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Dopamine transporter imaging to predict the risk of aspiration in patients with Parkinson's disease

Jun Tanimura [a,b], Toshiyuki Yamamoto [a,*], Yoko Shigemoto [c], Noriko Sato [c], Yuji Takahashi [a]

[a] Department of Neurology, National Center Hospital, National Center of Neurology and Psychiatry (NCNP), 4-1-1 Ogawa Higashicho, Kodaira, Tokyo, 187-8551, Japan
[b] Department of Neurology, Aizawa Hospital, 2-5-1 Honjo, Matsumoto, Nagano, 390-0814, Japan
[c] Department of Radiology, National Center Hospital, National Center of Neurology and Psychiatry (NCNP), 4-1-1 Ogawa Higashicho, Kodaira, Tokyo, 187-8551, Japan

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ABSTRACT

Introduction: Aspiration is a critical complication of dysphagia in Parkinson's disease (PD). Current methods for predicting aspiration are unsuitable for routine implementation owing to time constraints, cost, or insufficient predictive accuracy. We assessed the predictive performance of clinical measures, including dopamine transporter (DaT) imaging, for aspiration risk in patients with PD.

Methods: We retrospectively analyzed data from patients with PD who underwent videofluoroscopic swallowing examinations (VF) and DaT imaging within 12 months. Patients were divided into aspiration and non-aspiration groups based on VF findings. Logistic regression and receiver operating characteristic (ROC) analyses evaluated the predictive performance of DaT imaging parameters including striatal specific binding ratio (SBR) and subregional SBRs, calculated using DaT View and DaTQUANT software.

Results: Among 87 patients (38 females; mean age: 64 years; disease duration: 8.3 years [range: 1–20 years]; modified Hoehn and Yahr stages: 2 [range: 1–4]), 14.9 % experienced aspiration. DaT View striatal SBRs consistently showed significantly lower values in the aspiration group and negative associations with aspiration in logistic regression models, whereas DaTQUANT exhibited limited significance in intergroup differences and associations. ROC analysis showed DaT View striatal SBR of the better side (SBR*better*) as the optimal predictor (sensitivity 0.62, specificity 0.93 at cutoff: 2.03). DaTQUANT subregional analysis identified the anterior putamen as key in aspiration risk.

Conclusion: Reduced SBR in DaT imaging shows potential as an indicator of aspiration risk in patients with PD. These findings can help clinicians identify patients at risk of aspiration, allowing for proactive referral for detailed evaluation.

1. Introduction

Dysphagia is a common but critical symptom that significantly affects the prognosis of patients with Parkinson's disease (PD). Videofluoroscopic swallowing examinations (VF) have shown that most patients with PD exhibit varying degrees of dysphagia [1]. Aspiration, a severe dysphagia form and pneumonia cause [2], is the leading cause of death in patients with PD [3], necessitating timely and appropriate intervention.

Efficient screening for predicting aspiration is pivotal, given the time and financial constraints of detailed examinations like VF. Subjective measures, such as patient declarations and questionnaires (e.g., the Movement Disorder Society Unified Parkinson's Disease Rating Scale [MDS-UPDRS] and non-motor symptoms questionnaire), inadequately predicting aspiration risk [4]. While comprehensive questionnaires such as the Swallowing Disturbance Questionnaire (SDQ) or SDQ-J (version in Japanese) have been used to assess the risk of aspiration in PD with suspected dysphagia [5], these subjective assessments pose reliability concerns as they are potentially influenced by conditions such as cognitive function or risk awareness. Therefore, objective predictors based on PD pathophysiology are needed.

Objective measures, including PD-related movement symptoms, disease stage, and duration, have been shown to correlate with dysphagia [6]. However, many patients experience swallowing

* Corresponding author.
E-mail address: yamamoto@ncnp.go.jp (T. Yamamoto).

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problems in early disease stages [7], indicating its limitation as a predictive measure for aspiration. Although a recent study suggested an association between cardiac ^{123}I-metaiodobenzylguanidine (MIBG) scintigraphy and SDQ-assessed dysphagia [8], but the predictive value of imaging studies for aspiration remains underexplored.

Dopamine transporter (DaT) imaging has been used to evaluate striatal dopamine levels or the loss of dopaminergic neurons in the substantia nigra, which is the area of central pathology of PD [9–11]. Reduced DaT imaging signals in the striatum, where the axons of dopaminergic neurons terminate, are related to disease progression and motor symptoms severity [11]. Considering that dysphagia in PD is at least partly attributed to a dopamine-dependent motor deficit [12–14], the potential of reduced DaT imaging signals to predict aspiration in individual patients with PD appears plausible.

We aimed to evaluate the predictive performance of clinical measures, including DaT imaging, for aspiration in patients with PD using data from VF. Our findings could have potential implications for the earlier detection of aspiration complications by providing a more effective predictive marker.

2. Methods

2.1. Study design and setting

This retrospective, observational, single-center study was conducted at the National Hospital of the National Center of Neurology and Psychiatry (Tokyo, Japan). We retrospectively reviewed the medical records of all consecutive patients diagnosed with idiopathic PD, consistent with clinically established PD according to the International Parkinson and Movement Disorder Society PD criteria (MDS-PD criteria) [15], who underwent VF from July 1, 2015 to December 1, 2023. We targeted patients between 50 and 69 years to avoid the influence of presbyphagia. Patients at various disease stages were recruited for VF regardless of suspected or self-reported dysphagia, as part of routine clinical assessment.

The inclusion criterion was DaT imaging within 12 months before or after VF. The exclusion criteria were as follows: patients with familial PD or suspected familial history, as they potentially presented variant clinical phenotypes of idiopathic PD; patients with cognitive impairment (Mini-Mental State Examination [MMSE] score $\leq$23), as our focus was on patients with PD, not dementia with Lewy bodies or PD with dementia; patients with cerebrovascular disease, brain tumors, or other neurological conditions potentially affecting swallowing function as detected by brain MRI, to avoid confounding effects on the study results; patients in poor general condition during VF to ensure reliable data analysis; patients with nasogastric tubes or those who underwent gastrostomy, as they were not appropriate subjects for a study aimed at detecting dysphagia earlier (however, patients receiving device-aided therapies such as LCIG [which requires gastrostomy] or DBS were not excluded); and patients with inadequate evaluation of predefined clinical measures within 3 months before and after VF to ensure the quality of clinical assessment. The predefined clinical measures included demographic characteristics (age, sex, and body mass index [BMI]) and PD status (disease duration, modified Hoehn and Yahr scale [mH&Y], levodopa equivalent daily dose [LEDD], status of device-aided therapy, MDS-UPDRS, MMSE, Frontal Assessment Battery, and SDQ-J).

The predefined clinical measures described above and the specific binding ratio (SBR) values of DaT imaging were obtained within 3 and 12 months before and after VF, respectively. To clarify, DaT imaging was conducted at various stages of disease progression, as reflected by the wide range of disease durations in our VF database cohort.

2.2. Patient selection and demographics

A total of 200 VF were conducted on 174 patients aged 50–69 years with clinically established PD. Of these, 116 patients were included because they underwent DaT imaging within 12 months before or after VF. Of those, 29 patients met the exclusion criteria (Fig. 1). Finally, we analyzed 87 patients (38 females) with PD who met the eligibility criteria, with a mean age of 64 years (range: 51–69 years), disease duration of 8.3 years (range: 1–20 years), and mH&Y score of 1–4.

2.3. Videofluoroscopic swallowing examinations

VF was performed according to previously reported methods [2]. During VF, the patients were positioned similarly to their regular mealtime posture. Fluoroscopic imaging was performed on one side. A two-fold diluted solution of liquid barium (110 % w/v) was administered into the patient's oral cavity using a syringe. The patients were instructed to swallow, and their swallowing actions were recorded at 30 frames per second. A trained evaluator reviewed the recordings to detect aspirations. Patients reporting difficulty in swallowing underwent initial testing with 5 mL of thickened liquid. If no signs of aspiration were observed, subsequent tests were conducted using 5 and 10 mL of thinner liquids. Each swallowing sequence was captured once with an X-ray fluoroscopy duration of <5 min. Patients experiencing wearing-off fluctuations were tested during their "on" state. Aspiration was determined when liquid from the VF entered the trachea beyond the vocal cords, corresponding to a standard penetration-aspiration scale score of 6–8 [16]. Finally, the patients were divided into the aspiration and non-aspiration groups based on VF results. The VF was evaluated independently of other clinical and imaging assessments. For patients with repeated VF, we analyzed the data that met the eligibility criteria.

2.4. DaT imaging

For DaT single-photon emission computed tomography (SPECT) imaging (referred to as DaT imaging), each patient was injected with an average dose of 168 MBq [^{123}I]FP-CIT (DaTSCAN; Mediphysics, Tokyo, Japan). Image acquisition was initiated 3 h after tracer injection, with a median total scan time of 28 min. We used two SPECT/CT systems (Siemens Symbia T6 with a low-to medium-energy general-purpose

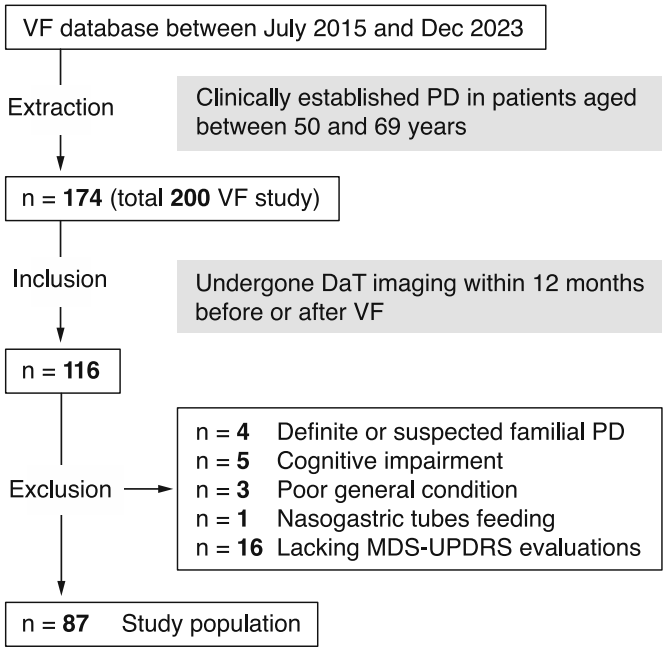

Fig. 1. Study flow diagram showing patient enrollment, inclusion, and exclusion based on the videofluoroscopic swallowing examination database and medical records. VF, videofluoroscopic swallowing examinations; PD, Parkinson's disease; DaT, dopamine transporter; MDS-UPDRS, Movement Disorder Society Unified Parkinson's Disease Rating Scale.

collimator [Siemens Healthineers, Erlangen, Germany] and GE Discovery NM/CT 670 pro with an extended low-energy general-purpose collimator [GE Healthcare, Chicago, IL]), both calibrated with a striatal phantom, as reported previously [17]. Image reconstruction was performed using the ordered-subset expectation–maximization method [17] and then filtered with a Butterworth filter (cutoff frequency 0.55–0.76 cycles/cm, order of 4–10). Reconstructions were performed with attenuation correction using only CT images and no scatter correction.

Two different approaches were employed for the quantitative analysis of DaT imaging: DaT View and DaTQUANT. DaT View software (version 8.0; Nihon Medi-Physics, Tokyo, Japan) was used to obtain striatal SBR, whereas DaTQUANT software (GE Healthcare, Little Chalfont, UK) facilitated comparative analysis of striatal SBR and further subregional assessments.

With DaT View, striatal SBR values were obtained using the Southampton method in accordance with previously reported protocols [18]. SBR was defined as the ratio of binding in the striatum to the reference region. The striatal volume of interest (VOI) was first automatically placed on hyperaccumulated voxels and then manually adjusted to include all striatal binding with reference to a multidirectional cross-section. The reference VOI was placed within the boundaries of the brain parenchyma, with an iso-contour threshold of 30 % for each image.

By contrast, DaTQUANT software utilizes a normalized VOI template with automatic image reorientation and adaptation to the reconstruction procedure [19]. We calculated SBR values for the striatum and its subregions, including the caudate, anterior putamen, and posterior putamen, as well as the putamen-to-caudate ratio. SBR values were computed for the better side (high SBR), the worse side (lower SBR), and their mean. In DaTQUANT, SBR is defined as the mean binding value of the striatal (or subregional) VOI divided by that of the occipital reference VOI, which differs from the calculation method used in DaT View.

2.5. Statistical analysis

We evaluated clinical measures and striatal SBR values obtained from DaT View and DaTQUANT software, analyzing hemispheric values (SBR*better* for the better side, SBR*worse* for the worse side) and their mean (SBR*mean*). Descriptive statistics are presented as median and interquartile range (IQR) for continuous data or counts and proportions for categorical data. Group comparisons between aspiration and non-aspiration groups were performed using the Mann-Whitney *U* test for continuous variables and the chi-squared test for categorical variables.

For striatal SBR values from each software, we evaluated their association with aspiration and their predictive performance. For the association analysis, logistic regression was conducted with two models: a crude model (unadjusted) and a multivariate model adjusted for age and sex as covariates, as these are established factors affecting dysphagia [7]. Results are presented as odds ratios with 95 % confidence intervals (95%CI). For predictive performance assessment, receiver operating characteristic (ROC) analysis was used. The area under the ROC curve (AUC) was calculated to evaluate overall predictive ability. Optimal cutoff points were determined using the Youden index. Sensitivity, specificity, positive likelihood ratio (PLR), and negative likelihood ratio (NLR) were calculated at the determined cutoff points.

For subregional analyses, we used DaTQUANT to calculate SBR values for each striatal subregion (caudate, anterior putamen, and posterior putamen) and putamen-to-caudate ratios. For each SBR measurement, we performed Mann-Whitney U-tests between groups, logistic regression analysis (unadjusted and adjusted for age and sex), and ROC analyses to evaluate their associations with aspiration and predictive

Table 1
Demographic and clinical characteristics of the study population.

	Aspiration group (n = 13)	Non-aspiration group (n = 74)	p-value
Age, years	66.0 (65.0–69.0)	65.0 (60.3–67.0)	0.184
Sex (female)	3/13 (23.1 %)	35/74 (47.3 %)	0.187
BMI, kg/m^2	21.8 (19.1–23.7)	22.0 (19.5–24.8)	0.366
Disease duration, years	8.0 (6.0–12.0)	7.0 (4.3–11.0)	0.393
mH&Y (“on”)	2.0 (2.0–3.0)	2.0 (2.0–3.0)	0.268
LEDD, mg	517 (445–680)	545 (381–866)	0.753
Device-aided therapy			
Any device	1/13 (7.7 %)	2/74 (2.7 %)	0.932
DBS	1/13 (7.7 %, bl STN-DBS)	1/74 (1.4 %, bl GPi-DBS)	
LCIG	0/13 (0 %)	1/74 (1.4 %)	
MDS-UPDRS Part I	5.0 (4.0–14.0)	9.0 (6.3–13.0)	0.322
MDS-UPDRS Part II	16.0 (10.0–22.0)	13.0 (9.3–19.0)	0.317
MDS-UPDRS Part III	27.0 (24.0–46.0)	26.5 (16.3–37.8)	0.446
MDS-UPDRS Part IV	1.0 (0.0–5.0)	1.5 (0.0–7.0)	0.570
MMSE	28.0 (27.0–29.0)	29.0 (27.0–30.0)	0.128
FAB	16.0 (12.5–17.0)	16.0 (15.0–17.0)	0.298
SDQ-J			
Above cutoff (≥11)	2/13 (15.4 %)	11/74 (14.9 %)	0.547
Total (max 41.5)	6.0 (4.5–7.8)	4.5 (1.5–7.5)	0.102
Oral (max 15)	3.0 (1.8–5.0)	2.0 (0.0–4.0)	0.381
Pharyngeal (max 26.5)	3.5 (2.5–4.0)	2.5 (0.5–4.5)	0.183
Striatal SBR			
DaT View SBR*better*	1.97 (1.71–2.82)	3.36 (2.71–4.14)	<0.001**
DaT View SBR*worse*	1.69 (1.19–2.78)	2.90 (2.29–3.78)	0.006**
DaT View SBR*mean*	1.71 (1.45–2.80)	3.08 (2.49–3.98)	<0.001**
DaTQUANT SBR*better*	0.74 (0.59–0.82)	0.94 (0.73–1.13)	0.037*
DaTQUANT SBR*worse*	0.73 (0.52–0.77)	0.79 (0.62–0.94)	0.104
DaTQUANT SBR*mean*	0.74 (0.54–0.79)	0.87 (0.67–1.06)	0.051

Striatal SBR values were analyzed using two different quantification methods: DaT View and DaTQUANT. For each method, values were evaluated for the better side (higher SBR), the worse side (lower SBR), and the mean of both sides. Continuous variables are presented as the median (interquartile range). Categorical variables are presented as counts (proportions). P-values are calculated using the Mann–Whitney *U* test or the chi-squared test. *p < 0.05, ** <0.01.
BMI, body mass index; DBS, deep brain stimulation; FAB, frontal assessment battery; GPi, globus pallidus interna; mH&Y, modified Hoehn and Yahr scale; LCIG, levodopa-carbidopa intestinal gel; LEDD, levodopa equivalent daily dose; MDS-UPDRS, Movement Disorder Society Unified Parkinson’s Disease Rating Scale; MMSE, mini-mental state examination; meanSBR, mean striatal-specific binding ratio; SDQ-J, Swallowing Disturbance Questionnaire, version in Japanese; STN, subthalamic nucleus.

performance.

Statistical significance was set at p-values <0.05. All statistical analyses were performed using R software (version 4.3.1; R Foundation, Vienna, Austria).

3. Results

3.1. Association between aspiration and demographic/clinical factors

Of the 87 patients, 13 (14.9 %) exhibited aspiration. Table 1 presents the demographic and clinical characteristics of the study population. No significant intergroup differences were noted in age, sex, disease duration, motor symptoms, nutritional status, cognitive function, or dysphagia awareness between the aspiration and non-aspiration groups, except for the striatal SBR values (Table 1).

3.2. Striatal DaT imaging and aspiration risk

Analysis of group differences in striatal SBR values revealed consistently lower values in the aspiration group with both software programs (Table 1). With DaT View, significant differences were observed in SBR*better* (1.97 [IQR 1.71–2.82] vs 3.36 [2.71–4.14], p < 0.001), SBR*worse* (1.69 [IQR 1.19–2.78] vs 2.90 [2.29–3.78], p = 0.006), and SBR*mean* (1.71 [IQR 1.45–2.80] vs 3.08 [2.49–3.98], p < 0.001). DaTQUANT analysis showed similar trends, with significant differences only in SBR*better* (0.74 [IQR 0.59–0.82] vs 0.94 [0.73–1.13], p = 0.037).

Further analyses evaluated the association between striatal SBR values and aspiration, as well as their predictive performance. All DaT View SBR values demonstrated significant associations with aspiration, with SBR*better* (crude OR = 0.25 [95%CI 0.11–0.60], adjusted OR = 0.21 [0.08–0.55]) and SBR*mean* (crude OR = 0.25 [95%CI 0.10–0.60], adjusted OR = 0.21 [0.08–0.56]) showing stronger associations than SBR*worse* (Supplementary Table 1). In DaTQUANT analysis, only SBR*better* showed a significant association (crude OR = 0.07 [95%CI 0.01–0.87], adjusted OR = 0.05 [0.00–0.83]). ROC analysis revealed superior predictive performance in DaT View SBR values compared to DaTQUANT, with SBR*better* showing the highest AUC in both software programs (DaT View: 0.80 [95%CI 0.65–0.95], DaTQUANT: 0.68 [0.53–0.83]) (Fig. 2). The optimal cutoff values were 2.03 for DaT View SBR*better* (sensitivity: 0.62, specificity: 0.93, PLR: 8.86, NLR: 0.41) and 0.84 for DaTQUANT SBR*better* (sensitivity: 0.77, specificity: 0.62, PLR: 2.03, NLR: 0.37).

Table 2
Subregional analysis of DaT imaging SBR within the striatum in patients with Parkinson's disease with and without aspiration.

Striatal subregion	Aspiration group (n = 13)	Non-aspiration group (n = 74)	p-value
Caudate			
Better side	0.93 (0.68–1.28)	1.20 (0.91–1.47)	0.096
Worse side	0.91 (0.64–1.03)	0.98 (0.77–1.27)	0.162
Mean	0.92 (0.65–1.14)	1.12 (0.83–1.39)	0.105
Anterior Putamen			
Better side	0.62 (0.60–0.81)	0.88 (0.70–1.07)	0.008**
Worse side	0.58 (0.47–0.74)	0.73 (0.60–0.87)	0.047*
Mean	0.59 (0.54–0.78)	0.82 (0.67–0.97)	0.018*
Posterior Putamen			
Better side	0.46 (0.38–0.54)	0.54 (0.42–0.64)	0.082
Worse side	0.36 (0.28–0.47)	0.43 (0.35–0.53)	0.091
Mean	0.42 (0.34–0.48)	0.50 (0.37–0.59)	0.086
Putamen/Caudate Ratio			
Mean	0.87 (0.73–0.89)	0.83 (0.76–0.88)	0.681

SBR values, calculated by DaTQUANT, were analyzed for striatal subregions (anterior putamen, posterior putamen, caudate) and putamen-to-caudate ratio. For each region, hemispheric (better and worse side) and mean SBR values were calculated. Data are presented as median (interquartile range). p-values calculated by the Mann–Whitney *U* test. *p < 0.05, ** <0.01.
DaT, dopamine transporter; SBR, striatal-specific binding ratio.

3.3. Subregional analysis of DaT imaging and aspiration risk

In subregional analysis using DaTQUANT, the anterior putamen showed significant differences between groups in the better side (0.62 [IQR 0.60–0.81] vs 0.88 [0.70–1.07], p = 0.008), worse side (0.58 [0.47–0.74] vs 0.73 [0.60–0.87], p = 0.047), and mean values (0.59 [0.54–0.78] vs 0.82 [0.67–0.97], p = 0.018) (Table 2). No significant differences were observed in the caudate, posterior putamen, or putamen-to-caudate ratios between groups.

Logistic regression analysis showed that anterior putamen SBR values were significantly associated with aspiration across all analytical approaches (better side, worse side, and mean values, in crude and multivariate models) (Supplementary Table 2). ROC analysis of the anterior putamen revealed predictive performance (AUC: 0.73 [95%CI 0.60–0.87] for the better side) that exceeded DaTQUANT striatal SBR (SBR*better* AUC: 0.68) but remained inferior to DaT View striatal SBR (SBR*better* AUC: 0.80).

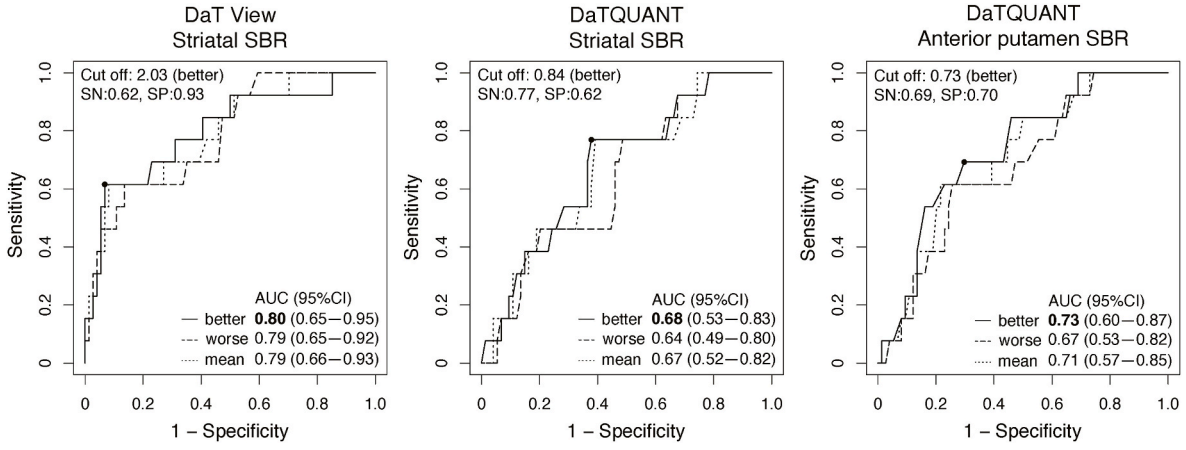

Fig. 2. Receiver operating characteristic (ROC) analysis showing the predictive performance of DaT View striatal SBR values (left), DaTQUANT striatal SBR values (middle), and DaTQUANT anterior putamen SBR values (right) for aspiration.
For each analysis, results for the better (higher SBR) and worse (lower SBR) sides and mean values are shown with their respective AUC (95%CI). The optimal cutoff points were calculated for the SBR of the better side, which showed the highest AUC value in each analysis.
AUC, area under the receiver operating characteristic curve; CI, confidence interval; SN, sensitivity; SP, specificity.

4. Discussion

4.1. Study significance

Our findings suggest a plausible association between reduced SBR on DaT imaging and propensity for aspiration. Notably, DaT View analysis consistently demonstrated significant associations between striatal SBR values with aspiration risk in logistic regression, with reliable predictive performance indicated by ROC analysis. Although DaTQUANT exhibited limited discriminative ability in striatal analysis, its subregional analysis identified the anterior putamen as a key region associated with aspiration risk, showing more reliable predictive properties within the DaTQUANT software. These findings are credible because aspiration was confirmed using VF, the gold standard for evaluating swallowing.

Previous studies have explored the relationship between DaT imaging and dysphagia in PD. Polychronis et al. conducted pioneering research in a large cohort of drug-naïve patients with PD, suggesting potential links between reduced DaT uptake and dysphagia, using subjective measures of swallowing [20]. Kim et al. further advanced this field by using advanced image statistical methods to investigate the anatomical distribution of dopamine loss within the basal ganglia in relation to dysphagia, providing valuable insights into the striatal subregions associated with various swallowing impairments and deepening our understanding of the underlying pathophysiology [21].

Although these studies advanced our understanding, they did not provide practical guidance for clinicians on when to pursue detailed swallowing evaluations in individual patients. Our study addresses this gap by proposing a simple predictive model for aspiration risk using the clinically convenient SBR as a measure and by identifying specific subregions of interest. Furthermore, we focused specifically on aspiration rather than other aspects of dysphagia, allowing for clearer clinical interpretation given its established prognostic significance in patients with PD [2].

4.2. Comparison with other established predictors

We demonstrated that DaT View striatal SBR values may serve as a promising predictor for identifying patients at risk for aspiration, outperforming previously established screening methods in terms of reliability, specificity, and ease of routine implementation. Notably, DaT View SBR*better* exhibited the highest predictive performance (AUC: 0.80) among all measurements, including DaTQUANT SBR values.

Direct questioning, such as in the SDQ and SDQ-J [5,22], is a feasible and well-validated approach established as an aspiration predictor in PD (sensitivity 0.78, specificity 0.85) [5]. However, given the reliability concerns of subjective assessments, objective measures are needed as predictors. In addition, the wide range of motor and nonmotor symptoms in PD makes it difficult to focus on a single symptom in daily practice. These indicate the need to identify predictors of aspiration based on basic and objective clinical information or standard tests.

Age >63.5 years and LEDD >475 mg are potential objective predictors for VF-confirmed aspiration, with AUCs of 0.59 and 0.63, respectively [6]. Although factors such as male sex, BMI, mH&Y, and UPDRS Part III have been associated with aspiration, their predictive values have not been validated [6,23]. PD duration is a relatively effective predictor of VF-confirmed penetration and milder dysphagia than aspiration, with an AUC of 0.75 at a cutoff of 4.5 years; however, it clearly showed no association with aspiration [24]. The association of MIBG myocardial scintigraphy, which is associated with questionnaire-validated dysphagia, remains unconfirmed with aspiration or other objective observation [8].

In our study, DaT View striatal SBR*better* demonstrated the highest predictive performance, with an AUC of 0.80, indicating it is a more reliable predictor of aspiration than age or LEDD. Notably, it achieved high specificity (0.93) and moderate sensitivity (0.62) with a cutoff of 2.03, indicating its potential utility in ascertaining aspiration risk rather than screening. Of note, DaTQUANT analysis of anterior putamen SBR demonstrated fair predictive ability (AUC: 0.73), which was superior to age (0.59) or LEDD (0.63) but inferior to PD duration (0.75) in previous studies [6,24]. Furthermore, DaT imaging has a practical advantage, as it is already integrated into routine practice, unlike specialized tests such as cough reflex sensitivity testing [24]. Taken together, DaT imaging analysis, particularly using DaT View, shows potential as a predictor of aspiration risk in patients with PD, offering possible advantages in specificity compared to some established markers, although further validation is needed.

4.3. Dopaminergic role in swallowing

The observed association between reduced striatal binding on DaT imaging and aspiration is consistent with previous understanding [25] of how dopaminergic deficits influence dysphagia in patients with PD. Levodopa partially improves specific phases of swallowing associated with aspiration [12–14]. These levodopa-responsive components of swallowing are believed to be governed by the nigrostriatal dopaminergic system [25], deficits of which are detectable using DaT imaging [10,11]. Striatal binding on DaT imaging likely reflects the degree of impairment within this “dopaminergic” swallowing system.

Notably, there is also a “non-dopaminergic” swallowing system that comprises the levodopa-unresponsive component of dysphagia in PD [25]. According to the dysphagia development model in PD, considering the progression of Lewy bodies based on Braak’s model, subclinical dysphagia arises from impairment in the “non-dopaminergic” system, followed by clinical dysphagia onset resulting from disruption in the compensatory “dopaminergic” system at an advanced stage [25]. In line with this model, our results imply that DaT imaging may predict early aspiration by detecting the critical phase of dysphagia pathophysiology in PD when the compensatory dopaminergic swallowing system is disrupted.

4.4. Anterior putamen and aspiration in PD

Our subregional analysis reveals a significant association between dopaminergic loss in the anterior putamen and aspiration risk in PD. The anterior putamen, part of the associative striatum along with the caudate [26], is involved in non-motor symptoms such as cognitive deficits [27] and orthostatic hypotension [28], as well as goal-directed (non-habitual) behavior and movement [26]. If we adhere to the traditional view [26], which regards dysphagia as a habitual movement, our results suggest that disruption in the "goal-directed" swallowing system may play a key role in clinical aspiration, potentially compensating when the "habitual" system fails. This raises questions about the striatal origin of swallowing movements and whether swallowing is truly a habitual movement predominantly associated with the posterior putamen.

Our findings highlighting the anterior putamen align with those of Kim et al. [21], with both studies agreeing that the posterior striatal components contribute less to aspiration risk. Kim et al. found a stronger association between the anterior caudate and aspiration, which we did not observe, possibly because of methodological differences, as our DaTQUANT software approach could not subdivide the caudate into anterior and posterior parts.

Our study emphasizes the associative striatum, particularly the anterior putamen, as crucial in PD-related aspiration risk. This raises the possibility of the anterior putamen’s distinctive role within the associative striatum in dysphagia. It also prompts reconsideration of the striatal origins of dysphagia in terms of habitual versus goal-directed actions and compensatory mechanisms.

4.5. Methodological differences in DaT imaging analysis

Although DaT View revealed a significant association of striatal SBR

values with aspiration and demonstrated reliable predictive performance in patients with PD, DaTQUANT showed limited association and discriminative ability in striatal analysis. This discrepancy may reflect DaTQUANT's template-based analysis with smaller VOIs, which is more susceptible to partial volume effects. This phenomenon occurs when striatal and surrounding signals mix at VOI boundaries, particularly in the presence of striatal atrophy [29]. By contrast, DaT View uses a larger VOI that encompasses the entire striatum, potentially reducing the impact of partial volume effects. DaTQUANT, however, may have masked true differences in striatal SBR because of these effects while still providing valuable subregional insights through its segmentally defined VOI approach. These methodological differences highlight the importance of selecting the appropriate analysis method when quantifying DaT imaging in neurodegenerative conditions for clinical and research applications.

4.6. Differences from previous studies

Our findings are, in part, inconsistent with those of previous research, as we did not find significant differences in age, disease stage, or motor symptoms between the aspiration and non-aspiration groups [6]. The inconsistency in age and disease stage could be attributed to the homogeneity of our study cohort, particularly in terms of the age cutoff.

Notably, no intergroup differences were observed in motor symptoms or MDS-UPDRS Part III scores, despite significant differences in striatal SBR values and anterior putamen binding. This could be explained by the potential differences in susceptibility to anti-parkinsonian medication between dysphagia and other motor symptoms. Dysphagia in patients with PD is at most only partially responsive to levodopa or even not clinically responsive [12–14]. Furthermore, the plateau effect of levodopa on motor symptoms could contribute to this observation. The responsiveness of motor symptoms to levodopa plateaus at a certain dosage [30]. This explains why both groups achieved similar levels of motor symptoms with comparable LEDD despite different SBR values. However, the specific relationship between quantified DaT SPECT indicators and favorable LEDD titration remains unclear, which is a limitation of our explanation. Our results further support previous findings that dysphagia could be less responsive to levodopa than other motor symptoms measured by the MDS-UPDRS Part III. The relatively small number of patients may have also affected the statistical power, potentially contributing to the inconsistency with previous studies. This limitation underscores the need for larger-scale investigations to further validate our findings.

In our study, SDQ-J scores were not significantly different between the aspiration and non-aspiration groups, although the aspiration group tended to have higher scores (prone to dysphagia). This discrepancy with the original SDQ-J paper may be owing to differences in the background of the study population. As DaT imaging is more performed in the early stages of the disease rather than in advanced stages, the patients in the present study were younger (mean age, 64 years) and at an earlier stage of mH&Y (median stage, 2) than those in the original SDQ-J paper (mean age, 67 years; median stage, 3), in which patients at mH&Y stage 5 were also included, accounting for 33 % of patients in the aspiration group [5]. Given these differences from previous studies, our findings may be applicable to relatively early-stage patients.

4.7. Limitations

This study has some limitations. First, the small sample size, owing to strict eligibility criteria and the requirement of both VF and DaT imaging, may have reduced statistical power, limiting the detection of differences in various parameters. Second, the homogeneity of our study population, wherein older patients and those with familial PD were excluded, may limit the broad application of our findings to clinical settings. Third, as our study focused on a population at a relatively early stage due to the eligibility criteria requiring DaT imaging, caution is necessary when applying our findings to patients at advanced stages, where DaT imaging is not routinely used. Finally, although our findings are promising, further research with prospective cohorts is essential to validate these results, minimize potential biases, and establish the clinical utility of DaT imaging SBR values as a predictor of aspiration risk.

5. Conclusion

We suggest that DaT imaging analysis, particularly using DaT View striatal SBR values, may serve as a potential predictor of aspiration risk in patients with idiopathic PD. Our findings can help clinicians identify patients at risk of aspiration earlier, allowing for proactive referral for a detailed swallowing evaluation. These findings shed light on the pathophysiology of dysphagia in PD and highlight the critical role of dopaminergic dysfunction, particularly in the anterior putamen, in the manifestation of aspiration. Further prospective research is needed to validate these findings and establish the clinical utility of DaT imaging SBR values as a predictor of aspiration risk.

CRediT authorship contribution statement

Jun Tanimura: Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Toshiyuki Yamamoto:** Writing – review & editing, Visualization, Validation, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Yoko Shigemoto:** Writing – review & editing, Software, Methodology. **Noriko Sato:** Writing – review & editing, Methodology. **Yuji Takahashi:** Writing – review & editing, Supervision, Project administration, Conceptualization.

Ethical compliance statement

This study was approved by the Ethics Committee of the National Center of Neurology and Psychiatry (No. A2023-121) and was conducted in accordance with the Declaration of Helsinki. All patients and their families received a written explanation of the VF procedure and the use of the results for research, and they signed the informed consent form.

Data statement

The data that support the findings of this study are available upon reasonable request. Restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. https://www.ncnp.go.jp/about/data_policy.html (in Japanese) can provide information on the data access policy.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2025.107307.

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