)
Heart washout rate	22.1	90	70	30	10	84
H.M. washout rate	18.6	90	80	20	10	87

Table 9 Area under the curve for MIBG early and MIBG delayed as a diagnostic tool to distinguish Parkinson's patients and other neurological diseases

Test result variable(s)	AUC	P value	95% Confidence interval	
			Lower bound	Upper bound
MIBG early	0.813	0.000	0.729	0.897
MIBG delayed	0.878	0.000	0.810	0.945

Table 10 Validity and accuracy for MIBG early and MIBG delayed as a diagnostic tool to distinguish Parkinson's patients and other neurological diseases

	Cut off point	Sensitivity (%)	Specificity (%)	False positive rate (%)	False negative rate (%)	Accuracy (%)
MIBG early	2.39	87.5	71	29	12.5	76.6
MIBG delayed	2.31	96.9	71	29	3.5	79.8

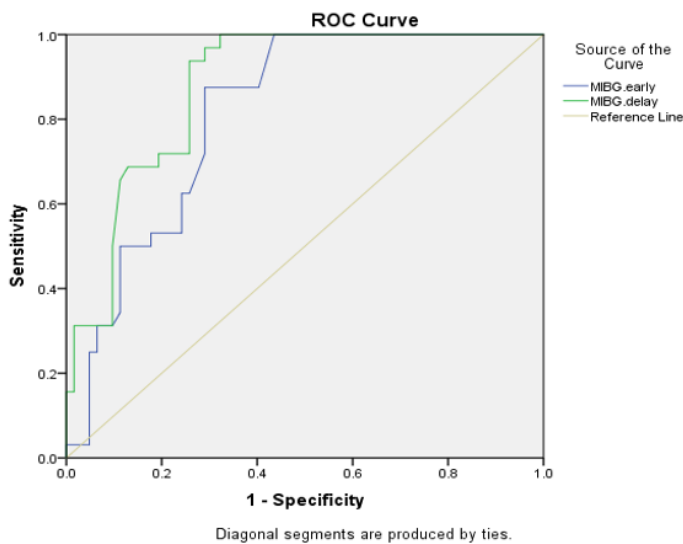


Figure 12 ROC curve showing MIBG early and MIBG delayed as a diagnostic tool to distinguish Parkinson's participants and other neurological diseases.

Figure 13, Tables 11 & 12: A Receiver Operating Characteristic (ROC) curve to determine the best cut-off value of Heart washout rate (25.57) AUC 0.812 with sensitivity 82.3%, specificity 68.7%, accuracy 77.7% and H.M. washout rate (28.35) AUC 0.873 with sensitivity 82.3%, specificity 84.4%, accuracy 83% as diagnostic tool for distinguishing between Parkinson's patients and other neurological diseases.

Table 11 Area under the curve for Heart washout rate and H.M. washout rate as diagnostic tool to distinguish Parkinson's patients and other neurological diseases.

	AUC	P value	95% Confidence interval	
			Lower bound	Upper bound
Heart washout rate	0.812	0.000	0.723	0.901
H.M. washout rate	0.873	0.000	0.804	0.942

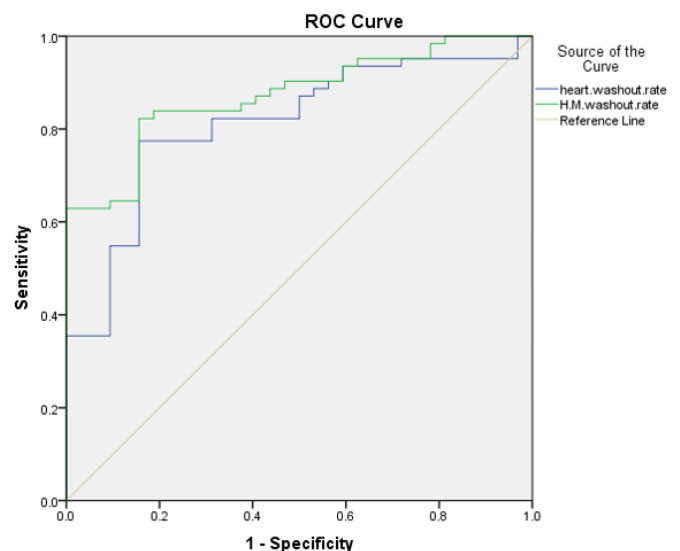


Figure 13 ROC curve showing Heart washout rate and H/M washout rate as diagnostic tool to distinguish Parkinson's participants and other neurological diseases.

Table 12 Validity and accuracy for Heart washout rate and H.M. washout rate as diagnostic tool to distinguish Parkinson's patients and other neurological diseases.

	Cut off point	Sensitivity (%)	Specificity (%)	False positive rate (%)	False negative rate (%)	Accuracy (%)
Heart.Washout rate	25.57	82.3	68.7	31.3	17.7	77.7
H.M. washout rate	28.35	82.3	84.4	15.6	17.7	83

Discussion

Iodine-123 meta-iodobenzylguanidine ($[^{123}\text{I}]\text{MIBG}$) is a radioiodinated analogue of norepinephrine used as a tracer for functioning of sympathetic neurons. $[^{123}\text{I}]\text{MIBG}$ accumulates in storage vesicles of sympathetic nerve pre-synaptic terminals (13B). MIBG competes with norepinephrine for neuronal uptake (uptake one) (13C) and is also taken up by a non-neuronal mechanism (uptake two) (13D). $[^{123}\text{I}]\text{MIBG}$ has been reported to be a useful source of unique information regarding cardiac sympathetic function (13E, 13F). Cardiac MIBG uptake in the early image mainly reflects the density of the presynaptic cardiac sympathetic nerve endings. MIBG is mainly stored in NE vesicles, and is quickly washed out in non-neuronal uptake and almost disappears after 4 h. By contrast, MIBG clearance in neuronal uptake is low, therefore the delayed image also reflects the presynaptic functional tone of the cardiac sympathetic nerves, which is more accurate for the evaluation of the sympathetic nervous system. The delayed H/M ratio combines information on neuronal function from uptake to release through the storage vesicles at the nerve terminals.¹⁵

Accurate diagnosis of PD is important for prognosis and therapy. Our results showed that $[^{123}\text{I}]$ Age was correlated with early and delayed H/M ratio in Parkinson's participants as well as Heart and H/M Hamada et al.¹⁶ supported these findings, reporting a negative correlation between age and H/M ratio in PD participants (early: $r = -0.42$, $P < 0.001$; delayed: $r = -0.44$, $P < 0.001$).

Additional studies further support the association between H/M ratio and disease severity. Orimo et al.¹² reported that lower H/M ratios are associated with more severe PD symptoms, reflecting greater cardiac sympathetic denervation. Carli et al.¹⁷ demonstrated that the H/M ratio is negatively correlated with age, suggesting that older PD participants experience more pronounced cardiac sympathetic denervation, potentially due to the cumulative effects of aging on the autonomic nervous system. Additionally, Gong et al.¹⁸ linked lower H/M ratios to non-motor symptoms such as dysphagia and anxiety, suggesting a potential nondopaminergic mechanism in PD.

Furthermore, Treglia et al.¹⁵ conducted a meta-analysis and analyzed 19 studies comprising 1972 participants. The pooled sensitivity of MIBG scintigraphy in detecting PD was 88% (95% CI 86–90%) and the pooled specificity of MIBG scintigraphy in discriminating between PD and other parkinsonisms was 85% (95% CI 81–88%).

Additionally, Kwon et al.¹⁹ found that while H/M ratio mildly correlates with basal sympathetic nerve activity (as measured by plasma noradrenaline levels), it does not significantly correlate with other autonomic cardiovascular responses. This suggests that MIBG scintigraphy primarily reflects basal sympathetic activity rather than dynamic autonomic responses. However, the study's limitations include a small sample size, and single-center research setting, which may affect the generalizability of the results. Future research should involve larger, multicenter cohorts, longitudinal designs, and standardized imaging protocols to confirm and expand upon these findings, ensuring greater reliability and applicability in clinical practice.

In the present study, MIBG early (2.12) at AUC 0.684 with sensitivity 90%, specificity 60%, accuracy 69.5% and MIBG delayed (1.98) at AUC 0.753 with sensitivity 90%, specificity 68%, accuracy 75% were diagnostic tool for distinguishing between Parkinson's participants and controls. The heart washout rate (22.1) at AUC

0.817 with sensitivity 90%, specificity 70%, accuracy 84% and H/M washout rate (18.6) AUC 0.837 with sensitivity 90%, specificity 80%, accuracy 87% as diagnostic tool for distinguishing between Parkinson's participants and controls.

In our results, MIBG early and MIBG delayed as well as Heart washout rate and H/M washout rate as diagnostic tool to distinguish Parkinson's participants and other neurological diseases.

The uptake of myocardial ^{123}I MIBG serves as a key indicator of the density and functional integrity of postganglionic sympathetic nerve endings. Reduced cardiac ^{123}I MIBG uptake is often employed to differentiate PD from multiple system atrophy (MSA), as postganglionic sympathetic fibers are differentially affected in these conditions¹²⁰. While some studies^{21,22} have linked a lower ^{123}I -MIBG H/M ratio in PD to longer disease duration, autonomic dysfunction, and non-motor symptoms, other research²³ had not corroborated these findings.

The diagnostic utility of MIBG scintigraphy in PD is well-supported. Shafie et al.²⁴ found a statistically significant difference in MIBG uptake between PD and drug-induced parkinsonism (DIP) ($P < 0.001$), with a sensitivity of 84.4% and specificity of 86.36% for diagnosing PD. Similarly, Pitton et al.²⁵ reported that MIBG uptake patterns effectively differentiate PD from MSA, which typically lacks significant cardiac denervation. Catalan et al.²⁶ reinforced this distinction, showing that H/M ratios were lower in PD compared to non-PD and MSA. Their findings also indicated that MIBG scintigraphy is particularly effective in PD participants with dysautonomia, with a second scintigraphy improving diagnostic accuracy by 22%. Additionally, Nuvoli et al.²⁷ confirmed that early and delayed H/M ratios are significantly lower in PD compared to non-PD participants, further emphasizing its diagnostic relevance.

In Parkinson's disease (PD) participants, REM sleep behavior disorder (RBD), characterized by the loss of muscle atonia during REM sleep, is often observed and may be a prodromal marker, meaning it can appear before other motor symptoms of PD. Specifically, a decreased ratio of high-frequency (HF) to mid-frequency (MF) activity (H/M ratio) in the electroencephalogram (EEG) during REM sleep has been associated with Parkinson's disease. This decreased H/M ratio, along with the presence of RBD, can be helpful in the diagnosis of Parkinson's disease, particularly in the early stages.²⁸

Dementia with Lewy Bodies (DLB) is associated with significant dysfunction of the autonomic nervous system, which regulates involuntary functions like heart rate and blood pressure. The sympathetic nervous system, which is assessed by MIBG scintigraphy, is often affected. Studies have shown that decreased H/M ratios in DLB correlate with other clinical features of the disease, such as fluctuating cognition, visual hallucinations, and Parkinsonism.^{29,30}

A decreased H/M ratio on ^{123}I -MIBG myocardial scintigraphy can be also a helpful biomarker in differentiating DLB from other forms of dementia, particularly Parkinson's disease dementia (PDD). This imaging technique assesses the integrity of the sympathetic nerve terminals in the heart, and reduced uptake, reflected in a lower H/M ratio, is characteristic of DLB.³¹ While both DLB and PDD can present with cognitive impairment and motor symptoms, the timing of these symptoms differs. In PDD, cognitive decline typically occurs after the onset of motor symptoms (Parkinsonism), often by a year or more. In DLB, cognitive decline can occur concurrently with or before the onset of motor symptoms. The H/M ratio can help distinguish between these two conditions, as reduced uptake is more pronounced in DLB.³²

In line with our results, Orimo et al.⁷ analyzed 13 studies comprising 845 participants, including 625 participants with PD and 220 participants with other neurodegenerative parkinsonism. The pooled sensitivity in differentiating PD from other neurodegenerative parkinsonisms by a delayed H/M ratio was 89.7% and the specificity was 82.6%; however, when the PD participants were limited to the early stage (H-Y stage I or II), the pooled sensitivity by delayed H/M ratio was as high as 94.1% and the specificity was 80.2%. The authors also analyzed the accuracy of MIBG scintigraphy in differentiating PD from MSA, and found that the sensitivity and specificity were 90.2% and 81.9% respectively. The evidence thus indicates that both the sensitivity and specificity of MIBG myocardial scintigraphy in the diagnosis and differential diagnosis of PD are high.³³

In agreement with our results, Xue et al.³⁴ discusses the value of various parameters in I-123 MIBG scintigraphy for the diagnosis and differential diagnosis of PD. Overall, the 15 min and 4 h H/M ratios, as well as the cardiac WR, demonstrate high diagnostic efficacy in both diagnosis and differential diagnosis. They also showed that PD participants exhibit significantly reduced MIBG uptake compared to MSA or PSP participants.

An autopsy-based pathological study conducted by Matsubara et al.¹⁴ revealed that I-123 MIBG myocardial scintigraphy exhibited a robust diagnostic accuracy in differentiating PD from other similar diseases, demonstrating 70.0% sensitivity and 96.2% specificity for the early H/M ratio, 80.0% sensitivity and 92.3% specificity for the delayed H/M ratio, and 80.0% sensitivity and 84.6% specificity for the washout rate. Additionally, some research suggests that the mild reduction in MIBG uptake in PSP participants may be related to brainstem atrophy.³⁵

Jeong et al.³⁶ evaluated the clinical significance of the washout rate on I-123 MIBG scans through the analysis of the relationship between the I-123 MIBG scans and autonomic status in participants with Parkinson's disease. The WR is related to autonomic dysfunction. An I-123 MIBG cardiac scan is considered to be a good method to evaluate not only the differential diagnosis of Parkinson's disease but also the degree of autonomic dysfunction.

In Adachi et al.³⁷ autopsy-confirmed PSP patient, MIBG uptake was reduced, but pathological results showed that cardiac sympathetic nerves were intact. Thus, although some participants may exhibit decreased H/M ratios, our study indicates that MIBG imaging still holds significant diagnostic value in differentiating PD. However, when clinical presentations are inconsistent, other causes of false positives should also be considered.

Also, Yang et al.³⁸ concluded that I-123 MIBG myocardial scintigraphy can help distinguish participants with PD from those with MSA or ET with good sensitivity and specificity.

It is noteworthy that there is some controversy regarding this aspect of the research. Since the pathology of MSA occurs in the pre-ganglionic sympathetic nerve fibers, despite the severe clinical manifestations of autonomic dysfunction in MSA participants, significant reductions in cardiac MIBG uptake are usually not observed. Some studies have noted that certain MSA and PSP participants may exhibit reduced MIBG uptake, and early H/M ratios may not reliably distinguish PD from PPS.³⁵

Conclusions

MIBG early and MIBG delayed as well as Heart washout rate and H/M washout rate are diagnostic tool to distinguish Parkinson's

participants and controls also, in distinguish Parkinson's participants and other neurological diseases. Incorporating these parameters could enhance the accuracy of PD diagnosis, particularly in clinical scenarios where concurrent cardiac disease may confound the diagnosis.

Finally, we recommended that Alzheimer's disease show no decreased H/M ration that why I-123 MIBG scintigraphy is very useful for differential diagnosis of dementia beside dopamine transporter scintigraphy.

Declarations

Ethics approval and consent to participate

All study techniques involving human subjects adhered to the ethical norms of the institution's research committee and the Declaration of Helsinki and its later revisions. Informed consent to participate in the study is obtained from participants.

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Conflicts of Interest: Nil

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