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# Sensitivity and specificity of cardiac $^{123}$I-MIBG scintigraphy for diagnosis of early-phase Parkinson's disease

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ABSTRACT

*Introduction:* The purpose of this study was to investigate the diagnostic accuracy of cardiac $^{123}$I-metaiodobenzylguanidine (MIBG) scintigraphy for the diagnosis of Parkinson's disease (PD), especially in the early stages.
*Methods:* We investigated 600 patients who underwent cardiac $^{123}$I-MIBG scintigraphy to diagnose their parkinsonism and/or cognitive impairment. Of 600 research subjects, 272 patients were clinically diagnosed with PD. MIBG uptake was compared between patients with PD and other diseases. Furthermore, the sensitivity and specificity of cardiac $^{123}$I-MIBG scintigraphy to diagnose PD was estimated by disease duration (< 3 years: early group vs. over 3 years: late group). We also assessed the relationship between MIBG uptake and Hoehn & Yahr stage.
*Results:* MIBG uptakes of PD patients were significantly decreased compared with those of other diseases except dementia with Lewy bodies and pure autonomic failure ($p < .05$ for all). In the early group, the sensitivity and specificity of the delayed heart to mediastinum (H/M) ratio were 68.7% and 91.7%, respectively, while in the late group, the sensitivity was 86.3% and the specificity was 74.0%. In addition, the early and delayed H/M ratios were decreased with higher Hoehn & Yahr stages in PD patients.
*Conclusion:* Our findings demonstrated that cardiac $^{123}$I-MIBG scintigraphy had sufficient diagnostic accuracy to detect the early phase of PD. Indeed, this study of a large number of patients provides further external validation that MIBG has diagnostic ability to distinguish PD from atypical parkinsonism.

## 1. Introduction

Parkinson's disease (PD) is usually diagnosed based on clinical criteria such as the UK Parkinson's Disease Society Brain Bank Research Center (UKPDSBRC) diagnostic clinical criteria, which are used worldwide by experts in the area of movement disorders [1]. However, a previous study reported that the pooled diagnostic accuracy of PD based on these criteria was just 82.7%, suggesting suboptimal accuracy in the clinical diagnosis of PD [2]. Furthermore, gold standard clinical tests for diagnosing PD have not yet been established. Thus, it is still challenging to diagnose PD clinically, particularly during its early phase.

$^{123}$I-metaiodobenzylguanidine (MIBG) is an analog of noradrenaline, and cardiac $^{123}$I-MIBG scintigraphy has mainly been used as a radionuclide imaging tool to evaluate myocardial postganglionic sympathetic innervation [3]. A number of studies have shown that MIBG uptake is decreased in PD, dementia with Lewy bodies (DLB), and pure autonomic failure (PAF), which are collectively known as Lewy body diseases (LBDs) [3–5]. The low uptake of MIBG in these diseases is presumably due to an accumulation of Lewy bodies in the peripheral sympathetic nervous system among patients with LBDs [6]. Previous studies have reported that cardiac $^{123}$I-MIBG scintigraphy can be used to differentiate LBDs from atypical parkinsonism or diseases with cognitive impairments, such as Alzheimer's disease (AD) [3,4]. However, the diagnostic accuracy of cardiac $^{123}$I-MIBG scintigraphy in diagnosing early-phase PD, and the association of MIBG uptake with PD symptoms and severity, have not been fully established [7–9].

The aim of this study was to investigate the usefulness of cardiac $^{123}$I-MIBG scintigraphy in the diagnosis of early-phase PD in a large-scale observational study of Japanese patients. We also aimed to

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**Table 1**
Baseline characteristics of patients according to final diagnosis.

| | PD ($n$ = 272) | DLB ($n$ = 43) | PAF ($n$ = 2) | MSA ($n$ = 33) | PSP ($n$ = 28) | CBD ($n$ = 12) | VaP ($n$ = 10) | Drug-induced ($n$ = 4) | Unclassified parkinsonian syndrome ($n$ = 10) | ET ($n$ = 6) | AD/MCI ($n$ = 39) | Others ($n$ = 27) | Undetermined ($n$ = 114) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Male | 119 (43.8%) | 17 (39.5%) | 1 (50.0%) | 13 (39.4%) | 19 (67.9%) | 6 (50.0%) | 7 (70.0%) | 0 (0.0%) | 4 (40.0%) | 4 (66.7%) | 14 (36.0%) | 15 (55.6%) | 53 (46.5%) |
| Age at onset (years) | 62.2 (12.8) | 72.3 (9.0) | 76.0 (14.1) | 60.9 (9.8) | 67.6 (6.5) | 71.9 (5.8) | 74.9 (9.0) | 59.3 (10.9) | 68.4 (5.5) | 62.8 (16.7) | 70.9 (9.6) | 58.3 (19.7) | 67.9 (12.2) |
| Age at MIBG test (years) | 66.4 (11.8) | 76.5 (6.9) | 82.0 (5.7) | 63.6 (9.6) | 71.8 (6.5) | 73.8 (6.1) | 78.7 (7.6) | 67.0 (10.7) | 72.9 (7.1) | 70.3 (10.7) | 74.1 (9.8) | 64.5 (13.3) | 71.3 (11.1) |
| Disease duration (years) | 4.1 (5.1) | 4.0 (5.0) | 6.0 (8.5) | 2.8 (2.9) | 3.8 (3.6) | 1.8 (0.9) | 3.8 (3.8) | 7.8 (9.3) | 3.1 (2.1) | 6.4 (8.7) | 3.1 (2.7) | 6.5 (11.7) | 2.96 (3.3) |
| Follow up time (years) | 4.8 (3.9) | 2.0 (1.7) | 6.7 (3.2) | 3.2 (2.8) | 4.0 (4.6) | 2.2 (1.7) | 3.0 (3.6) | 6.7 (3.2) | 3.5 (1.7) | 3.5 (1.7) | 3.1 (2.8) | 4.0 (3.3) | 0.4 (1.4) |

Values are expressed as $n$ (%) or mean (SD).
PD: Parkinson's disease, DLB: dementia with Lewy bodies, PAF: pure autonomic failure, MSA: multiple system atrophy, PSP: progressive supranuclear palsy, CBD: corticobasal degeneration, VaP: vascular parkinsonism, Drug-induced: drug-induced parkinsonism, ET: essential tremor, AD/MCI: Alzheimer's disease/mild cognitive impairment, MIBG: metaiodobenzylguanidine.

investigate the associations of MIBG uptake with Hoehn & Yahr (H & Y) staging and detailed motor and non-motor symptoms in PD patients.

## 2. Materials and methods

### 2.1. Study design and subjects

This was a single-center, retrospective cohort study. We enrolled 816 consecutive patients with parkinsonism and/or cognitive impairment at their first visits or their follow-up periods and performed cardiac $^{123}$I-MIBG scintigraphy on these patients to support diagnoses of PD or DLB, which can be clinically misdiagnosed as atypical parkinsonism (e.g., multiple system atrophy [MSA], progressive supranuclear palsy [PSP], and corticobasal degeneration [CBD]) or other cognitive disorders (e.g., AD). The study was performed at the Department of Neurology in the Fukuoka University Hospital between January 2005 and May 2016. After excluding patients with a history of diabetes mellitus ($n$ = 101) or cardiac disease ($n$ = 27), and those on tricyclic or tetracyclic antidepressants, selective serotonin reuptake inhibitors (SSRI), or antipsychotics (due to their possible influence on MIBG uptake [10]; $n$ = 91), a total of 600 subjects were included in this study.

The current study involved two sets of analyses: (1) In 600 patients, MIBG uptake was compared across different types of diseases, based on final diagnosis (see Section 2.2 for diagnostic criteria). (2) In the 272 patients who were diagnosed with PD, we analyzed the correlation between MIBG uptake and initial motor symptoms, motor and non-motor symptoms at the time of the MIBG test, and the staging of the motor symptoms. Patient demographics and clinical information were retrospectively gathered from clinical notes.

The study was approved by the Institutional Review Board–Independent Ethics Committee of Fukuoka University (16-9-11).

### 2.2. Definition of diagnosis

A diagnosis of probable PD was made based on UKPDSBRC diagnostic clinical criteria [1], and the other diseases were diagnosed based on widely accepted criteria [11–15]. Two patients who had an apparent family history of parkinsonism were classified as having unclassified parkinsonian syndrome, while 114 patients who did not fulfill any set of criteria were classified as undetermined. We evaluated the initial symptoms from medical records. The initial motor symptoms were defined as follows: (1) gait disturbance: stooped posture with short steppage gait and/or freezing of gait; (2) rigidity: complaints of stiffness in combination with resistance to passive movement in extremities; (3) tremor: symptoms of uncontrolled shaking in extremities and/or the jaw; and (4) bradykinesia: slowness of spontaneous movement and/or facial expression. Motor symptoms at the time of the MIBG test were evaluated based on medical history and standardized neurological examinations carried out by several neurologists (MK, TM, SF, JT, YT). Non-motor symptoms at the time of the MIBG test were also defined based on medical history and/or physical findings, and were classified as follows: (1) dementia and mild cognitive impairments: symptoms of memory problems that yielded an apparent disturbance of daily life, and/or Mini-Mental State Examination (MMSE) scores of < 20 points [16]; (2) orthostatic hypotension: subjectively, with complaints of lightheadedness or blurred vision in the upright posture and/or a decrease in systolic blood pressure of at least 20 mmHg during the head-up tilt test [17]; (3) depression: depressive symptoms and/or current/past use of anti-depressants; (4) constipation: bowel movement of twice a week or less and/or a chronic use of laxatives; (5) urinary disturbance: frequent urination, nocturia, and/or chronic use of drugs for the treatment of these symptoms; (6) hallucination and delusion: apparent episodes of vivid and visual hallucinations and/or a delusional disorder pointed out by others; (7) REM sleep behavior disorder (RBD): symptoms of arm/leg movement, and/or shouting, speaking, or laughing loudly during sleep that was reported by a bed-partner of a

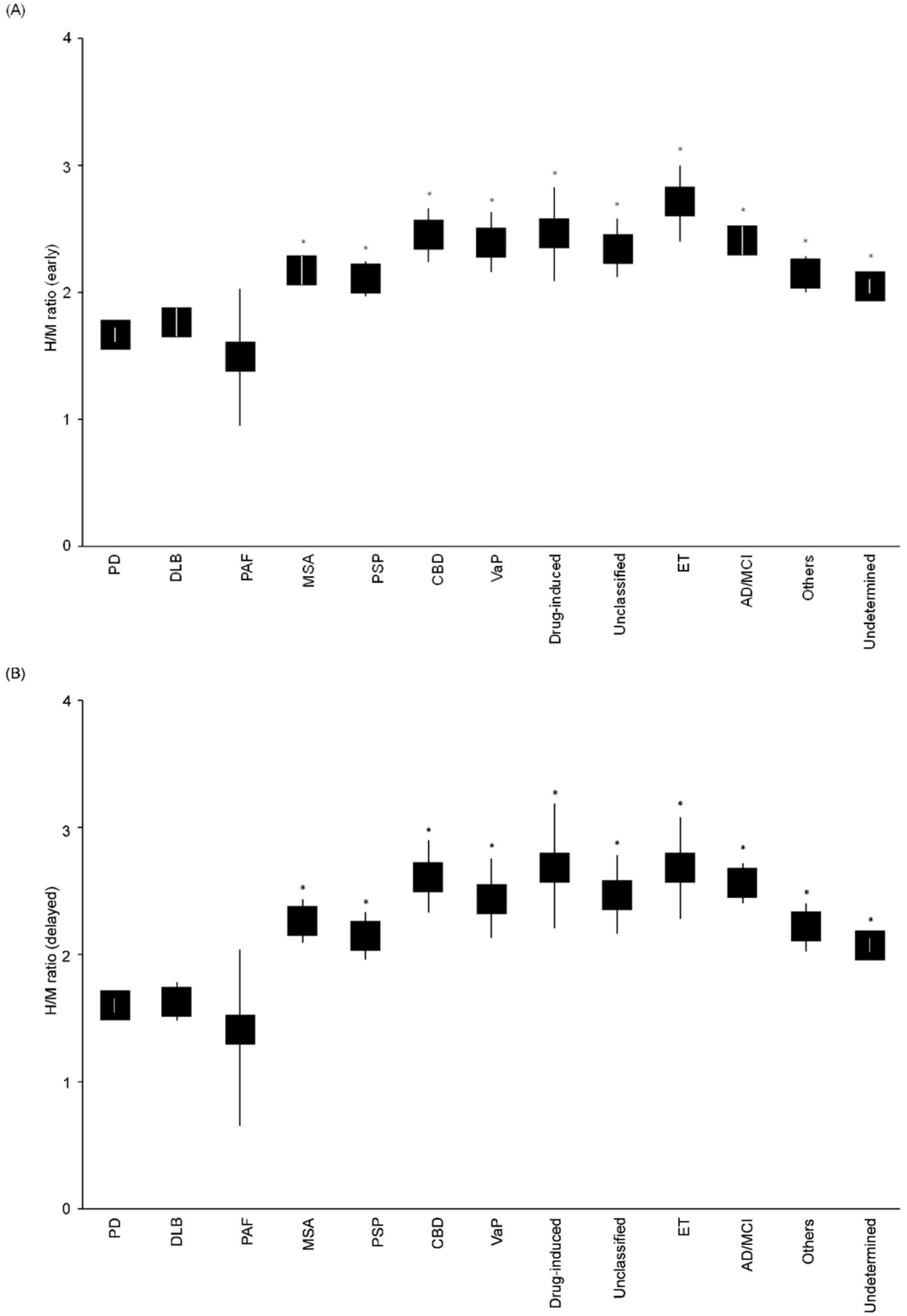


**Fig. 1.** Early (A) and delayed H/M ratio (B) according to final diagnosis.

Solid boxes represent estimates of mean heart to mediastinum (H/M) ratio. Vertical lines represent 95% confidence intervals. Values were adjusted for sex and age at time of $^{123}$I-metaiodobenzylguanidine (MIBG) testing. $^{*}p < .001$.

PD: Parkinson's disease, DLB: dementia with Lewy bodies, PAF: pure autonomic failure, MSA: multiple system atrophy, PSP: progressive supranuclear palsy, CBD: corticobasal degeneration, VaP: vascular parkinsonism, Drug-induced: drug-induced parkinsonism, Unclassified: unclassified parkinsonian syndrome, ET: essential tremor, AD/MCI: Alzheimer's disease/mild cognitive impairment.

**Table 2**
Characteristics of Parkinson's disease patients.

| | PD ($n$ = 272) | |
|---|---|---|
| Male (%) | 119 | (43.8%) |
| Age at onset: years | 62.2 | (12.8) |
| Age at MIBG test: years | 66.4 | (11.8) |
| Disease duration: years | 4.1 | (5.1) |
| Follow-up time: years | 4.8 | (3.9) |
| Initial symptoms | | |
| Motor symptoms | | |
| Gait disturbance/postural instability | 69 | (25.4%) |
| Rigidity | 48 | (17.7%) |
| Tremor | 127 | (46.7%) |
| Bradykinesia | 30 | (11.0%) |
| Non-motor symptoms | | |
| Dementia | 2 | (0.01%) |
| Orthostatic hypotension | 2 | (0.01%) |
| Depression | 10 | (0.04%) |
| Constipation | 1 | (0.004%) |
| Urinary disturbance | 0 | (0%) |
| Hallucination | 0 | (0%) |
| RBD | 2 | (0.01%) |
| Others | 1 | (0.004%) |
| Undetermined | 1 | (0.004%) |
| Symptoms at MIBG test | | |
| Motor symptoms | | |
| Gait disturbance/postural instability | 136 | (50.0%) |
| Rigidity | 189 | (69.5%) |
| Tremor | 56 | (20.6%) |
| Bradykinesia | 195 | (71.7%) |
| Non-motor symptoms | | |
| Dementia | 14 | (5.2%) |
| Orthostatic hypotension | 13 | (4.8%) |
| Depression | 28 | (10.3%) |
| Constipation | 126 | (46.3%) |
| Urinary disturbance | 57 | (21.0%) |
| Hallucination | 14 | (5.2%) |
| RBD | 40 | (14.7%) |
| Anti-parkinsonian medications at MIBG test | | |
| Levodopa | 116 | (42.7%) |
| Dose of levodopa: mg | 334.5 | (155.3) |
| Dopamine agonist | 74 | (27.2%) |
| Hoehn & Yahr stage | | |
| 0 | 1 | (0.4%) |
| 1 | 52 | (19.1%) |
| 2 | 62 | (22.8%) |
| 3 | 106 | (39.0%) |
| 4 | 17 | (6.3%) |
| 5 | 2 | (0.7%) |
| Undetermined | 32 | (11.8%) |

Values are expressed as $n$ (%) or mean (SD).
RBD: rapid eye movement sleep behavior disorder.
MIBG: metaiodobenzylguanidine.

patient [18]; and (8) other: non-motor symptoms that did not fit into categories (1)–(7). We defined PD severity according to the H & Y stage at the time of the MIBG test [19]. We also defined disease duration as the time from onset of first symptoms to MIBG scintigraphy, while follow-up time was defined as the time from MIBG scintigraphy to final diagnosis.

### 2.3. Cardiac $^{123}$I-MIBG scintigraphy

Cardiac $^{123}$I-MIBG scintigraphy was performed using the same protocol throughout this study. 111 MBq of $^{123}$I-MIBG (FUJIFILM RI Pharma Co., Ltd., Tokyo, Japan) was injected intravenously. Early and delayed images were obtained after 15 min and 180 min with a triple head gamma camera (PRISM 3000-IRIX, Philips Healthcare, Amsterdam, Netherlands) with low-energy general all-purpose (LEGAP) collimators. The photopeak of $^{123}$I was centered at 159 keV with ± 10% energy window, and all data were collected for 5 min with a 512 × 512 matrix. Regions of interest (ROIs) were manually drawn around the heart (H) and a square (2 × 2 cm) ROI was set on the upper mediastinum (M) on a planar image. Tracer uptake was used to calculate the early (15 min) and delayed (180 min) H/M ratio. We set a cut-off point of 2.0 for both the early and delayed H/M ratios [20,21].

### 2.4. Statistical analysis

All data were presented as mean ± SD or as $n$ (%). In the first set of analyses, we compared the mean H/M ratio values across different types of diseases using one-way analysis of variance (ANOVA) and analysis of covariance (ANCOVA), including sex and age at the time of the MIBG test as covariates. In the second set of analyses, H/M ratios in the PD group were compared according to the presence of initial symptoms or of motor/non-motor symptoms at the time of the MIBG test, and according to H & Y stages, using ANCOVA with adjustments for sex and age at the time of the MIBG test. Finally, we calculated the sensitivity, specificity and global accuracy of the MIBG test in detecting PD. Statistical analyses were performed using SAS software (version 9.4). A significant difference was defined as $p < .05$.

## 3. Results

### 3.1. Basic characteristics and H/M ratio according to final diagnosis

Basic characteristics of all study participants are summarized in Table 1. Of the 600 research subjects, 272 were male (45.3%). The mean age at onset and age at the time of the MIBG test were 65.2 ± 12.6 and 69.1 ± 11.4 years, respectively. The mean disease duration and follow-up time were 3.8 ± 5.0 years and 2.3 ± 2.7 years, respectively. The results of the H/M ratio comparison between PD and other diseases (according to final diagnosis) are shown in Fig. 1. Compared with PD patients, the early and delayed H/M ratios of all patients were significantly higher than those of all other diseases except for DLB and PAF patients, using both ANOVA and ANCOVA analyses (ANCOVA analysis results are shown in Fig. 1).

### 3.2. Basic characteristics of PD patients

Basic characteristics of PD patients are summarized in Table 2. Of the 272 PD patients, 119 (43.8%) were male. The mean age at onset and age at the time of the MIBG test were 62.2 ± 12.8 and 66.4 ± 11.8 years, respectively. The mean disease duration and follow-up time were 4.1 ± 5.1 years and 4.8 ± 3.9 years, respectively. When patients were divided by disease severity according to H & Y stages, results were as follows: H & Y 0, $n$ = 1 (0.4%); H & Y 1, $n$ = 52 (19.1%); H & Y 2, $n$ = 62 (22.8%); H & Y 3, $n$ = 106 (39.0%); H & Y 4, $n$ = 17 (6.3%); H & Y 5, $n$ = 2 (0.7%); H & Y unknown, $n$ = 32 (11.8%). Among the 127 patients (46.7%) who had experienced tremor during the course of their illness, tremor was clinically confirmed in 56 patients (20%) by neurologists during examination at the time of the MIBG test. One hundred and sixteen patients (42.7%) were taking levodopa at the time of the MIBG test, and the mean dose of levodopa was 334.5 ± 155.3 mg. Seventy-four patients (27.2%) were taking dopamine agonists at the time of the MIBG test (Table 2).

### 3.3. H/M ratio according to the clinical symptoms of PD patients

Among the 272 PD patients, the early and delayed H/M ratios were significantly lower in patients with rigidity at disease onset compared with those without rigidity at disease onset (early H/M ratio: difference 0.13, 95% CI 0.01 to 0.24, $p$ = .031; delayed H/M ratio: difference 0.21, 95% CI 0.06 to 0.35, $p$ = .006). The delayed H/M ratio was significantly lower in patients with tremor at the time of the MIBG test compared with those without tremor at testing (difference 0.14, 95% CI 0.002 to 0.28, $p$ = .047). In addition, in patients with the following symptoms at the time of the MIBG test, the early and delayed H/M

**Table 3**
Characteristics of PD and non-PD patients according to disease duration.

| | PD ($n$ = 272) | | Non-PD ($n$ = 169) | |
|---|---|---|---|---|
| | 0 < Duration ≤3 | Duration > 3 | 0 < Duration ≤3 | Duration > 3 |
| *n* | 155 | 117 | 96 | 73 |
| Males | 68 (43.9%) | 51 (43.6%) | 47 (49.0%) | 35 (48.0%) |
| Age at onset (years) | 65.3 ± 12.3 | 58.2 ± 12.5 | 68.8 ± 10.6 | 63.1 ± 13.1 |
| Age at MIBG test (years) | 66.4 ± 12.3 | 66.4 ± 11.1 | 70.0 ± 10.7 | 70.1 ± 10.4 |
| Disease duration (years) | 1.0 ± 0.7 | 8.2 ± 5.6 | 1.2 ± 0.7 | 7.0 ± 7.1 |
| Hoehn & Yahr | | | | |
| 0 | 1 (0.6%) | 0 | | |
| 1 | 32 (20.6%) | 20 (17.1%) | | |
| 2 | 41 (26.5%) | 21 (17.9%) | | |
| 3 | 67 (43.2%) | 39 (33.3%) | | |
| 4 | 2 (1.3%) | 15 (12.8%) | | |
| 5 | 0 | 2 (1.7%) | | |
| Undetermined | 12 (7.7%) | 20 (17.1%) | | |
| Hoehn & Yahr | 2.3 ± 0.8 | 2.6 ± 1.0 | | |
| Early H/M < 2.0 | 100 (64.5%) | 102 (87.2%) | 12 (13.0%) | 18 (24.7%) |
| Delayed H/M < 2.0 | 103 (66.5%) | 101 (86.3%) | 8 (8.0%) | 19 (26.0%) |

Values are expressed as $n$ (%) or mean ± SD.
Non-PD patients included MSA, PSP, CBD, VaP, drug-induced, unclassified, ET, AD/MCI, and others.
PD: Parkinson's disease, DLB: dementia with Lewy bodies, PAF: pure autonomic failure, MSA: multiple system atrophy, PSP: progressive supranuclear palsy, CBD: corticobasal degeneration, VaP: vascular parkinsonism, Drug-induced: drug-induced parkinsonism, Unclassified: unclassified parkinsonian syndrome, ET: essential tremor, AD/MCI: Alzheimer's disease/mild cognitive impairment, MIBG: metaiodobenzylguanidine.

ratios were significantly lower compared with those without each of the following symptoms: constipation (early H/M ratio: difference 0.19, 95% CI 0.10 to 0.27, $p < .001$; delayed H/M ratio: difference 0.21, 95% CI 0.10 to 0.32, $p < .001$), urinary disturbance (early H/M ratio: difference 0.14, 95% CI 0.03 to 0.24, $p = .011$; delayed H/M ratio: difference 0.17, 95% CI 0.04 to 0.31, $p = .013$), and RBD (early H/M ratio: difference 0.17, 95% CI 0.05 to 0.29, $p = .005$; delayed H/M ratio: difference 0.20, 95% CI 0.04 to 0.35, $p = .015$) (Table 4).

### 3.4. H/M ratio according to the H & Y stage of PD patients

Among the 272 PD patients, we classified 240 patients into four groups according to disease severity based on H & Y stage: H & Y stage 0–1 ($n$ = 53), H & Y stage 2 ($n$ = 62), H & Y stage 3 ($n$ = 106) and H & Y stage 4–5 ($n$ = 19). The remaining 32 PD patients were excluded from this analysis because their H & Y stages were undetermined. We then analyzed the correlation between H/M ratio and disease severity in these 240 PD patients. The early H/M ratio decreased with H & Y stage progression, and was significantly lower in H & Y stage 3 and stage 4–5 patients compared with H & Y stage 0–1 (H & Y stage 0–1 vs. H & Y stage 3: difference 0.13, 95% CI 0.002 to 0.26, $p = .047$; H & Y stage 0–1 vs. H & Y stage 4–5: difference 0.24, 95% CI 0.03 to 0.44, $p = .024$). The delayed H/M ratio also decreased with H & Y stage progression, and was significantly lower in H & Y stage 3 and stage 4–5 patients compared with H & Y stage 0–1 (H & Y stage 0–1 vs. H & Y stage 3: difference 0.22, 95% CI 0.04 to 0.39, $p = .015$; H & Y stage 0–1 vs. H & Y stage 4–5: difference 0.44, 95% CI 0.16 to 0.71, $p = .002$) and in H & Y stage 4–5 compared with H & Y stage 2 (H & Y stage 2 vs. H & Y stage 4–5: difference 0.29, 95% CI 0.02 to 0.56, $p = .036$).

### 3.5. Sensitivity and specificity of cardiac $^{123}$I-MIBG scintigraphy

Finally, to calculate the sensitivity and specificity of the MIBG test in detecting PD, 441 patients were grouped into either PD ($n$ = 272) or non-PD ($n$ = 169; 33 MSA, 28 PSP, 12 CBD, 10 vascular parkinsonism [VaP], 4 drug-induced parkinsonism, 10 unclassified parkinsonism, 6 essential tremor [ET], 39 AD/mild cognitive impairment and 27 others) patients after excluding the other 159 patients (43 DLB, 2 PAF, and 114 undetermined patients) from the 600 total research subjects. Characteristics of PD and non-PD patients according to disease duration are summarized in Table 3. The sensitivity, specificity and global accuracy of the early H/M ratio were 74.3% (95% CI: 69.1 to 79.5), 82.2% (95% CI: 76.4 to 88.0) and 77.3% (95% CI: 73.4 to 81.2), and those of the delayed H/M ratio were 75.0% (95% CI: 69.9 to 80.1), 84.0% (95% CI: 78.5 to 89.5) and 78.5% (95% CI: 74.7 to 82.3), respectively. Additionally, we divided the 441 patients into two groups according to disease duration, of either < 3 years (early group) or over 3 years (late group), and the sensitivity, specificity and global accuracy of the MIBG test were also calculated for each group. In the early group, the sensitivity, specificity and global accuracy of the early H/M ratio were 64.5% (95% CI: 57.0 to 72.0), 87.5% (95% CI: 80.9 to 94.1) and 73.3% (95% CI: 67.7 to 82.9), and those of the delayed H/M ratio were 68.7% (95% CI: 61.4 to 76.0), 91.7% (95% CI: 86.2 to 97.2) and 76.1% (95% CI: 70.8 to 81.4), respectively. In the late group, the sensitivity, specificity and global accuracy of the early H/M ratio were 87.2% (95% CI: 81.1 to 93.3), 75.3% (95% CI: 65.4 to 85.2) and 82.6% (95% CI: 77.2 to 88.0), and those of the delayed H/M ratio were 86.3% (95% CI: 80.1 to 92.5), 74.0% (95% CI: 63.9 to 84.1) and 81.6% (95% CI: 76.1 to 87.1), respectively.

## 4. Discussion

In this large-scale study performed in present-day Japan, we demonstrated that MIBG scintigraphy was a useful tool to detect LBDs with high specificity, and particularly for early PD. Additionally, the H/M ratio decreased with disease progression in PD patients. A decrease in the H/M ratio was also observed in PD patients with constipation, urinary disturbance, or RBD.

Further, our study showed that cardiac $^{123}$I-MIBG scintigraphy is beneficial for distinguishing LBDs from various movement disorders including atypical parkinsonism, vascular parkinsonism, drug-induced parkinsonism, and ET (Fig. 1). Although the usefulness of MIBG scintigraphy has been demonstrated in previous reports [3,4,32], our study has corroborated this finding using a large number of cases. Moreover, it has not been confirmed whether cardiac $^{123}$I-MIBG scintigraphy is sufficiently accurate in the diagnosis of early PD. Recent meta-analyses showed that the sensitivity and specificity of MIBG scintigraphy (the delayed H/M ratio) were 88% and 85%, respectively, for the diagnosis of PD vs. other parkinsonisms [22], and 89.7% and 82.6%, respectively, for the diagnosis of PD vs. other neurodegenerative parkinsonisms [23].

**Table 4**
Clinical symptoms and early and delayed H/M ratio.

| | Early H/M ratio | | | | Delayed H/M ratio | | | |
|---|---|---|---|---|---|---|---|---|
| | Yes | No | Difference (95% CI) | *p* Value | Yes | No | Difference (95% CI) | *p* Value |
| | Mean (95% CI) | Mean (95% CI) | | | Mean (95% CI) | Mean (95% CI) | | |
| Initial symptoms | | | | | | | | |
| Motor symptoms | | | | | | | | |
| Gait disturbance/postural instability | 1.73 (1.65 to 1.82) | 1.75 (1.70 to 1.79) | 0.02 (−0.08 to 0.11) | .758 | 1.59 (1.53 to 1.66) | 1.62 (1.51 to 1.73) | −0.03 (−0.16 to 0.10) | .686 |
| Rigidity | 1.64 (1.54 to 1.74) | 1.76 (1.72 to 1.81) | 0.13 (0.01 to 0.24) | .031* | 1.43 (1.30 to 1.56) | 1.64 (1.58 to 1.70) | 0.21 (0.06 to 0.35) | .006* |
| Tremor | 1.78 (1.72 to 1.84) | 1.71 (1.65 to 1.76) | −0.08 (−0.16 to 0.01) | .078 | 1.65 (1.57 to 1.74) | 1.55 (1.48 to 1.63) | −0.10 (−0.21 to 0.01) | .075 |
| Bradykinesia | 1.69 (1.56 to 1.82) | 1.75 (1.70 to 1.79) | 0.06 (−0.08 to 0.20) | .379 | 1.55 (1.38 to 1.72) | 1.61 (1.55 to 1.67) | 0.06 (−0.12 to 0.24) | .512 |
| Symptoms at MIBG test | | | | | | | | |
| Motor symptoms | | | | | | | | |
| Gait disturbance/postural instability | 1.72 (1.66 to 1.78) | 1.76 (1.70 to 1.82) | 0.04 (−0.05 to 0.12) | .389 | 1.56 (1.48 to 1.63) | 1.65 (1.57 to 1.72) | 0.09 (−0.02 to 0.20) | .111 |
| Rigidity | 1.75 (1.70 to 1.80) | 1.72 (1.65 to 1.80) | −0.03 (−0.12 to 0.07) | .565 | 1.63 (1.56 to 1.70) | 1.53 (1.43 to 1.63) | −0.10 (−0.22 to 0.02) | .117 |
| Tremor | 1.68 (1.59 to 1.77) | 1.76 (1.71 to 1.81) | 0.08 (−0.03 to 0.18) | .137 | 1.49 (1.37 to 1.61) | 1.63 (1.57 to 1.69) | 0.14 (0.002 to 0.28) | .047* |
| Bradykinesia | 1.75 (1.70 to 1.80) | 1.73 (1.65 to 1.81) | −0.02 (−0.11 to 0.08) | .743 | 1.60 (1.54 to 1.67) | 1.59 (1.48 to 1.69) | −0.02 (−0.14 to 0.11) | .809 |
| Non-motor symptoms | | | | | | | | |
| Dementia | 1.62 (1.43 to 1.81) | 1.75 (1.70 to 1.79) | 0.13 (−0.07 to 0.33) | .193 | 1.46 (1.21 to 1.71) | 1.61 (1.55 to 1.67) | 0.15 (−0.11 to 0.41) | .250 |
| OH | 1.68 (1.48 to 1.87) | 1.74 (1.70 to 1.79) | 0.07 (−0.13 to 0.27) | .513 | 1.38 (1.13 to 1.64) | 1.61 (1.55 to 1.67) | 0.23 (−0.03 to 0.49) | .088 |
| Depression | 1.72 (1.59 to 1.86) | 1.74 (1.70 to 1.79) | 0.02 (−0.12 to 0.16) | .788 | 1.55 (1.38 to 1.72) | 1.61 (1.55 to 1.67) | 0.06 (−0.13 to 0.24) | .557 |
| Constipation | 1.64 (1.58 to 1.70) | 1.83 (1.77 to 1.88) | 0.19 (0.10 to 0.27) | < .001* | 1.49 (1.41 to 1.57) | 1.70 (1.62 to 1.77) | 0.21 (0.10 to 0.32) | < .001* |
| Urinary disturbance | 1.63 (1.54 to 1.73) | 1.77 (1.72 to 1.82) | 0.14 (0.03 to 0.24) | .011* | 1.46 (1.34 to 1.59) | 1.64 (1.57 to 1.70) | 0.17 (0.04 to 0.31) | .013* |
| Hallucination | 1.64 (1.45 to 1.83) | 1.75 (1.70 to 1.79) | 0.11 (−0.09 to 0.30) | .274 | 1.47 (1.23 to 1.72) | 1.61 (1.55 to 1.66) | 0.13 (−0.12 to 0.39) | .303 |
| RBD | 1.60 (1.49 to 1.71) | 1.77 (1.72 to 1.81) | 0.17 (0.05 to 0.29) | .005* | 1.43 (1.29 to 1.58) | 1.63 (1.57 to 1.69) | 0.20 (0.04 to 0.35) | .015* |

CI: confidence interval; OH: orthostatic hypotension; RBD: rapid eye movement sleep behavior disorder.
* $p < .05$.

In the latter analysis, the sensitivity and specificity to detect early PD (H & Y 1 or 2) were 94.1% and 80.2%, respectively; therefore, the authors concluded that MIBG scintigraphy may be a useful tool to distinguish early PD. Our study revealed that the specificity of the delayed H/M ratio to diagnose early-phase PD (disease duration < 3 years) was very high (91.7%), suggesting that MIBG scintigraphy can be very useful to confirm PD at its early stages. Here, we confirmed these findings and also demonstrated higher specificity of MIBG scintigraphy for diagnosis of early-phase PD compared with late-phase PD. The mechanisms underlying reduced specificity in late-phase PD are not clear, however, one explanation may involve an increase in pseudo-positive cases because H/M ratios decrease modestly in neurodegenerative diseases other than PD (e.g., MSA) in their later stages [24].

Most prior studies demonstrated an association between a reduction in the H/M ratio and the progression of motor symptoms [25,26]. Our study confirmed these findings, and clearly demonstrated that the early and delayed H/M ratios significantly decreased with disease progression, taken as H & Y stages. The association between the progression of motor symptoms and the decline in H/M ratio may reflect a parallel decline among patients with PD in motor function and autonomic function [9,26], which is mainly evaluated by cardiac $^{123}$I-MIBG scintigraphy.

Regarding the phenotype of motor symptoms, in our study, delayed H/M ratio significantly decreased in patients with tremor at MIBG testing, which is similar to the findings of Chiaravalloti et al., [27]. Contrarily, other studies have shown greater impairments in MIBG uptake with akinetic rigid type (ART) or postural instability and gait disturbance type (PIGD) than tremor dominant type (TDT) [28–30]. We also found that H/M ratios clearly decreased in patients with non-motor symptoms (such as constipation, urinary disturbance, and RBD), but did not in patients with dementia, orthostatic hypotension, depression, or hallucinations. These findings are consistent with previous studies [9,31,32], although several studies demonstrated reduced H/M ratios in orthostatic hypotension and dementia [9,33]. Discrepancies in findings across different studies may be partially attributable to differences in study design, settings, participants, and assessment/definition of symptoms.

In 2015, the Movement Disorder Society (MDS) has launched the MDS clinical diagnostic criteria for PD, which recommend MIBG scintigraphy for confirmation of the diagnosis [34]. It has been suggested that diagnostic accuracy of the MDS clinical diagnostic criteria is superior to that of the UKPDSBRC diagnostic clinical criteria [35]. Considering high specificity of MIBG test for diagnosis of PD observed in this study, we also support usefulness of the MDS clinical diagnostic criteria for PD.

Several limitations to this study should be discussed. First, as a single-center study, there may be selection bias; however, a single-center study is also advantageous because of the uniform procedures in clinical practice and imaging tests at a single site. Second, each diagnosis has not been confirmed pathologically. Third, we could not confirm each diagnosis using MDS criteria because most participants were evaluated before the determination of this criteria. Fourth, all the demographic and clinical information were retrospectively gathered, meaning that some clinical data may have been missed. Finally, because genetic analyses were not performed, recessive PD, in which the H/M ratio is usually preserved [36,37], may have been misdiagnosed as idiopathic PD.

In conclusion, cardiac $^{123}$I-MIBG scintigraphy appears to be helpful in the confirmation of diagnosis in early PD. Previous studies have suggested that early intervention with dopamine replacement therapy can contribute to quality of life in PD patients [38,39], earlier and more accurate PD diagnoses using cardiac $^{123}$I-MIBG scintigraphy would be helpful for patients with suspected PD who have mild symptoms.

## Conflicts of interest

All authors declare that there is no conflict of interest to disclose.

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