

The Utility of the Combined Use of ^{123}I -FP-CIT and ^{123}I -MIBG Myocardial Scintigraphy in Differentiating Parkinson's Disease from Other Parkinsonian Syndromes

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ABSTRACT

Background ^{123}I -metaiodobenzylguanidine (MIBG) myocardial scintigraphy and ^{123}I -FP-CIT dopamine transporter single photon emission computed tomography (DAT-SPECT) provide specific information that distinguish Parkinson's disease (PD) from parkinsonian syndromes other than PD (non-PD), including atypical parkinsonian disorder (APD) and non-PD other than APD (nPD-nAPD). The purpose of this study was to determine whether combining DAT-SPECT and MIBG myocardial scintigraphy using multiparametric scoring system (MSS) could improve diagnostic test accuracy in discriminating PD from APD or discriminating PD from nPD-nAPD.

Methods A total of 52 patients, including 36 PD, eight APD and eight nPD-nAPD, underwent both MIBG myocardial scintigraphy and DAT-SPECT, were evaluated. The heart-to-mediastinum (H/M) ratios (early and delayed), washout-rate (WR), the average (Ave) and asymmetry index (AI) of specific binding ratio (SBR) were calculated. Cutoff values were determined, using ROC analysis, for discriminating PD from APD and for discriminating PD from nPD-nAPD, on five parameters. All cases were scored as either 1 (PD) or 0 (nPD-nAPD or APD) for each parameter according to its threshold in each discrimination. These individual scores were summed for each case, yielding a combined score to obtain a cutoff value for the MSS in each discrimination.

Results For discriminating PD from nPD-nAPD, the

highest accuracy was 80% at a cutoff value of 19% for the WR and a cut off value of 2 improved diagnostic accuracy to 84% for MSS. For discriminating PD from APD, the highest accuracy was 86% at a cutoff value of 2.8 for the H/M ratio (late) and a cut off value of 2 showed diagnostic accuracy of 86% for MSS.

Conclusion A MSS has comparable or better accuracy compared to each parameter of MIBG myocardial scintigraphy and DAT-SPECT in distinguishing PD from nPD-nAPD or distinguishing PD from APD.

Key words ^{123}I -FP-CIT; ^{123}I -MIBG; Parkinson's disease; combined analysis

Parkinson's disease (PD) is characterized by the degeneration of both dopaminergic and nondopaminergic neurons with neuronal intracytoplasmic inclusions known as Lewy bodies. Clinically, PD is characterized by resting tremor, muscle rigidity, bradykinesia and postural instability. Clinical differentiation of PD from parkinsonian syndromes other than PD (non-PD), such as atypical parkinsonian disorder (APD), including multiple system atrophy (MSA), progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD), or non-PD other than APD (nPD-nAPD), including vascular parkinsonism and drug-induced parkinsonism, is often difficult because of their overlapping clinical features. Improving diagnostic accuracy is critical for the differentiation of PD and non-PD because their prognoses are very different, and the choice of treatment strategy is extremely important.

Molecular imaging techniques using single photon emission computed tomography (SPECT) or positron emission tomography (PET) offer a variety of tools for diagnosing patients with parkinsonian syndromes.¹⁻³ Dopamine transporter SPECT (DAT-SPECT) using N-v-fluoro-propyl-2b-carbomethoxy-3b-(4- ^{123}I -iodophenyl)nor-tropane (^{123}I -FP-CIT) is a sensitive method for detection of presynaptic dopamine neuronal dysfunction and has presently become an essential method for evaluating parkinsonism.⁴ On the other hand, ^{123}I -metaiodobenzylguanidine (MIBG) myocardial scintigraphy traces uptake and

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Abbreviations: AI, asymmetry index; Ave, average; CBD, corticobasal degeneration, DAT-SPECT, ^{123}I -FP-CIT dopamine transporter single photon emission computed tomography; H/M ratio, heart-to-mediastinum ratio; MIBG, ^{123}I -metaiodobenzylguanidine; MM, mild to moderate; MSA, multiple system atrophy; MSS, multiparametric scoring system; non-PD, parkinsonian syndromes other than PD; PD, Parkinson's disease; S, severe; SBR, specific binding ratio; PSP, progressive supranuclear palsy; ROI, regions of interest; WR, washout-rate

transport both in noradrenaline presynaptic sympathetic nerve terminals and in subsequent vesicular storage. A reduction of MIBG uptake indicates postganglionic sympathetic dysfunction.⁵

DAT-SPECT allows differentiation of degenerative parkinsonian syndromes from nPD-nAPD that are not associated with dopaminergic deficit, such as essential tremor, vascular parkinsonism and drug-induced parkinsonism.⁶ However, DAT-SPECT alone does not differentiate the various types of degenerative parkinsonian syndromes including APD and PD with sufficient accuracy.^{7,8} Whereas, cardiac MIBG uptake is reduced in patients with Lewy body diseases such as PD, as well as dementia with Lewy bodies, and MIBG myocardial scintigraphy can also help to differentiate PD from n-PD.^{9–12}

However, all these molecular imaging techniques are limited in terms of their test accuracy. The use of DAT-SPECT or MIBG myocardial scintigraphy as stand-alone diagnostic mean is currently not recommended for differentiating PD from n-PD.⁸ The usefulness of the combination of DAT-SPECT and MIBG myocardial scintigraphy has been reported in patients with parkinsonian syndrome.^{13–23}

A multiparametric scoring system (MSS) is an original simple method using summed scores obtained by each parameter according to its threshold for discriminating two groups. In our previous studies, MSS has improved accuracy compared to each parameter of multiple physiologic MR studies including diffusion weighted imaging, perfusion weighted imaging, and MR spectroscopy in differentiating tumor progression from radiation change.²⁴ Furthermore, MSS also has improved accuracy compared to each parameter of ¹²³I-FP-CIT dopamine transporter single photon emission computed tomography and Neuromelanin-MRI in differentiating Parkinson's disease from non-degenerative parkinsonian syndrome.²⁵ Therefore, this scoring system can potentially offset an incorrect classification based on any single parameter and is expected to be a more useful indicator than any single parameters.

We performed a retrospective study of patients with parkinsonian syndrome to determine whether combining DAT-SPECT and MIBG myocardial scintigraphy using multiparametric scoring system (MSS) could improve diagnostic test accuracy in discriminating PD from APD or discriminating PD from nPD-nAPD.

MATERIALS AND METHODS

Patients

Fifty-two patients, who underwent both MIBG myocardial scintigraphy and DAT-SPECT for a differential di-

agnosis between PD and other parkinsonian syndromes were consecutively enrolled in this retrospective study, which was evaluated between March 2014 and April 2017. All of 52 patients were confirmed to the results of both MIBG myocardial scintigraphy and DAT-SPECT. Thirty-six of 52 patients were diagnosed with probable PD according to the criteria of the United Kingdom Brain Bank and prospective follow-up including positive response to dopaminergic medications. Patients with PD were assigned to groups either mild to moderate-PD (MM-PD) or severe-PD (S-PD) on the basis of Hoehn and Yahr staging.²⁶ Also, MM-PD comprised stages I and II ($n = 16$), and S-PD comprised stages III, IV and V ($n = 20$). Furthermore, no patients were diagnosed with dementia with Lewy bodies in 52 patients. Eight of 52 patients were diagnosed with APD and eight of 52 patients were diagnosed with nPD-nAPD. APD comprised PSP ($n = 4$), MSA ($n = 3$) and CBD ($n = 1$) and nPD-nAPD comprised Alzheimer disease ($n = 3$), essential tremor ($n = 1$), vascular parkinsonian syndrome ($n = 2$), organophosphorus poisoning ($n = 1$) and folic acid deficiency ($n = 1$). Diagnosis of MSA, PSP or CBD was made based on the accepted diagnostic criteria for each disease.^{27–29} None of the patients had diabetes mellitus or cardiac disease, and none was taking any medication known to influence uptake of ¹²³I-FP-CIT or to affect MIBG accumulation.^{30,31} Clinical characteristics of the four groups; nPD-nAPD, APD, MM-PD and S-PD, are shown in Table 1. The institutional review board of Tottori Prefectural Central Hospital approved this retrospective study (approval number: 2017-8), and the requirement for written informed consent of the participants was waived by the review board due to the retrospective nature of the study.

Image acquisition and analysis

¹²³I-MIBG myocardial scintigraphy

The patient received an intravenous injection of 111 MBq of ¹²³I-MIBG and static planar images of the chest were acquired 30 minutes and 3 hours later for 10 minutes in a 512 × 512 matrix of 0.67 mm pixels by use of a dual-head gamma camera with a low-medium energy, general purpose collimator (Symbia E; Siemens, Erlangen, Germany). Relative organ uptake was determined by setting the regions of interest (ROI) on the anterior view. The heart-to-mediastinum (H/M) ratio was calculated by dividing the count density of the left ventricular ROI by that of the mediastinal ROI. For the comparison study, H/M ratios calculated from the ROI counts both in early and delayed images were used for analysis. In this study, we also calculated washout rate (WR), which is an index of the rate at which MIBG is

Table 1. Clinical characteristics of nPD-nAPD, APD, MM-PD and S-PD patients

	nPD-nAPD	APD	MM-PD	S-PD
Number	8	8	16	20
Age (years), range	65–86	65–83	53–82	62–87
Age (years), mean ± SD	73 ± 8	71 ± 6	66 ± 9	79 ± 8
Female/male	3/5	4/4	8/8	11/9
Hoehn and Yahr stage	/	/	I: 9, II: 7	III: 12, IV: 5, V: 3
Duration (years), mean ± SD	2.3 ± 2.2	3.7 ± 2.1	1.2 ± 1.3	2.4 ± 2.5

APD, atypical parkinsonian disorder; MM, mild to moderate; nPD-nAPD, parkinsonian syndromes other than PD or APD; PD, Parkinson's disease; S, severe.

washed out between the early image and the delayed image, according the following equation;

$$WR = [(early\ heart\ uptake - early\ mediastinum\ uptake) - (delayed\ heart\ uptake - delayed\ mediastinum\ uptake)] / (early\ heart\ uptake - early\ mediastinum\ uptake) \times 100\ (%)$$

DAT-SPECT imaging

The patients received an intravenous injection of 167 MBq of ¹²³I-FP CIT, and SPECT images of the head were acquired 3 hours later for 20 min (2.5 min × 8 repeats × 1 cycle) in a 128 × 128 matrix of 2.7-mm pixels by use of a dual-head gamma camera with a low-medium energy, general purpose collimator (Symbia E; Siemens, Erlangen, Germany). SPECT images were reconstructed with the iterative algorithm; the ordered subset expectation maximization and specific binding ratio (SBR) were defined as the uptake ratio of (striatum-whole brain)/ whole brain by using DatView (Nihon Medi-Physics, Tokyo, Japan) based on Tossici-Bolt's method.³²

The average of SBR (Ave-SBR) was calculated using the following equations;

$$Ave-SBR = (right\ SBR + left\ SBR) / 2 \times 100[\%].$$

The asymmetry index of SBR (AI-SBR) was also calculated using the following equations:

$$AI-SBR\ (absolute\ value) = (right\ SBR - left\ SBR) \times 2 / (right\ SBR + left\ SBR) \times 100[\%].$$

Statistical analysis

Differences among four groups; nPD-nAPD, APD, MM-PD and S-PD groups in the H/M ratio (early), H/M ratio (delayed) and WR on MIBG myocardial scintigraphy were statistically analyzed using the Kruskal-Wallis test followed by the Mann-Whitney *U* test. Furthermore, difference among four groups in the Ave-SBR and AI-SBR (absolute value) on DAT SPECT were statistically

analyzed using the same test.

Evaluations of five parameters for two statistical discriminations

We statistically evaluated two statistical discriminations; the discrimination of PD group (MM-PD group plus S-PD group) from nPD-nAPD group and the discrimination of PD group from APD group. In each statistical discrimination, cutoff values that provided the best combination of sensitivity and specificity for each parameter were selected using receiver operating characteristic (ROC) analysis. Cutoff values were determined using the Youden index. We determined the accuracy, sensitivity, specificity, positive predictive value, and negative predictive value of each parameter using Chi-square analysis. Also, as described below, both MSS and simple combined analysis were performed in each of the two statistical discriminations.

Evaluations of MSS for two statistical discriminations

For two statistical discriminations; discriminating PD from nPD-nAPD and PD from APD, we used all five parameters, including H/M ratio (early), H/M ratio (delayed), WR, Ave-SBR and AI-SBR. For discriminating PD from nPD-nAPD, all cases were scored as either 1 (PD) or 0 (nPD-nAPD) for each parameter according to its threshold. For discriminating PD from APD, all cases were scored as either 1 (PD) or 0 (APD) for each parameter according to its threshold. In each of the two discriminations, these individual scores were summed for each subject, yielding a combined score for each case. ROC analysis was performed to obtain a cutoff value for the scoring system in each of the two discriminations. Finally, we calculated the accuracy, sensitivity, specificity, positive predictive value, and negative predictive value of the MSS using Chi-square analysis in each of the two discriminations.

Evaluations of simple combined analysis for two statistical discriminations

For two statistical discriminations, we adapted a parameter with the best accuracy in each DAT-SPECT (Ave-SBR and AI-SBR) and MIBG myocardial scintigraphy [H/M ratio (early), H/M ratio (delayed) and WR] respectively; total two parameters were selected in each of the two discriminations. Combined analysis using two parameters, according to their thresholds, was performed in each of the two statistical discriminations. Finally, we calculated the accuracy, sensitivity, specificity, positive predictive value, and negative predictive value of the combined analysis using Chi-square analysis in each of the two discriminations.

All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria).³³ $P < .05$ was considered indicative of a significant difference.

RESULTS

H/M ratio (early), H/M ratio (delayed), WR, Ave-SBR and AI-SBR in nPD-nAPD, APD, MM-PD and S-PD are shown in Table 2. Scatterplots of all these parameters are shown in Fig. 1.

For the H/M ratio (early), H/M ratio (delayed) and WR, significant differences were observed among the 4 groups; nPD-nAPD, APD, MM-PD and S-PD groups. Significant differences were observed between nPD-nAPD and S-PD and between MM-PD and S-PD in H/M ratio (early and delayed) and WR. For the Ave-SBR, significant differences were observed among the 4 groups. Significant differences were observed between MM-PD and S-PD. For the AI-SBR (absolute value), no significant differences were observed among the 4 groups.

Evaluations of five parameters for two statistical discriminations

As for discriminating PD from nPD-nAPD, ROC analyses showed that for the H/M ratio (early), the accuracy was 68% at a cutoff value of 2.1. For the H/M ratio (delayed), the accuracy was 70% at a cutoff value of 1.9. For the WR, the accuracy was 80% at a cutoff value of 19%. For the Ave-SBR, the accuracy was 70% at a cutoff value of 4.29%. For the AI-SBR, the accuracy was 59% at a cutoff value of 16.9%. The accuracy, sensitivity, specificity, positive predictive value and negative predictive value of each adapted parameter in differentiating PD from nPD-nAPD are summarized in Table 3.

As for discriminating PD from APD, ROC analyses showed that for the H/M ratio (early), the accuracy was 82% at a cutoff value of 2.51. For the H/M ratio (delayed), the accuracy was 86% at a cutoff value of 2.8. For the WR, the accuracy was 80% at a cutoff value of 22%. For the Ave-SBR, the accuracy was 57% at a cutoff value of 3.31%. For the AI-SBR, the accuracy was 77% at a cutoff value of 21.8%. The accuracy, sensitivity, specificity, positive predictive value and negative predictive value of each adapted parameter in differentiating PD from APD are summarized in Table 4.

Evaluations of MSS for two statistical discriminations

For the evaluation of MSS, we used five parameters, including H/M ratio (early), H/M ratio (delayed), WR, Ave-SBR and AI-SBR.

As for discriminating PD from nPD-nAPD, the scoring of each adapted parameter is shown in Table 3. For the MSS, the accuracy for discriminating PD from nPD-nAPD was 84% at a cutoff value of 2; PD diagnosis was indicated by total score 2, 3, 4 or 5 and nPD-nAPD diagnosis was indicated by total score 0 or 1. The accuracy, sensitivity, specificity, positive predictive value and negative predictive value of MSS in differentiating

Table 2. The parameters in nPD-nAPD, APD, MM-PD and S-PD

	nPD-nAPD range (median)	APD range (median)	MM-PD range (median)	S-PD range (median)	P value (Kruskal-Wallis Test)
MIBG					
H/M ratio (E)	2.13–4.43 (2.51)	1.56–3.82 (2.83)	1.53–3.27 (2.31)	1.18–3.27 (1.66)	$P < 0.001$
H/M ratio (D)	1.98–5.18 (2.66)	1.28–4.45 (3.12)	1.23–3.42 (2.24)	1.03–3.42 (1.59)	$P < 0.001$
WR (%)	1.9–31.7 (16.1)	4.5–79.4 (32.9)	10–78.4 (27.9)	9.6–93.7 (49)	$P < 0.001$
DAT-SPECT					
Ave SBR (%)	0.59–8.46 (6.15)	1.33–5.72 (3.87)	2.48–7.34 (4.65)	1.52–6.01 (2.59)	$P < 0.005$
AI SBR (%)	3.5–29.2 (5.88)	1.8–82.7 (27.25)	1.68–37.4 (17.35)	0.4–56.78 (16.47)	$P = 0.133$

AI, asymmetry index; APD, atypical parkinsonian disorder; Ave, average; D, delayed; DAT-SPECT, ¹²³I-FP-CIT dopamine transporter single photon emission computed tomography; E, early; H/M, heart to mediastinum; ¹²³I-FP-CIT, N-v-fluoro-propyl-2β-carbomethoxy-3β-(4-¹²³I-iodophenyl)nortropane; MIBG, ¹²³I-metaiodobenzylguanidine; MM, mild to moderate; nPD-nAPD, parkinsonian syndromes other than PD or APD; PD, Parkinson's disease; S, severe; SBR, specific binding ratio; WR, washout rate.

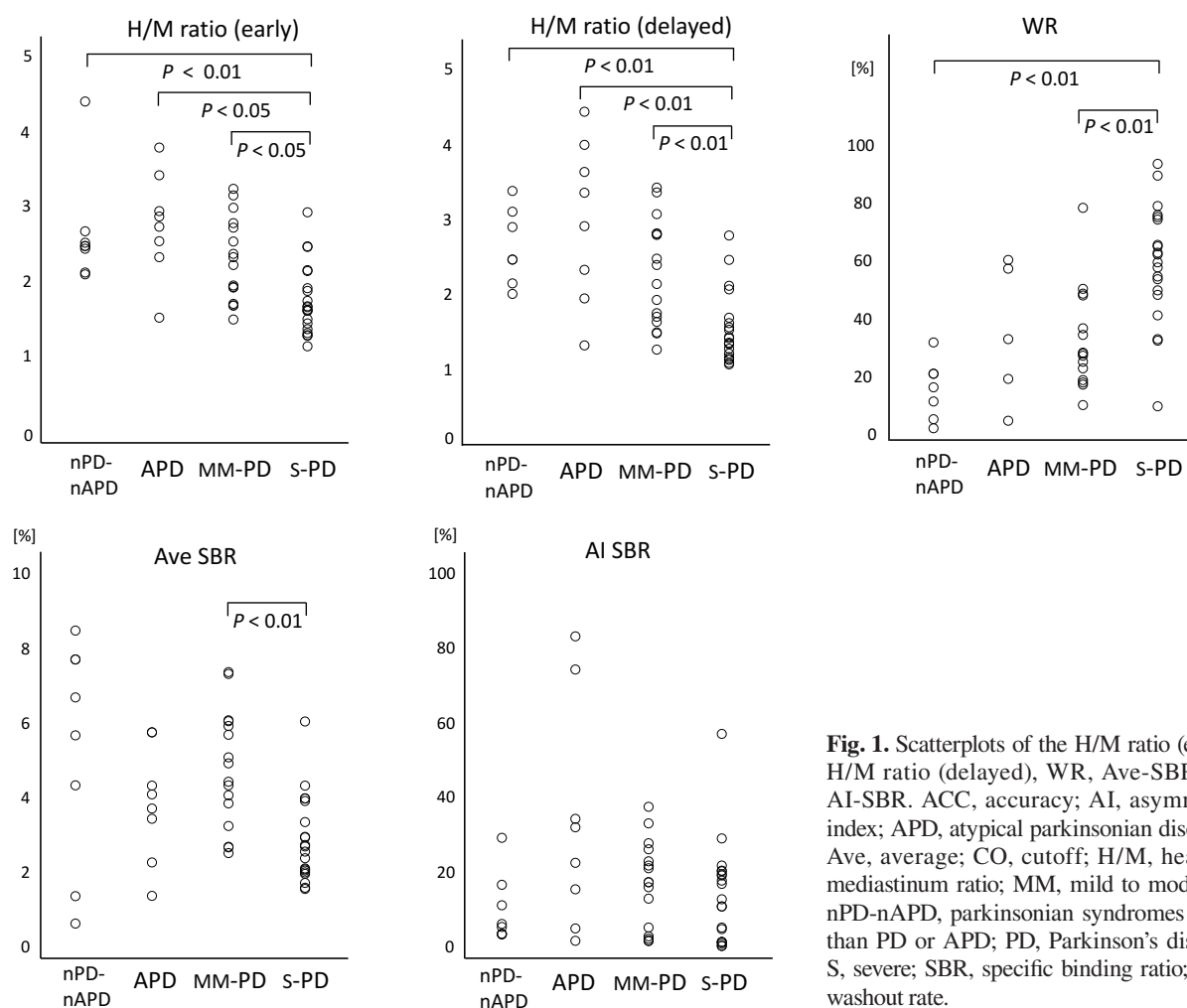


Fig. 1. Scatterplots of the H/M ratio (early), H/M ratio (delayed), WR, Ave-SBR and AI-SBR. ACC, accuracy; AI, asymmetry index; APD, atypical parkinsonian disorder; Ave, average; CO, cutoff; H/M, heart to mediastinum ratio; MM, mild to moderate; nPD-nAPD, parkinsonian syndromes other than PD or APD; PD, Parkinson's disease; S, severe; SBR, specific binding ratio; WR, washout rate.

Table 3. The diagnostic tests of each adapted parameter, of a MSS and of a simple combined analysis for discriminating PD from nPD-nAPD

	AUC	Cutoff value	ACC	SEN	SPE	PPV	NPV	P value	Classified as PD	Classified as nPD-nAPD
MIBG										
H/M ratio (E)	0.78	2.1	68%	61%	100%	100%	36%	$P < 0.001$	≤ 2.1 : score 1	> 2.1 : score 0
H/M ratio (D)	0.84	1.9	70%	64%	100%	100%	38%	$P < 0.001$	≤ 1.9 : score 1	> 1.9 : score 0
WR	0.89	19%	80%	83%	63%	91%	45%	$P < 0.001$	$\geq 19\%$: score 1	$< 19\%$: score 0
DAT-SPECT										
Ave-SBR	0.68	4.29%	70%	69%	75%	93%	86%	$P < 0.05$	$\leq 4.29\%$: score 1	$> 4.29\%$: score 0
AI-SBR	0.58	16.9%	59%	53%	88%	95%	29%	$P = 0.05$	$\geq 16.9\%$: score 1	$< 16.9\%$: score 0
MSS	0.9	2	84%	83%	88%	97%	54%	$P < 0.001$	score 2, 3, 4, 5	score 0, 1
SCA	NA	WR 19% Ave-SBR 4.29%	70%	64%	100%	100%	38%	$P < 0.001$	\geq WR 19% and \leq Ave-SBR 4.29%	$<$ WR 19% or $>$ Ave-SBR 4.29%

ACC, accuracy; AI, asymmetry index; AUC, area under the curve; Ave, average; D, delayed; DAT-SPECT, ^{123}I -FP-CIT dopamine transporter single photon emission computed tomography; E, early; H/M, heart to mediastinum ratio; ^{123}I -FP-CIT, N-v-fluoro-propyl-2b-carbomethoxy-3b-(4- ^{123}I -iodophenyl)nortropine; L, late; MIBG, ^{123}I -metaiodobenzylguanidine; MSS, multiparametric scoring system; NA, not applicable; nPD-nAPD, parkinsonian syndromes other than PD or APD; NPV, negative predictive value; PD, Parkinson's disease; PPV, positive predictive value; SBR, specific binding ratio; SCA simple combined analysis; SEN, sensitivity; SPE, specificity; WR, washout rate.

H/M ratio (E) scoring: H/M ratio (E) ≤ 2.1 , score 1; H/M ratio (E) > 2.1 , score 0. H/M ratio (D) scoring: H/M ratio (D) ≤ 1.9 , score 1; H/M ratio (D) > 1.9 , score 0. WR scoring: WR $\geq 19\%$, score 1; WR $< 19\%$, score 0. Ave-SBR scoring: Ave-SBR $\leq 4.29\%$, score 1; Ave-SBR $> 4.29\%$, score 0. AI-SBR scoring: AI-SBR $\geq 16.9\%$, score 1; AI-SBR $< 16.9\%$, score 0. MSS: Total score 2, 3, 4 or 5, classified as PD; Total score 0 or 1, classified as nPD-nAPD. SCA: \geq WR 19% and \leq Ave-SBR 4.29%, classified as PD; $<$ WR 19% or $>$ Ave-SBR 4.29%, classified as nPD-nAPD.

Table 4. The diagnostic tests of each adapted parameter, of a MSS and of a simple combined analysis for discriminating PD from APD

	AUC	Cutoff value	ACC	SEN	SPE	PPV	NPV	P value	Classified as PD	Classified as nPD-nAPD
MIBG										
H/M ratio (E)	0.80	2.51	82%	83%	75%	94%	50%	$P < 0.001$	≤ 2.51 : score 1	> 2.51 : score 0
H/M ratio (D)	0.81	2.8	86%	92%	63%	92%	63%	$P < 0.001$	≤ 2.8 : score 1	> 2.8 : score 0
WR	0.80	22%	80%	83%	63%	91%	45%	$P < 0.001$	$\geq 22\%$: score 1	$< 22\%$: score 0
DAT-SPECT										
Ave-SBR	0.54	3.31%	57%	53%	75%	90%	26%	$P = 0.25$	$\leq 3.31\%$: score 1	$> 3.31\%$: score 0
AI-SBR	0.70	21.8%	77%	81%	63%	91%	42%	$P < 0.05$	$\leq 21.8\%$: score 1	$> 21.8\%$: score 0
MSS	0.86	2	86%	92%	63%	92%	63%	$P < 0.001$	score 2, 3, 4, 5	score 0, 1
SCA	NA	H/M ratio (D) 2.8 AI-SBR 21.8%	80%	78%	88%	97%	47%	$P < 0.001$	\leq H/M ratio (D) 2.8 and \leq AI-SBR 21.8%	$>$ H/M ratio (D) 2.8 or $>$ AI-SBR 21.8%

ACC, accuracy; AI, asymmetry index; APD, atypical parkinsonian disorder; AUC, area under the curve; Ave, average; D, delayed; DAT-SPECT, ^{123}I -FP-CIT dopamine transporter single photon emission computed tomography; E, early; H/M, heart to mediastinum ratio; ^{123}I -FP-CIT, N-v-fluoro-propyl-2b-carbomethoxy-3b-(4- ^{123}I -iodophenyl) nortropine; L, late; MIBG, ^{123}I -metaiodobenzylguanidine; MSS, multiparametric scoring system; NA, not applicable; NPV, negative predictive value; PD, Parkinson's disease; PPV, positive predictive value; SBR, specific binding ratio; SCA, simple combined analysis; SEN, sensitivity; SPE, specificity; WR, washout rate.

H/M ratio (E) scoring: H/M ratio (E) ≤ 2.51 , score 1; H/M ratio (E) > 2.51 , score 0. H/M ratio (D) scoring: H/M ratio (D) ≤ 2.8 , score 1; H/M ratio (D) > 2.8 , score 0. WR scoring: WR $\geq 22\%$, score 1; WR $< 22\%$, score 0. Ave-SBR scoring: Ave-SBR $\leq 3.31\%$, score 1; Ave-SBR $> 3.31\%$, score 0. AI-SBR scoring: AI-SBR $\leq 21.8\%$, score 1; AI-SBR $> 21.8\%$, score 0. MSS: Total score 2, 3, 4 or 5, classified as PD; Total score 0 or 1, classified as nPD-nAPD. SCA: \leq H/M ratio (L) 2.8 and \leq AI-SBR 21.8%, classified as PD; $>$ H/M ratio (L) 2.8 or $>$ AI-SBR 21.8%, classified as APD.

PD from nPD-nAPD are summarized in Table 3.

As for discriminating PD from APD, the scoring of each adapted parameter is shown in Table 4. For the MSS, the accuracy for discriminating PD from APD was 86% at a cutoff value of 2; PD diagnosis was indicated by total score 2, 3, 4 or 5 and APD diagnosis was indicated by total score 0 or 1. The accuracy, sensitivity, specificity, positive predictive value and negative predictive value of MSS in differentiating PD from APD are summarized in Table 4.

Evaluations of simple combined analysis for two statistical discriminations

As for discriminating PD from nPD-nAPD, WR and Ave-SBR were adapted for the simple combined analysis. The accuracy for discriminating PD from nPD-nAPD was 70%. The cutoff value, accuracy, sensitivity, specificity, positive predictive value and negative predictive value of the simple combined analysis in differentiating PD from nPD-nAPD are summarized in Table 3.

As for discriminating PD from APD, H/M ratio (delayed) and AI-SBR were adapted for the simple combined analysis. The accuracy for discriminating PD from APD was 80%. The cutoff value, accuracy, sensitivity, specificity, positive predictive value and negative predictive value of the simple combined analysis in differentiating PD from APD are summarized in Table 4.

Representative images of DAT-SPECT and MIBG myocardial scintigraphy for each group are shown in Fig. 2.

DISCUSSION

This study evaluated whether combining DAT-SPECT and MIBG myocardial scintigraphy using the MSS could improve diagnostic accuracy in differentiating PD from non-PD; differentiating PD from nPD-nAPD and differentiating PD from APD. The analysis showed mild to moderate test accuracy for PD versus nPD-nAPD differentiation using each parameter alone [H/M ratio (early), 68%, H/M ratio (delayed), 70%, WR, 80%, Ave-SBR, 70% and AI-SBR, 59%]. The highest accuracy resulted using MSS if at least 2 of the 5 parameters were positive for PD. MSS distinguished PD from nPD-nAPD with an accuracy of 84%. Also, the analysis showed mild to moderate test accuracy for PD versus APD differentiation using each parameter alone [H/M ratio (early), 82%, H/M ratio (delayed), 86%, WR, 80%, Ave-SBR, 57% and AI-SBR, 77%]. The highest accuracy resulted using MSS if at least 2 of the 5 parameters were positive for PD. MSS distinguished PD from APD with an accuracy of 86%. In clinical terms, cases with PD are needed to be differentiated from non-PD. Combining DAT-SPECT and MIBG myocardial scintigraphy using this scoring system to discriminate PD from non-PD

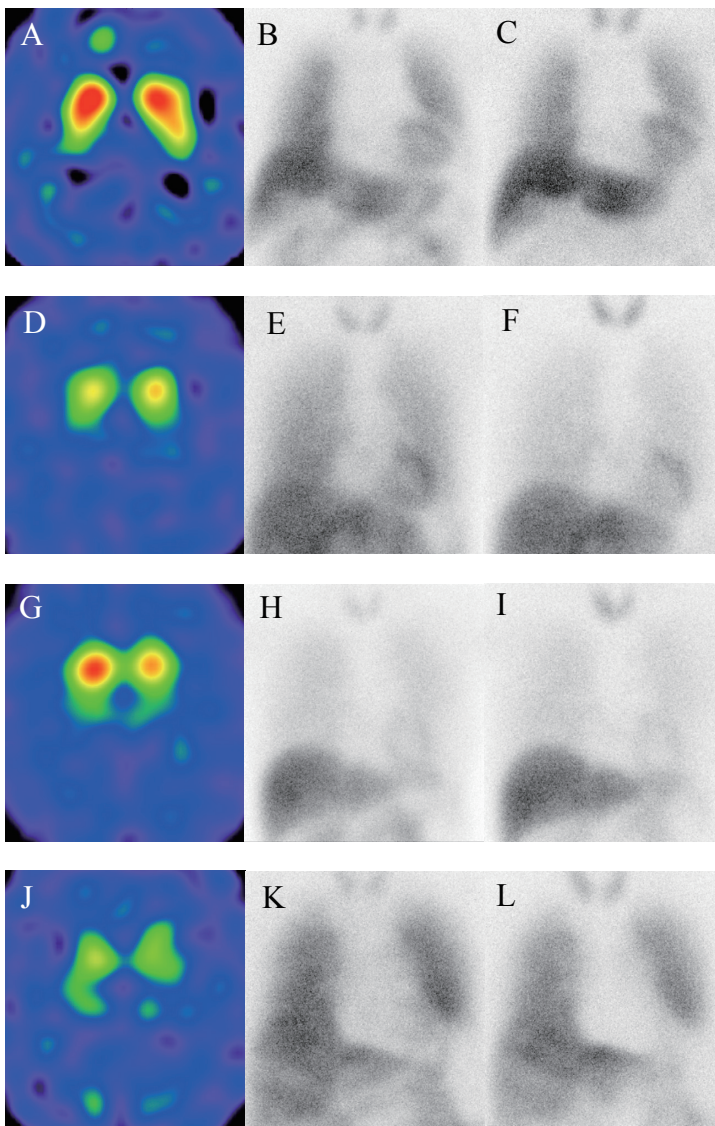


Fig. 2. Example images of DAT-SPECT and MIBG myocardial scintigraphy (early and delayed) for nPD-nAPD (A–C), APD (D–F), MM-PD (G–I) and S-PD (J–L) patients. (A–C) A 78-year-old man with vascular parkinsonian syndrome. Normal uptakes on both DAT-SPECT (A) and MIBG myocardial scintigraphy [early in (B) and delayed in (C)]. Values of 6.66% (score 0) for the Ave-SBR, 3.6% (score 0) for the AI-SBR, 2.71 (score 0) for the H/M ratio (early), 3.1 (score 0) for the H/M ratio (delayed) and 11.2% (score 0) for the WR are scored as 0 on MSS for discriminating nPD-nAPD from PD. The score 0 on MSS is correctly classified as nPD-nAPD. (D–F) A 69-year-old man with PSP. Moderate low uptakes on DAT-SPECT (D) and normal uptakes on MIBG myocardial scintigraphy [early in (E) and delayed in (F)]. Values of 4.06% (score 0) for the Ave-SBR, 15.5% (score 1) for the AI-SBR, 2.76 (score 0) for the H/M ratio (early), 2.9 (score 0) for the H/M ratio (delayed) and 19.1% (score 0) for the WR are scored as 1 on MSS for discriminating PD from APD. The score 1 on MSS is correctly classified as APD. (G–I) A 64-year-old woman with MM-PD. Moderate low uptakes on both DAT-SPECT (G) and MIBG myocardial scintigraphy [early in (H) and delayed in (I)]. Values of 5.89 % (score 0) for the Ave-SBR, 21.1% (score 1) for the AI-SBR, 1.98 (score 1) for the H/M ratio (early), 1.9 (score 1) for the H/M ratio (delayed) and 27.1% (score 1) for the WR are scored as 4 on MSS for discriminating PD from APD. The score 4 on MSS is correctly classified as PD. (J–L) A 83-year-old man with S-PD. Severe low uptakes on both DAT-SPECT (J) and MIBG myocardial scintigraphy [early in (K) and delayed in (L)]. Values of 2.7 % (score 1) for the Ave-SBR, 0.4% (score 1) for the AI-SBR, 1.78 (score 1) for the H/M ratio (early), 1.38 (score 1) for the H/M ratio (delayed) and 32.3% (score 1) for the WR are scored as 5 on MSS for discriminating PD from APD. The score 5 on MSS is correctly classified as PD.

AI, asymmetry index; APD, atypical parkinsonian disorder; Ave, average; DAT-SPECT, ^{123}I -FP-CIT dopamine transporter single photon emission computed tomography; H/M, heart-to-mediastinum; ^{123}I -FP-CIT, N-v-fluoro-propyl-2b-carbomethoxy-3b-(4- ^{123}I -iodophenyl)nortropine; MIBG, ^{123}I -metaiodobenzylguanidine; MM, mild to moderate; MSS, multiparametric scoring system; nPD-nAPD, parkinsonian syndromes other than PD or APD; PD, Parkinson's disease; S, severe; SBR, specific binding ratio; WR, washout-rate.

with higher accuracy possibly provides additional value for the correct differentiation between PD and non-PD.

DAT-SPECT is a sensitive modality to quantify the striatal density of dopamine transporters and detects nigrostriatal dysfunction due to cell loss at the substantia nigra. This method enables highly accurate differentiation of PD from other parkinsonian disorders that are not associated with a dopamine deficit, namely nPD-nAPD.⁸ For the discrimination of PD from nPD-nAPD in this study, the accuracy, sensitivity and specificity of Ave-SBR were as high as 70%, 69% and 75%, respectively ($P < 0.05$). A recent meta-analysis study of DAT-SPECT revealed relatively high pooled sensitivity and specificity values of above 85% and 80% in differentiating between

PD and vascular or drug-induced parkinsonism.³⁴ The other hand, for the discrimination of PD from APD in this study, the accuracy, sensitivity and specificity of Ave-SBR were as high as 57%, 53% and 75%, respectively ($P > 0.05$). DAT-SPECT is not enough for differentiating between PD and APD because loss of dopaminergic neurons in the substantia nigra and reduction of striatal dopamine projections are the histopathological hallmarks in these disorders. Furthermore, mild to moderate accuracy has been reported for distinguishing PD from degenerative parkinsonian syndromes.^{17, 20–22, 35}

It has been reported that the laterality of clinical symptoms in patients with PD contributes to the diagnosis of PD at an early stage.^{36, 37} On DAT-SPECT, the

binding of ligands in the most affected side, which is the opposite side as the symptoms, results in a lower value. AI-SBR in DAT-SPECT is often used for differentiation between drug-induced or vascular parkinsonism and PD.^{38–40} In this study, for the discrimination of nPD-nAPD from PD, the accuracy, sensitivity and specificity were as high as 59%, 53% and 88% ($P = 0.05$). Clinically, initial asymmetry in MM-PD decreases with the progression of the disease, and the value of AI-SBR is reduced gradually. Therefore, AI-SBR is a good clinical indicator for diagnosing PD in the MM-PD, but not in S-PD.^{20, 23} The low accuracy in our study might be associated with the large number of cases with S-PD (20 cases) in cases with PD (36 cases).

In this study, we evaluated three parameters of MIBG myocardial scintigraphy; H/M ratio (early), H/M ratio (delayed) and WR. For discriminating PD from nPD-nAPD, the accuracy was highest in WR (80%). For the WR, sensitivity and specificity for discriminating PD from nPD-nAPD were 83% and 63%, respectively. Also, for discriminating PD from APD, the accuracy was highest in H/M ratio (delayed) (86%). For the H/M ratio (delayed), sensitivity and specificity for discriminating PD from APD were 92% and 63%, respectively. The usefulness of MIBG myocardial scintigraphy in the diagnosis of Lewy body-related disorders was suggested recently in a meta-analysis. The sensitivity and specificity of MIBG myocardial scintigraphy in the differential diagnosis between PD and non-PD ranged from 71 to 100% and from 50 to 100%, respectively, with pooled estimates of 88% and 85%.³⁹ Therefore, as many studies have indicated, MIBG myocardial scintigraphy is usually a sensitive, but not specific test for PD in terms of diagnostic performance.^{41–47} Ishibashi et al. reported that both the early and delayed images for the differential diagnosis between PD and non-PD showed high sensitivity in the advanced stage of PD and showed low sensitivity in the early stage of PD.⁴⁸ In this study, the H/M ratio (early and delayed) showed significantly lower in S-PD than in nPD-nAPD, APD and MM-PD. Therefore, MIBG myocardial scintigraphy seems to be useful for differentiation between non-PD and S-PD or between MM-PD and S-PD, but not useful for differentiation between non-PD and MM-PD.

DAT-SPECT can assist the differentiation of degenerative parkinsonian syndromes from the other parkinsonian syndromes but is not capable of differentiating PD from APD. On the other hand, the accumulation is reduced in most PD cases on MIBG myocardial scintigraphy but is not capable of differentiating several MM-PD cases from non-PD cases. Therefore, to overcome the shortcomings of each modality, the combination of

DAT-SPECT and MIBG myocardial scintigraphy has been investigated for finding out PD in patients with parkinsonian syndrome.^{13–23} According to the recent studies, Yoshii et al. reported the combination of the SBR in DAT-SPECT and H/M ratio (delayed) in MIBG myocardial scintigraphy, using cut off values of less than 4.5 for the SBR and less than 2.2 for the H/M ratio (delayed) showed moderate accuracy (77.1%) in differentiating PD from APD.²⁰ Uyama et al. reported the combination of the SBR in DAT-SPECT and H/M ratio (delayed) in MIBG myocardial scintigraphy, using cut off values of less than 3.24 for the SBR and less than 2.745 for the H/M ratio (delayed) showed moderate accuracy (79.4%) in differentiating PD from APD.²¹

In this study, we compared the test accuracies of five parameters, a MSS and a simple combined analysis in each of the two statistical discriminations. As for discriminating PD from APD, the highest accuracy of five parameters was 86% for the H/M ratio (delayed). The analysis of MSS using five parameters showed the highest accuracy (86%) resulted if at least 2 of the 5 parameters were positive for PD, using the following cutoff values: H/M ratio (early), 2.51; H/M ratio (delayed), 2.8; WR, 22%; Ave-SBR, 3.31; and AI-SBR, 21.8. For the simple combined analysis using the best accuracy in each DAT-SPECT and MIBG myocardial scintigraphy; H/M ratio (delayed) and AI-SBR, the accuracy for discriminating PD from APD was 80%. As for discriminating PD from nPD-nAPD, the highest accuracy of five parameters was 80% for the WR. The analysis of MSS using five parameters showed the highest accuracy (84%) resulted if at least 2 of the 5 parameters were positive for PD, using the following cutoff values: H/M ratio (early), 2.1; H/M ratio (delayed), 1.9; WR, 19%; Ave-SBR, 4.29%; and AI-SBR, 16.9%. For the simple combined analysis using the best accuracy in each DAT-SPECT and MIBG myocardial scintigraphy; WR and Ave-SBR, the accuracy for discriminating PD from nPD-nAPD was 70%. Hence, on the analysis combining DAT-SPECT and MIBG myocardial scintigraphy, MSS using five parameters had better accuracy compared to the simple combined analysis using two parameters in discriminating PD from non-PD.

The reason MSS was superior to the simple combined analysis remains unclear. For the analysis using MSS, 3 of the 5 parameters [H/M ratio (early and delayed) and WR] were used for the evaluation of the postganglionic sympathetic function, and 2 of the 5 parameters (Ave-SBR and AI-SBR) were used for the evaluation of the nigrostriatal dopaminergic system. The highest accuracy resulted using MSS if at least 2 of the 5 parameters were positive for PD in both discriminating

PD from nPD-nAPD and discriminating PD from APD. The other hand, for the simple combined analysis using two parameters; parameters with the best accuracy in each DAT-SPECT and MIBG myocardial scintigraphy, one was used for the evaluation of the postganglionic sympathetic function and another was used for the evaluation of the nigrostriatal dopaminergic system. Therefore, on the simple combined analysis using two parameters, cases with PD seemed to be correctly categorized by the combination of both dysfunctions whereas on the MSS using five parameters, cases with PD were correctly categorized not only by the combination of both dysfunctions but also by only sympathetic dysfunctions or only nigrostriatal dopaminergic dysfunctions.

Our study has several limitations. First, this study was carried out in a single hospital; thus, the study population was small. Second, we evaluated PD and various other parkinsonian syndromes, including APD, Alzheimer disease, essential tremor and vascular parkinsonian syndrome, because we attempted to evaluate cases with overall parkinsonian syndromes. Third, the clinical diagnosis was used as the gold standard in our study because of the absence of histopathological confirmation. Fourth, according to the official International Parkinson and Movement Disorder Society clinical diagnostic criteria for Parkinson's disease (MDS-PD criteria), the supportive criteria include abnormal finding on MIBG myocardial scintigraphy although the absolute exclusion criteria include normal finding of DAT-SPECT.⁴⁹ Therefore, it should be noted that abnormal finding of DAT-SPECT was used supportively in this study, unlike in MDS-PD criteria, because abnormal findings of both DAT-SPECT and MIBG myocardial scintigraphy were used for discriminating PD from non-PD in this study. Because of these limitations, the results of this study should be considered a preliminary pilot investigation. Further validation is needed with a larger number of cases. However, this evaluation method using MSS is expected to be a useful indicator for differentiating PD from other parkinsonian syndromes.

In conclusion, combining MIBG myocardial scintigraphy and DAT-SPECT results using a MSS has potential to improve diagnostic accuracy in distinguishing PD from non-PD.

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The authors declare no conflict of interest.

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