Aspiration pneumonia and life prognosis in Parkinson's disease and related disorders

（パーキンソン病およびパーキンソン病関連疾患における誤嚥性肺炎発症と生命予後に関する研究）

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RESEARCH ARTICLE

Impact of Aspiration Pneumonia on the Clinical Course of Progressive Supranuclear Palsy: A Retrospective Cohort Study

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Abstract

Introduction

Although aspiration pneumonia is the most common complication of progressive supranuclear palsy (PSP), the clinical impact of aspiration pneumonia on disease course and survival has not been fully estimated. Thus, we retrospectively analyzed the prognostic factors and clinical consequences of pneumonia in PSP.

Methods

The clinical course of patients with aspiration pneumonia was surveyed. The association between baseline clinical features (2 years from disease onset) and latency to the initial development of pneumonia was investigated using survival time and Cox regression analyses.

Results

Ninety patients with a clinical diagnosis of PSP were observed for 5.1±3.8 years (mean ±SD), and 22 had aspiration pneumonia. Subsequently, 20 patients (91%) had to discontinue oral feeding entirely and 13 (59%) died, whereas, of 68 patients without pneumonia, only three patients (4%) died. Time to initial development of pneumonia was strongly correlated with survival time (Spearman R = 0.92, $P<0.001$), with a mean latency of 2.3 years to death. Among baseline clinical features, early fall episodes and cognitive decline were significant predictors of pneumonia ($P = 0.001$ and $P<0.001$, respectively, log rank test). Cox regression analysis demonstrated that early fall episodes (adjusted hazard ratio: 3.9, 95% confidence interval: 1.2–12.5, $P = 0.03$) and cognitive decline (adjusted hazard ratio: 5.2, 95% confidence interval: 1.4–19.3, $P = 0.02$) independently predicted pneumonia. By contrast, dysphagia was not associated with pneumonia ($P = 0.2$, log rank test).

Conclusion

Initial development of pneumonia indicates an unfavorable clinical course and predicts survival time (mean survival time 2.3 years). Patients with early falls and cognitive decline were at high risk of early development of pneumonia.

Introduction

Progressive supranuclear palsy (PSP) is a neurodegenerative disease presenting with symptomatic parkinsonism including bradykinesia, muscular rigidity, and postural reflex disturbance. In addition, most patients with PSP suffer from dementia and dysphagia. The most common cause of death in PSP is pneumonia [1], which occurs subsequent to silent aspiration resulting from pre-existing dysphagia [2]. Dysphagia is a well-recognized complication of PSP [3], occurring in up to 80% of patients [4]. Both the time to development of dysphagia and that from dysphagia to death are shorter in PSP than in Parkinson disease (PD) [5]. In addition, PSP patients with early development of dysphagia have a short survival time [4] because repeated aspiration pneumonia can be fatal. Therefore, physicians attempt to prevent aspiration pneumonia by medication or palliative treatment, including adjusting food consistency, feeding techniques, and gastrostomy tube feeding [6]. The timely application of these treatments is important to maintain the quality of life of patients, and identification of predictive factors of early development of aspiration pneumonia is required to prevent serious consequences of dysphagia in PSP [7]. However, factors that reliably predict the early development of pneumonia and subsequent clinical courses have not been fully elucidated. PSP is clinically heterogeneous, especially in the early stages. Although several studies have reported early clinical features associated with prognosis of PSP [8–11], studies focusing on the impact of pneumonia on the clinical course of PSP are lacking. Here, we investigated the clinical consequences of pneumonia and the association between early clinical features and latency to the initial development of pneumonia, using a survival time analysis in a retrospective cohort.

Materials and Methods

Study Design

To identify factors associated with the early development of pneumonia in PSP, a retrospective cohort study was designed and a survival time analysis was adopted. The main outcome measure was the time from the start of study observation to the initial development of pneumonia. Observation began 2 years from clinical onset (2 years from an initial neurological symptom), and clinical symptoms and signs of PSP during these 2 years were regarded as baseline features.

Patients

We studied consecutive patients with parkinsonism who were followed in the Utano National Hospital Parkinson Disease Center between November 2006 and December 2014. Patients were admitted to our hospital and examined by two or more neurologists with expertise in movement disorders. Detailed clinical evaluations were undertaken to determine whether they fulfilled clinical criteria for a probable or possible diagnosis of PSP, according to the PSP criteria of the National Institute of Neurological Disorders and Stroke and the Society for PSP (NINDS-SPSP) [8]. Patients who fulfilled PD criteria in the UK Brain Bank Clinical Diagnostic Criteria (Steps 1 and 2) [12] were excluded. To exclude a possible diagnosis of multiple system

atrophy or other diseases manifesting as parkinsonism, brain magnetic resonance imaging was performed. To exclude dopa-responsive parkinsonism represented by PD, the response to an adequate dose of levodopa was confirmed in all cases. Patients observed for <2 years from the initial symptoms and signs were excluded because the start of the study observation was set at 2 years from disease onset. Patients with pseudobulbar palsy due to cerebrovascular diseases were also excluded. Immunocompromised patients (e.g., by hematological disorders) were also excluded because they are prone to infections including pneumonia.

Data Collection

Clinical factors such as early fall episodes, cognitive decline, supranuclear gaze palsy, tremor, and others were collected from medical records within 2 years from disease onset. The data were recorded on data sheets designed for this study. Structured interviews were performed with patients or their families at the hospital, or on the telephone to complete the data sheets. The following clinical data were also collected: age at disease onset, observation period, initial symptom at disease onset, time from disease onset to dysphagia, and cause of death. Smoking history was also noted because smoking is significantly associated with the development of aspiration pneumonia [13]. Patients who had smoked at disease onset were included in a smoker group.

Main Outcome Measure

The time from the start of the study observation to the first episode of pneumonia was the main outcome measure. A diagnosis of pneumonia was made according to the following criteria: clinical signs and symptoms, white blood cell count ≥10,000/μL or proportion of neutrophils ≥80%, serum C-reactive protein level ≥60 mg/L, fever (body temperature >37°C), and new infiltrates or consolidations on chest radiography (X-ray or computed tomography). Detailed data were collected for patients who had been treated for pneumonia in another hospital or by a primary care physician to determine whether the above criteria for pneumonia had been met. Patients who died before developing pneumonia were classified as having an alternative outcome.

Possible Predictive Factors

To identify predictive clinical factors for pneumonia, a comprehensive review of the symptoms and signs important in making a diagnosis of PSP was performed. We collected data on the following clinical features and phenotypes at the start of the study observation period: fall episodes, cognitive decline, bradykinesia, dysarthria, dysphagia, tremor, asymmetric onset of extrapyramidal signs, postural reflex disturbance, extra axial-dystonia, supranuclear gaze palsy, abnormal saccade or pursuit eye movements, and ever having a response to levodopa. These features have previously been used by Williams et al. to characterize clinical phenotypes of PSP [14]. The definitions of these symptoms and signs are shown in S1 Table. According to the definitions [14] proposed by Williams et al., patients were classified into Richardson's syndrome (RS) or PSP-parkinsonism (PSP-P) phenotypes on the basis of baseline clinical features. When clinical features supporting these two phenotypes were equal or data about baseline features were incomplete, patients were grouped as unclassifiable.

Statistical Methods

The incidence of pneumonia was estimated as the number of patients developing pneumonia divided by the corresponding person-years at risk. The relationship (A) between latency to

dysphagia and total survival time and (B) between latency to first pneumonia and total survival time was examined using Spearman's rank correlation coefficient (in deceased cases with experience of pneumonia). The risk of early development of pneumonia associated with each predictive factor was investigated by survival time analysis. Thereafter, the risk associated with significant predictive factors as detected by survival time analysis was evaluated using hazard ratios (HRs) by Cox regression analysis, adjusted by sex and age at disease onset. A previous large study of pathologically confirmed PSP patients has indicated that older age at onset and male sex are associated with poor life prognosis [10].

Analyses were performed using PASW Statistics version 18 (SPSS Inc., Chicago, IL, USA). Results are expressed as mean ± SD, and statistical significance was defined as $P<0.05$.

Ethics

This study was approved by the Bioethics Committee of Utano National Hospital (registry number: 25–21) and the protocol was consistent with the principles of the Declaration of Helsinki. The Bioethics committee waved the need for informed consent due to the retrospective nature of the study and anonymity of the collected data, according to the Ethical Guideline for Medical and Health Research Involving Human Subjects from Ministry of Health, Labour and Welfare, Japan.

Results

According to the NINDS-SPSP criteria, 100 patients were diagnosed as probable or possible PSP. All patients showed supranuclear gaze palsy. The response to levodopa was reviewed in detail in all patients, and none showed a moderate to excellent response, but dopaminergic therapy had a modest beneficial effect in 20 patients. Ten patients were excluded for the following reasons. Eight patients had disease duration <2 years, one had a history of cerebral infarction causing bulbar dysfunction, and one had comorbid multiple myeloma. As a result, 90 patients who were diagnosed with PSP were eligible and all were enrolled into the study.

Anonymized case data set of the study was registered at Dryad Data Repository site.

Demographic Characteristics of the Patients

The demographic characteristics of the 32 female and 58 male patients are shown in S2 Table. The mean age at PSP onset was 68.6 years and the mean disease duration at study enrollment was 7.1 years. The mean study observation period was 5.1 years. During the observation period, 22 patients developed pneumonia, and the incidence was 55 (95% confidence interval [CI]: 32–77) per 1,000 person-years. Initial symptoms at disease onset are shown in S2 Table. The most frequent initial symptom was fall, which occurred in 39% of patients. During the observation period, 16 patients died and the mean disease duration of these patients was 9.0 years. Ten (71%) of 14 patients in whom the cause of death was known died of complications associated with severe dysphagia; five of them died of recurrent pneumonia, three died of sepsis related to the total parenteral nutrition catheter, and two died of suffocation.

Clinical Course with Pneumonia

Fig 1 shows the chronological clinical course of 22 patients who had experienced pneumonia. In the study period, 13 (59%) of these patients died, and the cause of death was pneumonia (n = 5), sepsis (n = 2), suffocation (n = 1), and other (n = 5). Two of the deceased patients were investigated pathologically, and the diagnosis of PSP was confirmed according to

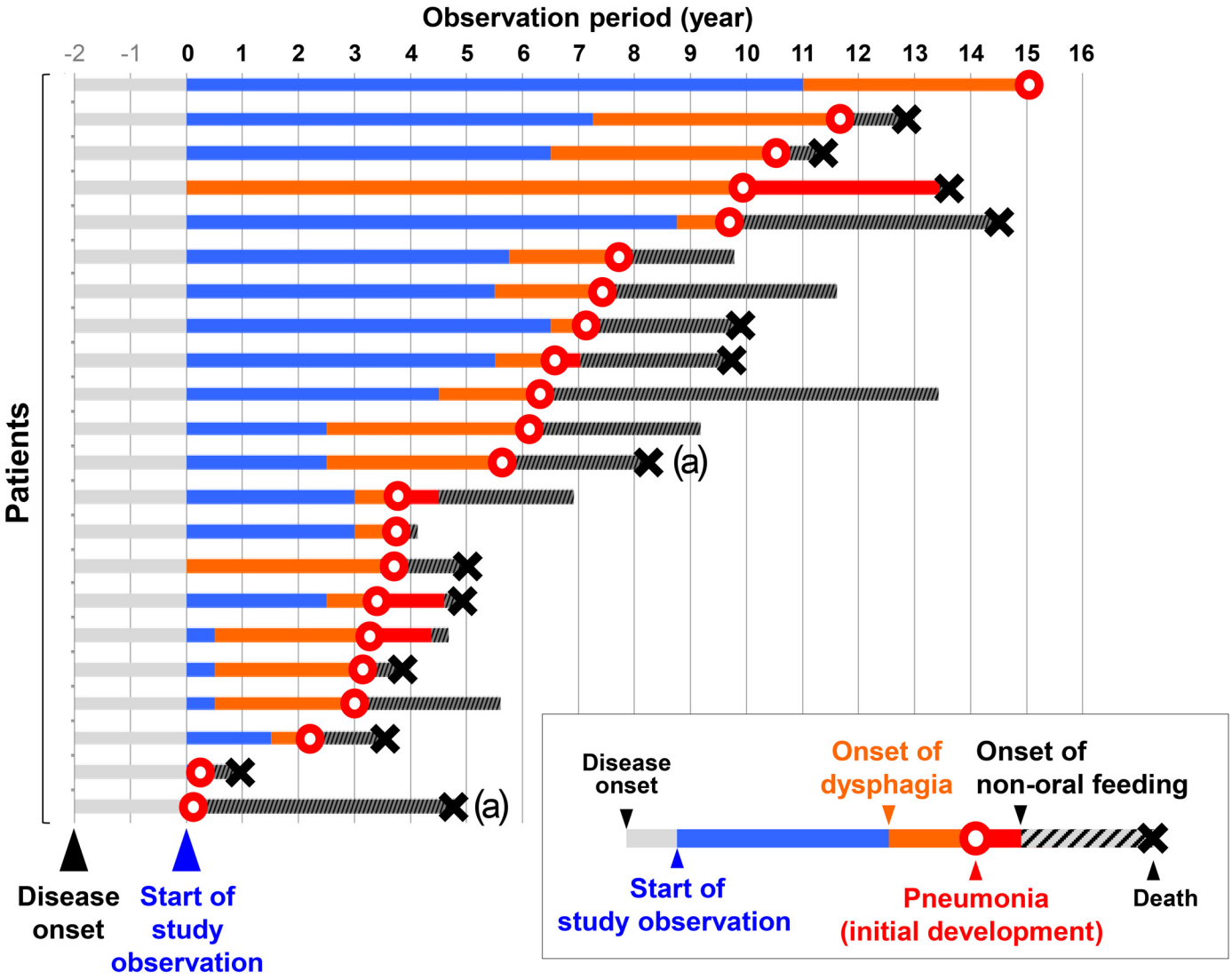

Fig 1. Clinical courses of 22 patients with experience of pneumonia. Pneumonia developed in 22 patients and 13 patients died in the observation period. [a]Pathologically confirmed cases of progressive supranuclear palsy.

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neuropathological diagnostic criteria [15]. Neuronal fibrillary tangles and glial inclusions (tufted astrocytes) were seen in the basal ganglia and brainstem, which is a typical distribution in PSP.

Of 22 patients with pneumonia, radiographic examinations by chest CT or X-ray showed new dorsal infiltration or consolidation consistent with aspiration pneumonia in 21 patients, but detailed radiological data were not obtained in one patient with pneumonia treated in another hospital. All 22 patients suffered from moderate to severe dysphagia before the development of pneumonia. Time to initial development of pneumonia from study enrollment was <4 years in 10 patients; however, it ranged from 0 to 15 years. After the initial development of pneumonia, 20 patients (91%) required non-oral feeding (NOF), including nasogastric tube feeding, percutaneous gastrostomy (PEG) tube feeding, and total parenteral nutrition (Table 1). Owing to severe or persistent dysphagia, NOF was not discontinued in any of these patients during the observation period. Of 20 patients with NOF, 18 finally required PEG tube

Table 1. Comparison of patients with and without the experience of aspiration pneumonia.

		Aspiration pneumonia		
	All (n = 90)	+ (n = 22)	- (n = 68)	P value
Total observation period, person-years	-	183.4	272.3	
Age of disease onset, years (mean ± SD)	68.6 ± 7.1	68.8 ± 7.7	68.5 ± 6.9	0.84[a]
Male, n (%)	58 (64)	16 (73)	42 (62)	0.45[b]
Smoking history, n (%)	19 (21)	5 (23)	14 (21)	1.00[b]
Latency[c] to dysphagia, years (mean ± SD)	4.4 ± 2.7	6.0 ± 3.1	4.0 ± 2.4	0.04[a]
Latency[c] to first pneumonia, years (mean ± SD)	-	7.9 ± 3.9	-	-
Cases with non-oral feeding, n (%)	21 (23)	20 (91)	1 (1)	<0.001[b]
Number of deceased cases, n (%)	16 (18)	13 (59)	3 (4)	<0.001[b]
Clinical features during the first 2 years of disease				
Fall episodes, n (%)	60 (67)	15 (68)	45 (66)	1.00[b]
Cognitive decline, n (%)	24 (27)	5 (23)	19 (28)	0.78[b]
Dysarthria, n (%)	42 (47)	9 (41)	33 (49)	0.63[b]
Dysphagia, n (%)	24 (27)	4 (18)	20 (29)	0.41[b]
Tremor, n (%)	18 (20)	7 (32)	11 (16)	0.13[b]
Asymmetric onset of extrapyramidal signs, n (%)	20 (23)	6 (29)	14 (21)	0.55[b]
Bradykinesia, n (%)	52 (78)	11 (79)	41 (77)	1.00[b]
Postural reflex disturbance, n (%)	52 (91)	10 (83)	42 (93)	0.28[b]
Extra axial-dystonia, n (%)	25 (50)	2 (20)	23 (57)	0.07[b]
Supranuclear gaze palsy, n (%)	35 (69)	9 (75)	26 (67)	0.73[b]
Abnormal saccade or pursuit eye movements, n (%)	34 (76)	4 (57)	30 (79)	0.34[b]
Response to levodopa ever, n (%)	21 (33)	7 (47)	14 (29)	0.23[b]
RS / PSP-P phenotype, n	48 / 13	10 / 5	38 / 8	0.28[b]

RS/PSP-P, Richardson syndrome / PSP-Parkinsonism

[a]Mann–Whitney test

[b]Fisher's exact test

[c]Latency from disease onset

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feeding, and two required total parenteral nutrition because of recurrent pneumonia under nasogastric tube feeding. Mean survival time after NOF was 2.0 years (range 0.2–4.8 years).

S1 Fig shows the correlation between survival time and latency to dysphagia and that between survival time and latency to first pneumonia in the 13 deceased patients with experience of pneumonia. Latency to dysphagia correlated with survival time (Spearman R = 0.60, $P = 0.03$), and latency to first pneumonia was strongly correlated with survival time (Spearman R = 0.92, $P<0.0001$). Mean life expectancy after initial development of pneumonia was 2.3 years (SD 1.4 years, range 0.7–4.8 years). The equation produced by a linear regression model of the relationship between total survival time (y) and latency to pneumonia (x) was $y = 1.05\ x + 1.9$ (years). As expected, there was also a moderate correlation between latency to the onset of dysphagia and pneumonia in the 22 patients (Spearman R = 0.67, $P = 0.01$).

A comparison of demographic data and baseline clinical features (in the first 2 years of the disease) between patients with and without experience of pneumonia is shown in Table 1. Patients with pneumonia had to discontinue oral feeding and died more frequently than those without pneumonia. The most frequent baseline clinical feature was postural reflex disturbance, and the second most frequent was abnormal saccade or pursuit eye movements. The least frequent feature was tremor. Forty-eight patients were classified as RS and 13 as PSP-P.

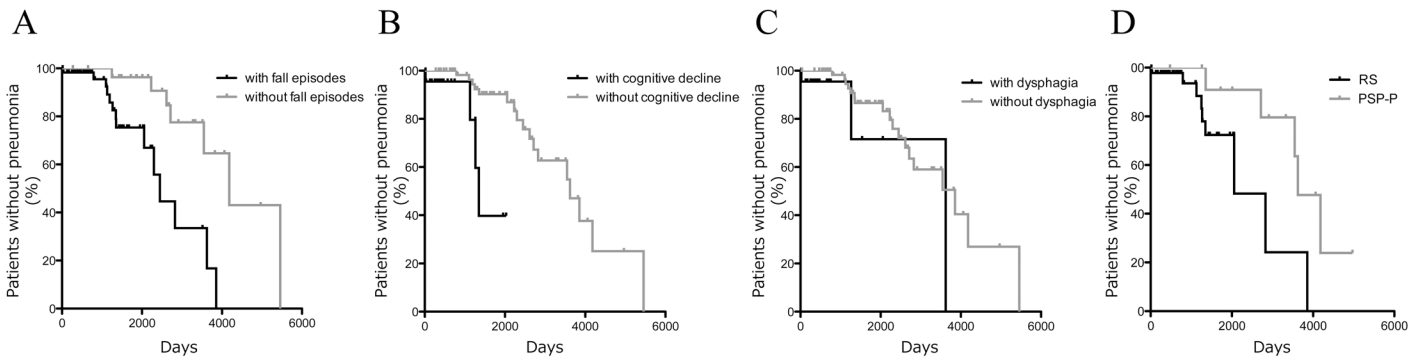

Fig 2. Survival analyses stratified by patients' clinical features and phenotypes during initial 2 years of disease. Latency from the start of the study to the initial development of pneumonia, stratified by with or without (A) fall episodes (log rank $P = 0.001$), (B) cognitive decline (log rank $P<0.001$), (C) dysphagia (log rank $P = 0.08$), and (D) clinical phenotypes (RS and PSP-P; log rank $P = 0.05$).

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There were no significant differences in baseline clinical features and phenotypes between patients with and without pneumonia.

Survival Time Analysis

Fig 2 shows the Kaplan–Meier curves of the cumulative proportion of patients without pneumonia stratified by baseline clinical features and phenotypes. Fall episodes (log rank test, $P = 0.0006$) and cognitive decline ($P = 0.0025$) were significant predictors of shorter latency to pneumonia; however, dysphagia was not significant ($P = 0.2$). The RS phenotype was a significant risk factor for early development of pneumonia ($P<0.0001$).

There was no significant difference in the pneumonia latency between patients stratified by dysarthria ($P = 0.2$), tremor ($P = 0.9$), asymmetric onset of extrapyramidal signs ($P = 0.9$), bradykinesia ($P = 0.4$), postural reflex disturbance ($P = 0.7$), extra axial-dystonia ($P = 0.07$), supranuclear gaze palsy ($P = 0.08$), abnormal saccade or pursuit eye movements ($P = 0.4$), or response to levodopa ever ($P = 0.2$).

Cox regression analysis indicated that cognitive decline at baseline was the most significant risk factor for pneumonia (adjusted HR: 5.2, 95% CI: 1.4–19.3, $P = 0.02$), and it was still the most significant risk factor in the model after adjustment for dysphagia as a baseline feature (adjusted HR: 5.2, 95% CI: 1.4–19.3, $P = 0.01$). Early fall episodes were also a significant risk factor of pneumonia (adjusted HR: 3.9, 95% CI: 1.2–12.5, $P = 0.03$; Table 2).

Discussion

The current study demonstrated that latency to the initial development of pneumonia was strongly correlated with survival time, and early clinical symptoms could predict shorter

Table 2. Cox proportional hazards regression models for the predictive factors of early development of aspiration pneumonia.

	Prognostic variables	Adjusted hazard ratio	95% confidence interval	*P* value
Model 1	**Cognitive decline**	**5.2**	**1.4–19.3**	**0.015**
	Fall episodes	**3.9**	**1.2–12.5**	**0.023**
Model 2	**Cognitive decline**	**6.0**	**1.4–19.3**	**0.014**
	Fall episodes	**4.0**	**1.2–12.9**	**0.021**
	Dysphagia	0.8	0.2–3.2	0.756

Model 1, HR adjusted by age and sex; Model 2, HR adjusted by age, sex, and dysphagia (yes/no) during the first 2 years of the disease.

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latency to pneumonia in PSP. After initial development of pneumonia, all patients required inpatient care and most had to discontinue oral feeding as a result of severe dysphagia. There was only a 2.3-year latency from the initial development of pneumonia to death. This report provides a reminder that the initial development of pneumonia is a noteworthy event in PSP because it has a serious negative affect on both quality of life and survival.

In this study, early fall episodes and cognitive decline predicted a shorter latency to pneumonia, and these features were independent significant risk factors in Cox regression analysis. In a series of recent studies, early clinical features such as fall [8, 9], cognitive decline [9, 11], dysphagia [8, 11], dysarthria, and diplopia [8] were associated with shorter survival time, in addition to the established risk factors, age at onset [9–11, 16] and male sex [10, 16]. The clinical phenotype of RS in which fall and cognitive decline are prominent is also a significant risk factor for shorter survival [10, 11]. In our cohort, early fall episodes, cognitive decline, and RS phenotype were confirmed as significant risk factors for shorter survival (S2 Fig). Therefore, our study results suggested that predictors of a shorter latency to pneumonia and shorter survival time were relevant, and the initial development of pneumonia could be used as a reliable surrogate marker of an increased risk of mortality in PSP.

The most common cause of death in PSP is aspiration pneumonia [4]. In our study cohort, dysphagia-related death, which included aspiration pneumonia, sepsis related to total parenteral nutrition catheter, and suffocation, accounted for 91% of deaths with a known cause. Intriguingly, dysphagia as a baseline feature was rarely associated with early development of pneumonia. Initially, dysphagia was regarded as an early sign of PSP and was listed as a supportive feature in diagnostic criteria [2, 17]. However, recent studies demonstrated that dysphagia is a less frequent feature in the early stage [14] but becomes more frequent in the mid-to-late stage [18–20]. Mean latency to dysphagia was 3.4–4.7 years in previous studies [5, 20–23] and 4.4 years in our study cohort, including RS patients as well as patients with PSP-P and pure akinesia with gait freezing (PAGF). The last two phenotypes have a slowly progressive clinical course and generally mild tau deposition [24–26]. Latency to dysphagia of RS patients (3.1±1.9 years) was significantly shorter than that of PSP-P patients (6.6±3.5 years; S3 Table).

PSP patients are more accurate in expressing their swallowing difficulties than PD patients, and a swallowing questionnaire is useful method to predict the swallowing disturbance in PSP [2]. To improve survival, an appropriate and timely swallowing evaluation and intervention for silent aspiration resulting from dysphagia may be important in pre-pneumonia phase. Actually, our patients were questioned about their swallowing problems at every interview, and then instructed to use a fluid thickener and avoid dry and sticky food prior to developing pneumonia. Although the results of the current study failed to show the association of early-onset dysphagia and pneumonia development, it does not exclude the possibility that the earlier detection of dysphagia and such instruction about food consistency does not delay the development of aspiration pneumonia.

While some patients with PSP show levodopa responsiveness and mild improvement of dysphagia [27, 28], management of dysphagia in the later stages of PSP is more difficult. In our study, most patients with NOF finally required PEG tube feeding. In spite of palliative treatments including adjusting food consistency and feeding techniques, a PEG tube was placed a few months after the initial development of pneumonia in most of the patients in the current study. Mean disease duration of the 16 deceased cases (including 10 patients with a PEG tube) was 9.0 years (S3 Table), which is longer than that previously reported (6.6–8.0 years) [4, 10, 11]. PEG tube feeding was expected to decrease the risk of pneumonia and prolong survival. In our cohort, it was unclear whether PEG placement prolonged survival. Further prospective study is required to confirm the life advantage effect of PEG placement in PSP.

The current study had several limitations. They include selection bias arising from a single-center population and a retrospective study design. In addition, the application of a clinical diagnosis of PSP remains a major methodological limitation. In the current study data were not collected according to predefined schedule and several data were missing; however, they were collected at least monthly in most patients. The neurological signs and symptoms were evaluated by expert neurologists. Therefore, the completeness and accuracy of the data were limited but enough to draw the conclusions.

Conclusions

In summary, better knowledge of the early symptoms of PSP, especially fall episodes and cognitive decline, will be useful for the prediction and prevention of the development of pneumonia, and will support a better clinical course. We found that the initial development of pneumonia predicted a short survival time and should be recognized as one of the significant clinical milestones in the middle or late stage of PSP.

Supporting Information

S1 Fig. Correlation between survival time and latency to dysphagia or initial pneumonia in 13 deceased patients. The starting point (zero) indicates the start of study observation (2 years from disease onset). A 95% CI is indicated in gray. (A, Spearman R = 0.60, $P = 0.03$; B, Spearman R = 0.92, $P<0.001$).
(TIFF)

S2 Fig. Survival analyses stratified by patients' clinical features and phenotypes during first 2 years of disease. (A–D) Survival time stratified by with or without (A) fall episodes (log rank $P = 0.015$), (B) cognitive decline (log rank $P<0.001$), (C) dysphagia (log rank $P = 0.018$), and (D) clinical phenotypes (RS and PSP-P; log rank $P = 0.002$).
(TIFF)

S1 Table. Definitions of baseline clinical symptoms and signs used in the study.
(DOCX)

S2 Table. Demographic characteristics of the 90 study patients.
(DOCX)

S3 Table. Comparison of patients with RS and PSP-P.
(DOCX)

Author Contributions

Conceived and designed the experiments: ST TO H. Sawada. Performed the experiments: ST TO AU MK KP KY H. Sugiyama H. Sawada. Analyzed the data: ST TO H. Sawada. Wrote the paper: ST TO H. Sawada. Pathological examinations and analyses in autopsy cases: CM KI HF.

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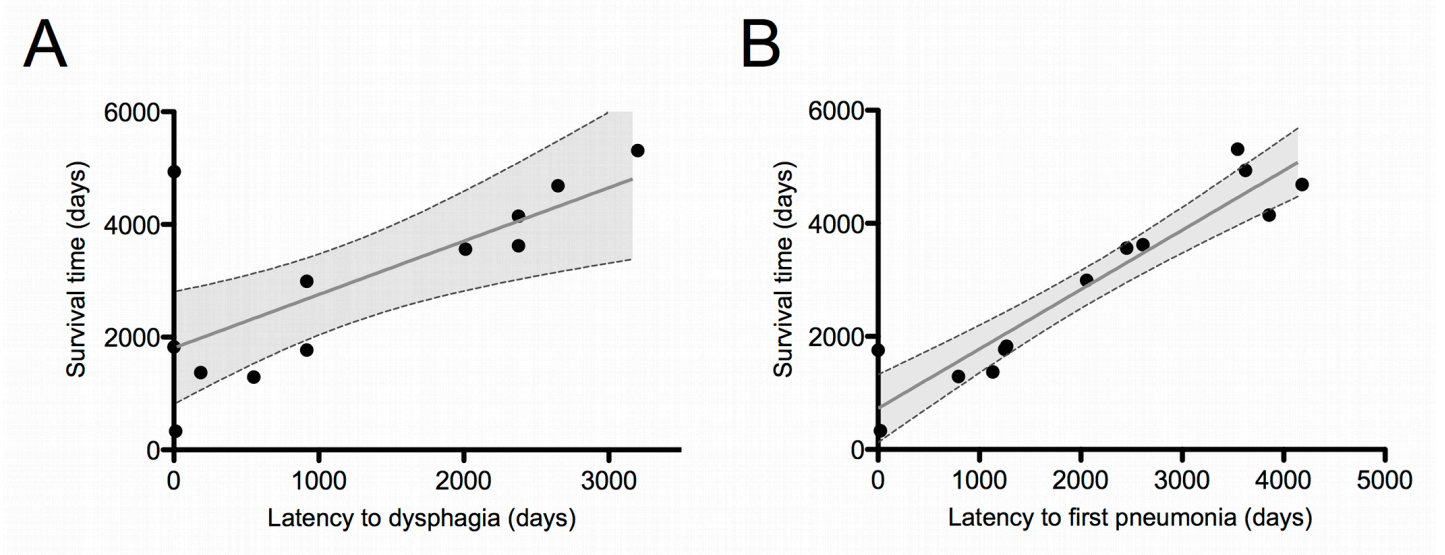
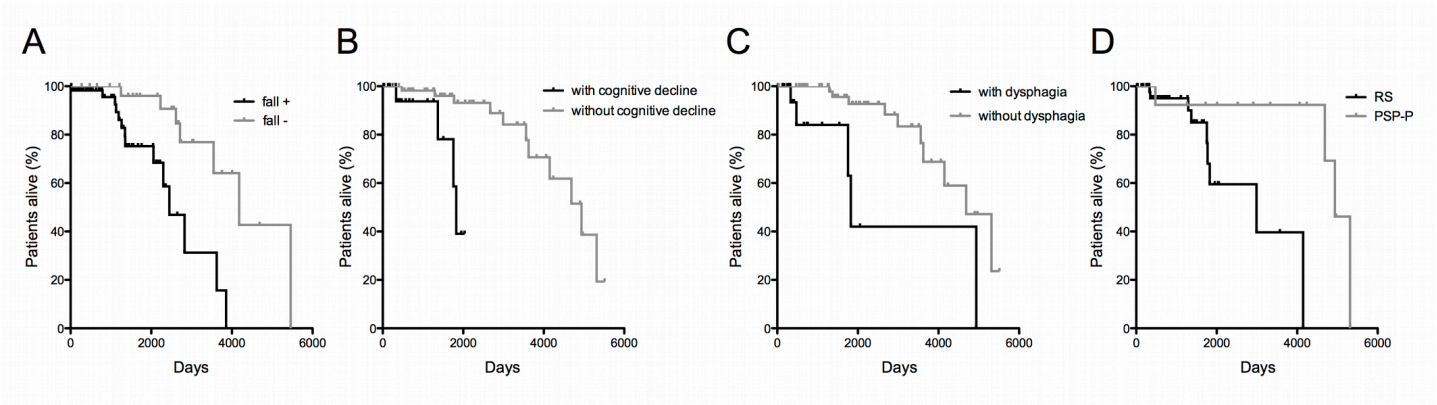


S1 Fig. Correlation between survival time and latency to dysphagia or initial pneumonia in 13 deceased patients. The starting point (zero) indicates the start of study observation (2 years from disease onset). A 95% CI is indicated in gray. (A, Spearman R = 0.60, $P = 0.03$; B, Spearman R = 0.92, $P<0.001$).
(TIFF)



S2 Fig. Survival analyses stratified by patients' clinical features and phenotypes during first 2 years of disease. (A–D) Survival time stratified by with or without (A) fall episodes (log rank $P = 0.015$), (B) cognitive decline (log rank $P<0.001$), (C) dysphagia (log rank $P = 0.018$), and (D) clinical phenotypes (RS and PSP-P; log rank $P = 0.002$).
(TIFF)

S1 Table. Definitions of baseline clinical symptoms and signs used in the study

Feature	Definition
Fall episodes	Description of fall episodes regardless of the cause.
Cognitive decline	Patient's, caregivers' or clinician's perception of any present cognitive decline. This included descriptions of episodes of bradyphrenia, changes in personality, and a slowing of thought processes. If patients underwent neuropsychological tests (e.g., the Mini-Mental State Examination (MMSE)), the results of such tests were referenced. When a combination of cognitive decline, positive neuropsychological tests, and DSM-IV[a] definition of dementia could not be obtained, the patient was treated as a missing value.
Bradykinesia	Presence of any mention of bradykinesia or motor slowing.
Dysarthria	Description of any alteration in speech quality compared with speech prior to disease onset.
Dysphagia	Description of swallowing abnormalities, including the documentation of patient's subjective and caregivers' objective impressions.
Tremor	Description of any type of tremor.
Asymmetric onset of extrapyramidal signs	If there was a difference in the motor signs between the left and the right sides of the body, asymmetry was recorded as being present. This included asymmetry of tremor, rigidity, bradykinesia, or functional decline.
Postural reflex disturbances	Postural reflex disturbances
Extra axial-dystonia	Presence of dystonia in any body part apart of the trunk and neck.
Supranuclear gaze palsy	Medical recording of a restricted range of eye movement in vertical directions.
Abnormal saccade or pursuit eye movements	Medical recording of abnormal saccadic or smooth pursuit eye movements.
Ever having a response to levodopa	Patient and clinician's interpretation of improvement was assessed from case notes, and in some cases, according to improvement in the motor scores of United Parkinson Disease Rating Scale (UPDRS part III) after levodopa administration.

[a]Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition.

S2 Table. Demographic characteristics of the 90 study patients

Number of patients	90
Age of disease onset, years (mean ± SD)	68.6 ± 7.1
Observation period[a], years (mean ± SD)	5.1 ± 3.8
Male, n (%)	58 (64)
Probable / Possible progressive supranuclear palsy, n (%)	55 (61) / 35 (39)
Incidence of pneumonia during observation period, n (%)	22 (24)
Number of deceased cases, n (%)	16 (18)
Total disease duration of deceased cases, years (mean ± SD)	9.0 ± 4.6
Initial symptom at disease onset	n (%)
Fall	35 (39)
Bradykinesia	14 (16)
Gait disturbance	15 (17)
Hand clumsiness	8 (9)
Tremor	8 (9)
Speech disturbance	5 (6)
Difficulty of eye-lid opening	4 (4)
Hypomimia	1 (1)
Cause of death in deceased cases	n (%)
Recurrent pneumonia	5 (31)
Sepsis (related to total parenteral nutrition catheter)	3 (19)
Suffocation	2 (13)
Cancer	2 (13)
Acute cholecystitis	1 (6)
Sudden death	1 (6)
Unknown	2 (13)

[a]From 2 years of the disease to the end of the observation.

S3 Table. Comparison of patients with RS and PSP-P

	All (n=90)	RS (n=48)	PSP-P (n=13)	RS vs. PSP-P (P value)
Age of disease onset, years (mean ± SD)	68.6 ± 7.1	70.6 ± 6.6	67.7 ± 8.7	0.20[b]
Male, n (%)	58 (64)	30 (63)	9 (69)	0.75[c]
Cases with the experience of pneumonia, n (%)	22 (24)	10 (21)	5 (38)	0.28[c]
Latency[a] to dysphagia, years (mean ± SD)	4.4 ± 2.7	3.1 ± 1.6	6.7 ± 3.4	<0.001[b]
Latency[a] to first pneumonia, years (mean ± SD)	7.9 ± 3.8	6.0 ± 3.3	10.4 ± 3.0	0.02[b]
Case with NOF (non-oral feeding), n (%)	21 (23)	10 (21)	4 (31)	0.45[c]
Number of deceased cases, n (%)	16 (18)	9 (19)	4 (31)	0.45[c]
Total disease duration of deceased cases, years (mean ± SD)	9.0 ± 4.6	6.8 ± 3.3	12.6 ± 6.2	0.048[b]
Clinical features during the first 2 years of disease				
Fall episodes, n (%)	60 (67)	47 (98)	2 (15)	<0.001[c]
Cognitive decline, n (%)	24 (27)	23 (48)	1 (8)	0.01[c]
Dysarthria, n (%)	42 (47)	27 (56)	5 (38)	0.35[c]
Dysphagia, n (%)	24 (27)	20 (42)	2 (15)	0.11[c]
Tremor, n (%)	18 (20)	7 (15)	7 (54)	0.006[c]
Asymmetric onset of extrapyramidal signs, n (%)	20 (23)	7 (15)	8 (62)	0.002[c]
Bradykinesia, n (%)	52 (78)	33 (77)	10 (91)	0.43[c]
Postural reflex disturbance, n (%)	52 (91)	42 (95)	3 (50)	0.009[c]
Extra axial-dystonia, n (%)	25 (50)	20 (49)	3 (60)	1.00[c]
Supranuclear gaze palsy, n (%)	35 (69)	30 (75)	2 (50)	0.30[c]
Abnormal saccade or pursuit, n (%)	34 (76)	31 (89)	1 (25)	0.01[c]
Response to levodopa ever, n (%)	21 (33)	14 (39)	3 (43)	1.00[c]

[a]Latency from disease onset

[b]Mann-Whitney test

[c]Fisher's exact test

PLOS ONE

RESEARCH ARTICLE

Video-fluoroscopic swallowing study scale for predicting aspiration pneumonia in Parkinson's disease

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Abstract

Introduction

A number of video-fluoroscopic swallowing study (VFSS) abnormalities have been reported in patients with Parkinson's disease (PD). However, the most crucial finding of subsequent aspiration pneumonia has not been validated fully. We conducted a retrospective and case-control study to determine the clinically significant VFSS findings in this population, and to propose a practical scale for predicting aspiration pneumonia in patients with PD.

Methods

We enrolled 184 PD patients who underwent VFSS because of suspected dysphagia. The patients who developed aspiration pneumonia within six months of the VFSS were assigned as cases and the patients without aspiration pneumonia at six months were designated as controls. Logistic regression analysis was performed to determine the prognostic VFSS features based on the data of swallowing 3 mL of jelly, which were used to make a PD VFSS scale (PDVFS). The validity of the new PDVFS was evaluated by ROC analysis. Additionally, we used the survival time analysis to compare time to death between groups, stratified by the PDVFS score.

Results

Twenty-five patients developed aspiration pneumonia. Among the previously-proposed VFSS features, mastication, lingual motility prior to transfer, aspiration, and total swallow time were identified as significant prognostic factors. We combined these factors to form the PDVFS. The PDVFS score ranges from 0 to 12, with 12 being the worst. ROC analysis revealed 92% sensitivity and 82% specificity at a cutoff point of 3. The higher PDVFS group showed shorter time-to-death than the lower PDVFS group (log rank $P = 0.001$).

Conclusion

Our newly developed VFSS severity scale (based on jelly swallowing) for patients with PD was easy to rate and could predict subsequent aspiration pneumonia and poor prognosis in patients with PD.

Introduction

Dysphagia is a common complication of the middle and later stages of Parkinson's disease (PD), occurring in over 80% of patients [1]. The most common cause of death in such patients is aspiration pneumonia, resulting from a preexisting dysphagia [2]. To prevent the serious consequences of dysphagia in PD, the predictive factors of pneumonia development need to be identified.

Video-fluoroscopic swallowing study (VFSS) is a widely performed procedure used for detecting dysphagia and reveals some abnormalities in 75% to 97% of individuals with PD [3–6]. In particular, a VFSS can reveal oropharyngeal dysphagia [7]. In the oral phase, abnormal bolus formation, residue on the tongue, and piecemeal deglutition can be noted. In the pharyngeal phase, pharyngeal dysmotility, pharyngeal stasis, and vallecular residue after swallowing are sometimes observed [4, 8, 9]. However, the factors that are the most crucial for predicting subsequent development of aspiration pneumonia (and its consequent effects on prognosis), among the various abnormal features that may be observed, are not validated fully for patients with PD.

The purpose of the study was to identify the most significant features on VFSS for predicting the development of aspiration pneumonia and poor prognosis in patients with PD and to create a simple VFSS scale that is suitable for practical use.

Materials and methods

Study design

To identify the VFSS findings that were associated with development of aspiration pneumonia in patients with PD, we performed a retrospective case-control study. The primary outcome measure was the development of aspiration pneumonia. The patients were divided into two groups: those who developed aspiration pneumonia within six months after VFSS (cases) and those who did not develop aspiration pneumonia (controls). The association between VFSS parameters and pneumonia was analyzed to identify the predictive features by multivariate analysis.

Subjects

For screening, we recruited consecutive PD patients who had never been diagnosed with aspiration pneumonia, and who underwent VFSS at the Utano National Hospital Parkinson's Disease Center between July 2005 and July 2015. At our hospital, the typical reasons for VFSS referral were oropharyngeal dysphagia suspected by patients or patients' caregivers, or objective swallowing problems (e.g., frequent productive cough, sialorrhea at a moderate level or higher, prolonged mealtime duration, or wet voice suggesting penetration or aspiration).

The diagnosis of PD was made according to the UK Brain Bank Clinical Diagnostic Criteria (Steps 1 and 2). All the subjects underwent brain magnetic resonance imaging to exclude other neurologic disorders. The patients were excluded if they were receiving tube feedings or had a

tracheostomy; if they had other diseases that could cause dysphagia (e.g., stroke, esophageal cancer, drug-induced encephalopathy, and other neurodegenerative diseases); and if they were observed for fewer than six months after VFSS.

Definition of aspiration pneumonia

The patients who were newly diagnosed by the supervising physician as demonstrating aspiration pneumonia fulfilled two or more of the following criteria: (1) clinical signs and symptoms compatible with pneumonia (e.g., rales or rhonchi on chest auscultation); (2) changes in inflammatory markers, including white blood cell count >10,000/μL, proportion of neutrophils >80%, or serum C-reactive protein level >60 mg/L; and (3) chest radiography findings of new infiltrates or consolidation in the lower dorsal (gravity dependent) segments, supporting a diagnosis of aspiration pneumonia. The most commonly-observed chest CT finding of a bronchopneumonia pattern with a gravity-dependent distribution [10] provides valuable information for diagnosing aspiration pneumonia [11].

Data collection

In addition to the VFSS findings, we collected the following clinical data on the day of the VFSS: age, disease duration, unified Parkinson's disease rating scale part III motor score (UPDRS-3), Hoehn-Yahr stage, dietary intake interventions related to dysphagia (ordinary diet or processed diet), and body mass index (BMI). If available within three months of VFSS, we recorded Mini-mental State Examination (MMSE) scores for cognitive evaluation and serum albumin concentrations.

According to the diagnostic criteria, a clinical diagnosis of aspiration pneumonia was confirmed by two of three investigators (S.T., T.O., and H.S.) by reviewing radiological evidence and checking patients' clinical signs and laboratory data within the medical record. If a definitive diagnosis was not documented, the diagnosis was made according to discussion amongst the researchers. The diagnosis was double marked by two auditors (H.O. and T.I.) who were physicians with considerable experience treating patients with pneumonia. S.T., T.O., and A. U. obtained other data from medical records, as necessary. All the obtained data were audited and certified as identical to the original medical record by K.W., the clinical research coordinator of our institute and an experienced auditor of clinical research studies.

The author (S.T.) retrospectively evaluated all the prerecorded VFSS movies retrospectively sequences, without the associated clinical data, in strict accordance with the standardized VFSS rating protocol of rating VFSS used in this study.

VFSS protocol

Registered dietitians prepared a jelly containing a nonionic contrast agent, according to a prescribed recipe. The patients were given 3 mL of jelly with a spoon and were asked to swallow voluntarily. Lateral views of the patients swallowing were recorded using a high-speed (30 frames per second) VFSS system. The VFSS was scored based on digitally recorded data. Anti-Parkinsonism medications were taken within one to two hours before the VFSS to evaluate swallowing function during the "on" medication period.

Selection of VFSS parameters as predictor variables

We extracted the VFSS parameters that predicted development of aspiration pneumonia in patients with PD from the available literature. A PubMed search was completed for articles published from 1986 to 2015 using the keywords "Parkinson's disease", "dysphagia", and

"videofluoroscopy". Studies that described prominent VFSS features in patients with PD who exhibited dysphagia were selected. We then searched the individual articles for definitions of selected VFSS parameters which were compiled and used as a tool to guide the VFSS rating process. Each variable of the various VFSS parameters was converted to a binary code for further analyses. Continuous variables were transformed to dichotomous based on the most discriminating cutoff point for predicting aspiration pneumonia, as determined by the receiver operating characteristic (ROC) curve.

Variable selection for Parkinson's disease VFSS scale

First, we assessed the association between each VFSS parameter and the development of aspiration pneumonia using Fisher's exact test; parameters with statistically significant ($p < 0.05$) associations and large effects (odds ratio >10.0) were selected for further analysis. Second, using binary logistic regression analysis with stepwise variable selection, we identified the statistically significant parameters to obtain the most suitable model for predicting aspiration pneumonia.

A Parkinson's disease VFSS scale (PDVFS) was devised based on the total value of the selected variables, which were weighed according to the regression coefficient in the model. The ROC curve of PDVFS for the development of pneumonia was used to test for validity and to determine the reference value (cutoff point) that showed optimal sensitivity and specificity. Additionally, ROC curves of PDVFS stratified by mean age, cognitive impairment (MMSE >24 vs. ≤ 24), disease severity (Hoehn-Yahr stage 1–3 or 4–5), and dietary interventions (processed or ordinary diet) were plotted to confirm the reproducibility of PDVFS across various conditions.

Reliability tests for Parkinson's disease VFSS scale

To examine the inter-rater reliability of the PDVFS, six speech-language-pathologists (SLPs) in our institute with extensive experience treating patients with PD and rating the VFSS sequences assessed the PDVFS sequences according to a standardized protocol. All the SLPs were blinded to the clinical data associated with the patients. The inter-rater reliability was determined as the intraclass correlation coefficient (ICC), based on repeat scoring of 15% of the VFSS (selected randomly), as derived from a two-way random effects analysis of variance model.

For checking the intra-rater reliability of the PDVFS the author re-rated the VFSS more than a month after the first evaluation. The intra-rater reliability was assessed using Cohen's kappa coefficient.

To evaluate the validity of the PDVFS discriminative properties to predict development of aspiration pneumonia after the VFSS sensitivity analyses in subgroups after stratification by age, cognitive impairment, disease severity, and dietary intervention were performed.

Survival time analysis of life prognosis

To validate the clinical efficacy of PDVFS, we compared the life prognosis after VFSS among the study participants. All-cause mortality was analyzed and a Kaplan-Meier curve was obtained. Observation was from the time of the VFSS to the day of death or censored; lost to follow-up was regarded as alternative outcome. The statistical significance of the differences was examined by a log rank test.

All the statistical analyzes were performed using PASW Statistics version 18 (SPSS Inc., Chicago, IL, USA). $P < 0.05$ was considered statistically significant.

Ethics

This study was approved by the Bioethics Committee of Utano National Hospital (registry number: 28–15) and the protocol was consistent with the principles of the Declaration of Helsinki. All the participants signed an informed consent form prior to enrollment.

Results

Subjects for analysis

A total of 331 consecutive PD patients who underwent VFSS were recruited for screening. After 147 patients were excluded according to the exclusion criteria, 184 patients were enrolled into the study. Twenty-five patients (13.6%) who developed aspiration pneumonia were assigned as cases, and 159 patients (86.4%) who did not develop aspiration pneumonia were assigned as controls (Fig 1).

Demographic characteristics of the study population

In the enrolled subjects, the mean (SD) age was 73.0 (8.0) years and the mean (SD) disease duration was 8.6 (5.6) years. The demographic characteristics of the cases and controls are shown in Table 1. In comparison with the controls, the cases were significantly older (P = 0.009) and the proportion of males was higher (P = 0.002). There was no difference in

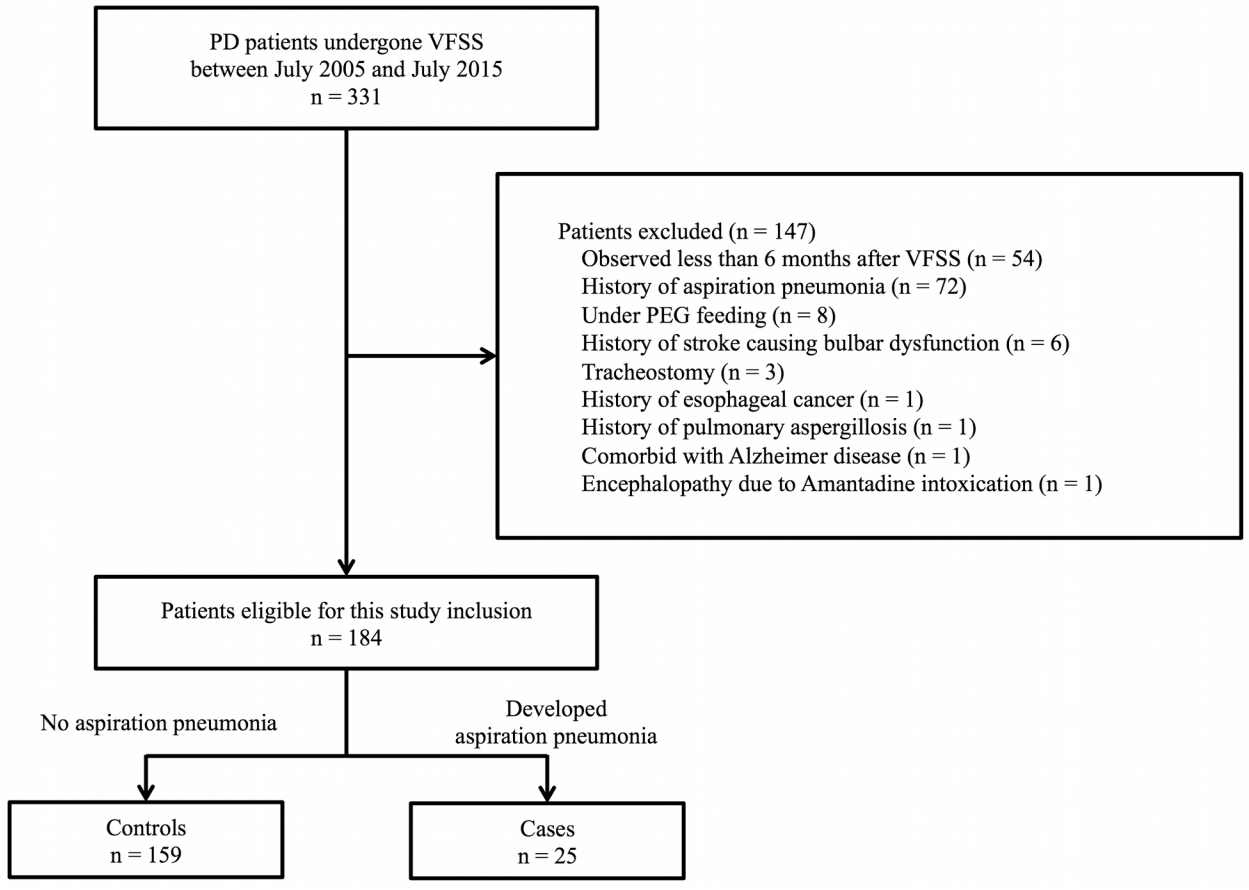

Fig 1. Flow diagram of participants included in the study.

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Table 1. Demographic and clinical profiles of cases and controls.

	Control	Case	P value
N	159	25	
Age at a VFSS[1], year (mean ± SD)	72.4 ± 8.1	76.8 ± 7.4	0.009[5]
Male, %	39.0	72.0	0.002[6]
Disease duration, year (mean ± SD)	8.4 ± 5.5	10.0 ± 6.1	0.2[5]
UPDRS-3[2] score (mean ± SD)	26.8 ± 11.1	38.0 ± 10.9	<0.001[5]
Hoehn-Yahr stage 4–5, %	28.9	64.0	0.001[6]
MMSE[3] ≤24, %	34.9	86.4	<0.001[6]
BMI[4] (mean ± SD)	20.9 ± 3.5	19.3 ± 3.4	0.04[5]
Serum albumin, g/dl (mean ± SD)	3.7 ± 0.4	3.4 ± 0.4	<0.001[5]
Patients consuming processed diets, %	39.0	72.0	0.002[6]

[1] Video-fluoroscopic Swallowing Study

[2] the unified Parkinson's disease rating scale part III motor score

[3] Mini Mental State Examination, missing values in 16 patients (13 in control and 3 in case)

[4] Body Mass Index

[5] P value from Mann–Whitney test

[6] P value from Fisher's exact test

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disease duration between the two groups. Compared with the controls, the cases had significantly higher Hoehn-Yahr stages (P = 0.001) and UPDRS-3 scores (P < 0.001), and significantly lower MMSE scores (P < 0.001), BMI (P = 0.004), and serum albumin concentrations (P < 0.001). There were significantly more cases than controls who were placed on processed diets (P = 0.002).

VFSS parameters associated with aspiration pneumonia development

PubMed search for articles on VFSS features in patients with PD generated 24 studies (S1 Table). We extracted 26 abnormal parameters from among all VFSS parameters proposed in these studies. There were 13 parameters involving the oral phase: pre-swallow anterior spill, lingual pumping, poor velopharyngeal closure, swallow hesitancy, piecemeal deglutition, lip closure, mastication, lingual motility prior to transfer, bolus formation, premature bolus loss, palatal elevation, poor bolus propulsion, and residue in the oral cavity. There were nine parameters involving the pharyngeal phase: triggering of pharyngeal swallow, vallecular residue, laryngeal elevation, pyriform sinus residue, reduced epiglottal tilt, coating of pharyngeal wall, repeated swallowing, aspiration, and cricopharyngeal dysfunction. Finally, there were four timed parameters: oral transit time, pharyngeal transit time, pharyngeal delay time, and total swallow time.

The continuous data from the parameters of lingual pumping, oral transit time, pharyngeal transit time, pharyngeal delay time and total swallowing time were transformed to dichotomous variables using ROC curves (S1 Fig). The optimal cutoff points were 4 times (lingual pumping), 5 seconds (oral mastication time), 5 seconds (oral transit time), 4 seconds (pharyngeal transit time), and 10 seconds (total swallow time). The definitions of the binary coded values for all parameters are shown in S2 Table.

The odds ratios of the VFSS parameters in predicting aspiration pneumonia based on univariate analyzes are shown in Table 2; 21 of 26 parameters were associated with aspiration pneumonia. Eight of the 21 parameters were incorporated into the logistic regression model; these included mastication, lingual motility prior to transfer, bolus formation, poor bolus

Table 2. Crude odds ratio of each VFSS parameter for the development of aspiration pneumonia.

Parameter	Positive in control, n (%)	Positive in case, n (%)	Odds Ratio	95% CI (lower limit)	95% CI (upper limit)	P value
Oral phase						
Pre-swallow anterior spill	1 (1)	0 (0)	0.99	0.98	1.01	1.00
Lingual pumping	54 (34)	9 (36)	0.25	0.03	1.90	0.21
Poor velopharyngeal closure	23 (14)	1 (4)	0.25	0.03	1.90	0.21
Swallow hesitancy	27 (17)	11 (44)	3.84	1.58	9.37	0.006
Piecemeal deglutition	52 (33)	14 (56)	2.62	1.11	6.17	0.04
Lip closure	1 (1)	1 (4)	6.58	0.40	108.79	0.25
Mastication	4 (3)	18 (72)	99.64	26.57	373.70	<0.001
Lingual motility prior to transfer	5 (3)	13 (52)	33.37	10.18	109.35	<0.001
Bolus formation	10 (6)	17 (68)	31.66	11.01	91.07	<0.001
Premature bolus loss	8 (5)	4 (16)	3.60	0.996	12.98	0.06
Palatal elevation	7 (17)	15 (60)	7.33	2.98	18.05	<0.001
Poor bolus propulsion	5 (3)	12 (48)	28.43	8.68	93.17	<0.001
Residue in the oral cavity	95 (60)	22 (88)	4.94	1.42	17.20	0.007
Pharyngeal phase						
Triggering of pharyngeal swallow	0 (0)	2 (8)	1.09	0.97	1.22	0.02
Vallecular residue	7 (4)	13 (52)	23.52	7.90	70.02	<0.001
Laryngeal elevation	38 (24)	18 (72)	8.19	3.18	21.09	<0.001
Pyriform sinus residue	24 (15)	15 (60)	8.44	3.40	20.97	<0.001
Reduced epiglottal tilt	12 (8)	5 (20)	5.43	1.57	18.74	0.01
Coating of pharyngeal wall	12 (8)	10 (40)	8.17	3.03	22.05	<0.001
Repeated swallowing	19 (12)	15 (60)	11.05	4.35	28.09	<0.001
Aspiration	2 (1)	4 (16)	14.95	2.58	86.69	0.003
Cricopharyngeal dysfunction	8 (5)	5 (20)	4.72	1.41	15.84	0.02
Timed parameters						
Oral transit time	15 (9)	7 (28)	3.73	1.34	10.38	0.02
Pharyngeal transit time	14 (9)	9 (36)	5.83	2.18	15.58	0.001
Pharyngeal delay time	17 (11)	9 (36)	4.70	1.80	12.26	0.003
Total swallow time	24 (15)	18 (72)	14.46	5.46	38.35	<0.001

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propulsion, vallecular residue, repeated swallowing, aspiration, and total swallow time; all parameters were dichotomous. Logistic regression analysis with stepwise variable selection identified mastication, lingual motility prior to transfer, aspiration, and total swallow time as significant predictors of aspiration pneumonia (Table 3). These four parameters were adopted to form the PDVFS.

Table 3. Multiple logistic regression model.

	Definitions	Coded value	Coefficient	Odds Ratio	95% CI (lower limit)	95% CI (upper limit)	P value
Mastication	Mastication is slow, hesitant, and delayed with ineffectual movements	0: intact, 1: inadequate	3.7	38.7	7.2	206.6	<0.001
Lingual motility prior to transfer	Tongue movement assisting mastication and bolus formation	0: intact, 1: inadequate	2.1	8.7	1.5	50.5	0.016
Aspiration	Entry of bolus into the lower respiratory tract	0: absent, 1: present	2.6	13.9	1.4	139.5	0.025
Total swallow time	From the initiation of mastication until the tail of the bolus passed through the upper esophageal sphincter	0: ≤10 sec, 1: >10 sec	2.6	14.1	2.9	67.2	0.001

https://doi.org/10.1371/journal.pone.0197608.t003

Table 4. PDVFS.

Parameter	Definitions	Coded value	Score
Mastication	Mastication is slow, hesitant, and delayed with ineffectual movements	Intact	0
		Inadequate	4
Lingual motility prior to transfer	Tongue movement assisting mastication and bolus formation	Intact	0
		Inadequate	2
Aspiration	Entry of bolus into the lower respiratory tract	Absent	0
		Present	3
Total swallow time	From the initiation of mastication until the tail of the bolus passed through the upper esophageal sphincter	≤10 sec.	0
		>10 sec.	3
Total			12

https://doi.org/10.1371/journal.pone.0197608.t004

PDVFS

According to the regression coefficient of the model, PDVFS was calculated as follows: PDVFS = 3.7 × mastication + 2.1 × lingual motility prior to transfer + 2.6 × aspiration + 2.6 × total swallow time (Table 3). To make a simple and practical scale, we rounded off the coefficients by a decimal point to finally obtain the PDVFS (PDVFS = 4 × mastication + 2 × lingual motility prior to transfer + 3 × aspiration + 3 × total swallow time) (Table 4).

Area under the ROC curve for PDVFS was 0.94 (95% confidence interval: 0.86–1.00). At a cutoff value of 3, the optimal sensitivity and specificity were 0.92 and 0.82, respectively (Fig 2).

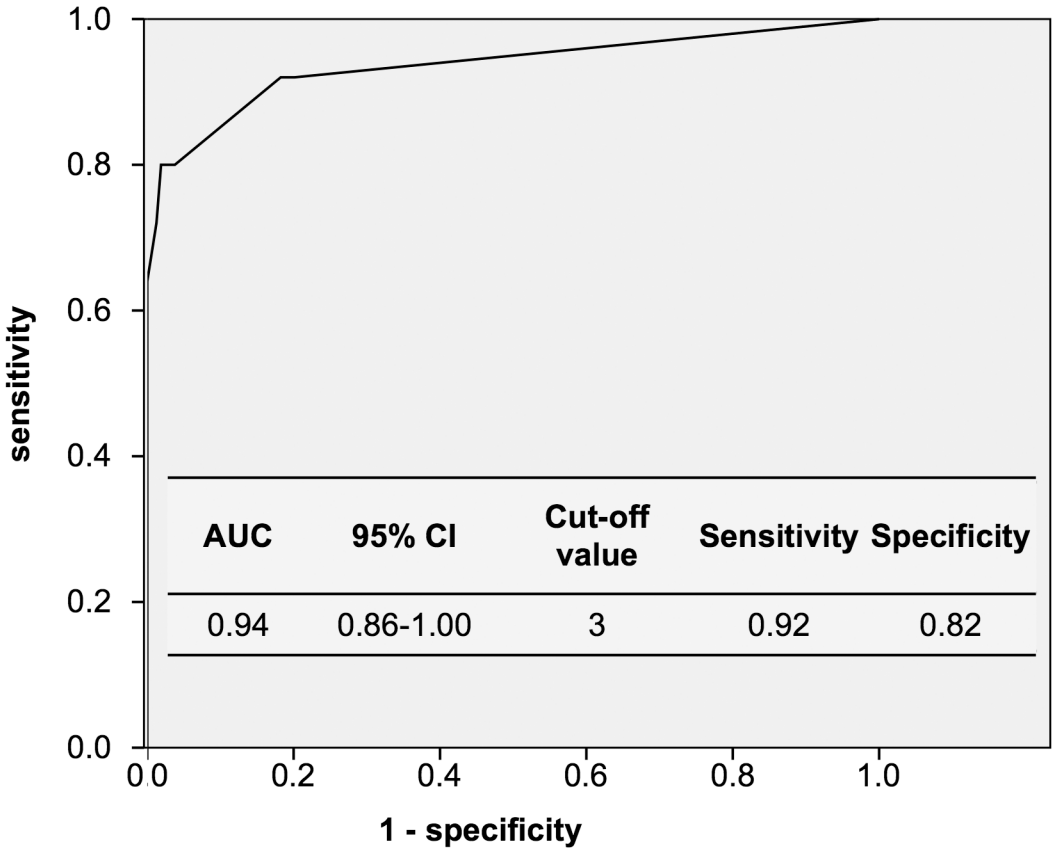

Fig 2. ROC curve of PDVFS and cutoff point for prediction of the development of aspiration pneumonia.

https://doi.org/10.1371/journal.pone.0197608.g002

Table 5. Inter-rater reliability of PDVFS and composite parameters.

Parameter	Intraclass coefficient (ICC)	95% CI (lower limit)	95% CI (upper limit)
Mastication	0.35	0.21	0.53
Lingual motility prior to transfer	0.52	0.37	0.69
Aspiration	1.00	-	-
Total swallow time	0.97	0.94	0.98
PDVFS Total	0.77	0.62	0.85

https://doi.org/10.1371/journal.pone.0197608.t005

This diagnostic accuracy of PDVFS was equivalent to that of the original model before rounding-off.

Reliability tests for PDVFS

Based on the assessments of the recorded VFSS images of 28 study participants (15%) by six SLPs, we found that the inter-rater reliability varied widely among the four components of the PDVFS; however, the total PDVFS score had a moderately acceptable inter-rater reliability (Table 5).

The intra-rater reliability of the PDVFS showed moderate (kappa coefficient, 0.82). Subgroup analyzes showed that the PDVFS retained its discriminative properties for predicting development of aspiration pneumonia after the VFSS even after stratification by age, cognitive impairment, disease severity, and dietary intervention (S2 Fig).

Analysis of prognosis

Of the 25 cases, 11 patients (44%) discontinued oral feeding immediately after aspiration pneumonia onset and 9 patients (36%) died within the entire observation period because of pneumonia (n = 6), cancer (n = 2), and renal failure (n = 1). Of the 159 controls, 9 patients (6%) discontinued oral feeding and 5 (3%) died because of cancer (n = 2), pneumonia (n = 2), and unknown cause (n = 1). Among the eight patients who died of PD-related complications, the only cause of death was aspiration pneumonia, which was a complication of dysphagia. The mean survival time after pneumonia onset was 364 days (range, 4–1659 days). Fig 3 shows the Kaplan-Meier curve of the cumulative percentage of survival stratified by the PDVFS cutoff score. A PDVFS score of $\geq$3 points was a significant predictor of poor prognosis (log rank P = 0.001).

Discussion

Among a series of previously-proposed VFSS features, four parameters (mastication, lingual motility prior to transfer, aspiration, and total swallow time) were strongly associated with the development of aspiration pneumonia in patients with PD. The PDVFS based on the data of swallowing 3 mL of jelly that was proposed in the current study could predict subsequent aspiration pneumonia, regardless of age, disease severity, or cognitive function. Furthermore, the PDVFS could predict life prognosis of patients with PD. The PDVFS was easy to rate and could be a useful index for preventing serious complications of dysphagia in patients with PD.

Among the various VFSS scales that have been developed, the PDVFS is the first scale solely designed for the prediction of subsequent pneumonia development in patients with PD. Han TR et al. [12] examined a sophisticated VFSS scale for pneumonia prediction in patients with stroke which consisted of 14 VFSS features that widely covered the oral to pharyngeal swallowing phases. In comparison of their results and the current results, pharyngeal phase parameters including pharyngeal residue and aspiration were significant features either in PD or stroke

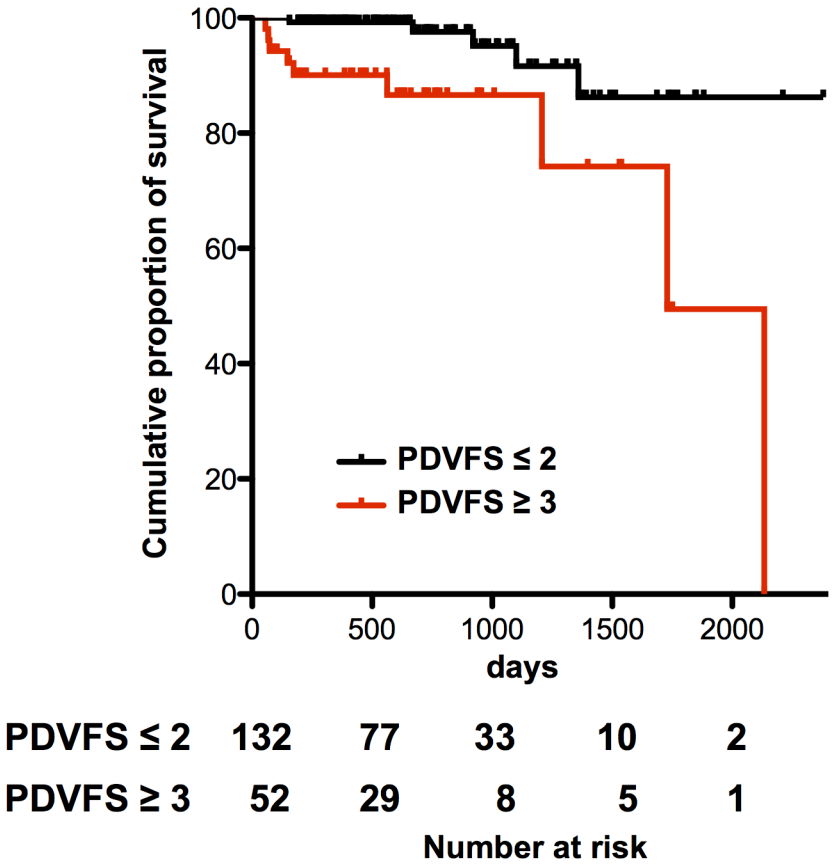

Fig 3. Cumulative survival rates according to PDVFS score (≤2 *vs.*≥3). There was statistically significant difference in the survival rate (Log rank P = 0.001).

https://doi.org/10.1371/journal.pone.0197608.g003

patients. In contrast, oral phase parameters including mastication and bolus formation were higher associated with aspiration pneumonia development in PD than in stroke patients. Additionally, there were a remarkable difference in cutoff values of timed parameters between the study by Han et al. and the present study; longer oral and pharyngeal transit times in patients with PD (5.0 sec.) than patients with stroke (1.0–1.5 sec.). These data may indicate that swallowing dysfunctions in the oral phase and a slow bolus transit were important in patients in PD compared to stroke.

Lee JH, et al. [13] and Argolo N, et al. [14] examined VFSS parameters in patients with PD. In their studies, pharyngeal residue, pharyngeal transit time, or piecemeal deglutition are specific predictors of aspiration in PD, and also in our study, all the parameters of pharyngeal phase, including these three parameters, were significantly associated with the development of aspiration pneumonia (Table 2). After adjusting for potential confounders by a logistic regression analysis, a combination of four parameters emerged as significantly associated with aspiration pneumonia: mastication, lingual motility prior to transfer, aspiration, and total swallow time.

The pathophysiology of dysphagia in PD remains unknown. Hypokinesia and bradykinesia due to Parkinsonism can cause motor dysfunction of the tongue and impaired mastication [8, 15]. Therefore, oral transit time is frequently prolonged [16]. In the pharyngeal phase, slow transit and pooling in the valleculae and pyriform sinuses may delay the swallowing reflex [17]. Aspiration and prolonged swallowing time are significant risk factors for aspiration

pneumonia [18]. Moreover, silent aspiration is one of the most common findings and an important predictive factor for aspiration in patients with PD [19]. In this study, of the six patients with aspiration, five patients (83%) showed no cough response after aspiration and three patients (50%) developed aspiration pneumonia within six months after VFSS. These three patients were forced to give up oral feeding after recovering from pneumonia. Decreased pharyngeal sensory inputs associated with sensory nerve denervation [20] may contribute to delayed swallowing response and aspiration. On the other hand, a patient who showed a cough response after aspiration also developed pneumonia. Multiple risk factors including swallowing function, decreased cough reflex (leading to silent aspiration), poor oral hygiene, impaired immunity, and reduced mucociliary transport are associated with the development of aspiration pneumonia [10].

The previous literature demonstrated subjective review of a VFSS was associated with insufficient inter- and intra-rater reliability [21]. The parameter of aspiration is well defined and showed high reliability; however, other parameters of oropharyngeal swallow, especially functional components, showed low reliability [22, 23]. Our data were obtained by having each patient swallow once or twice with a predefined amount of a predefined consistency and all the swallows were evaluated according to a strict protocol using binary scales. These modifications were thought to raise inter-rater reliability [22]. The reliability of composite parameters obtained in this study, as with the prior studies, was insufficient. Swallowing is a highly complex functional process and we usually perform VFSS evaluation with full access to a patient's clinical information and assess the study results using descriptive summaries which allow for, and capture, a wide degree of variability [22]. Taking the difficulty of VFSS evaluation into consideration, we may have to perform a multilateral analysis and a comprehensive evaluation for VFSS study assessments.

In recent studies, age, male sex, dementia, psychosis, postural instability, and early dysphagia were independent predictors of poor prognosis [24–26]. Although pharyngeal dysmotility had been observed in the early stages of dysphagia, patients with PD who were still ambulatory did not frequently develop aspiration pneumonia [27–29]. In this study, sex, age, disease severity, and dementia may have contributed to the development of aspiration pneumonia; however, disease duration did not.

Many PD patients with dysphagia exhibit concomitant reductions in QOL [30] due to insufficient medication intake, malnutrition, and dehydration; these factors may predispose a patient to aspiration pneumonia and subsequent mortality. At the baseline, the cases in this study had already lost weight and most of them were consuming a processed diet, as compared to the controls. In this context dysphagia might have exerted a negative influence on general conditions at the time of the VFSS. The results of the current study show that dysphagia should be an early warning sign of disease progression and shorter survival in patients with PD.

This study had several limitations because patients with mild dysphagia who did not undergo VFSS were not included, pharyngeal dysmotility and silent aspiration in the early stages of pneumonia were not assessed. In addition, liquid swallows are usually used for assessing the timing of swallowing reflex; however, we did not use a liquid consistency, but rather a small amount of jelly consistency for the purposes of safety, tolerability, and preventing VFSS-related pneumonia [31]. Though many clinicians use liquid for VFSS adjusting the viscosity to prevent VFSS-related pneumonia patients with PD and dysphagia are prone to aspiration of liquid consistencies, without a cough response, potentially incurring VFSS-related aspiration pneumonia and clinical deterioration due to systemic inflammation [32]. If 3 mL of liquid had been used for VFSS, PDVFS might have been a different one. Therefore, PDVFS is suitable for the assessment of swallowing jelly and the validity of PDVFS using liquid should be verified in the future. Lastly, the patients enrolled were clinically diagnosed as exhibiting PD, however

data collection was retrospective and single-center. In this study both prediction and validation were performed on the same group of patients. It is well known that predictive models derived from one population may have vastly different predictive validity when used in another population. This point is also a significant limitation. To validate the efficacy of PDVFS, further prospective multicenter studies are necessary.

Conclusions

The VFSS features of mastication, lingual motility prior to transfer, aspiration, and total swallow time based on jelly swallowing were strongly associated with the development of aspiration pneumonia in patients with PD. Our newly-developed PDVFS could predict subsequent aspiration pneumonia and poor prognosis in such patients.

Supporting information

S1 Fig. ROC curve analysis and associated data of lingual pumping and four timed parameters.
(PDF)

S2 Fig. ROC curve analyzes of PDVFS stratified by (A) age (>73 or ≤73), (B) cognitive impairment (MMSE >24 or ≤24), (C) disease severity (Hoehn-Yahr stage (H-Y) 1–3 or 4–5), and (D) dietary interventions.
(PDF)

S1 Table. List of selected studies on the abnormal VFSS features in PD.
(DOCX)

S2 Table. Definitions of the 26 VFSS parameters. *Article No. was cited from S1 Table.
(DOCX)

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Supervision: Satoshi Tomita.

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Visualization: Satoshi Tomita.

Writing – original draft: Satoshi Tomita, Tomoko Oeda, Hideyuki Sawada.

Writing – review & editing: Satoshi Tomita, Tomoko Oeda, Atsushi Umemura, Masayuki Kohsaka, Kwiyoung Park, Kenji Yamamoto, Hiroshi Sugiyama, Hideyuki Sawada.

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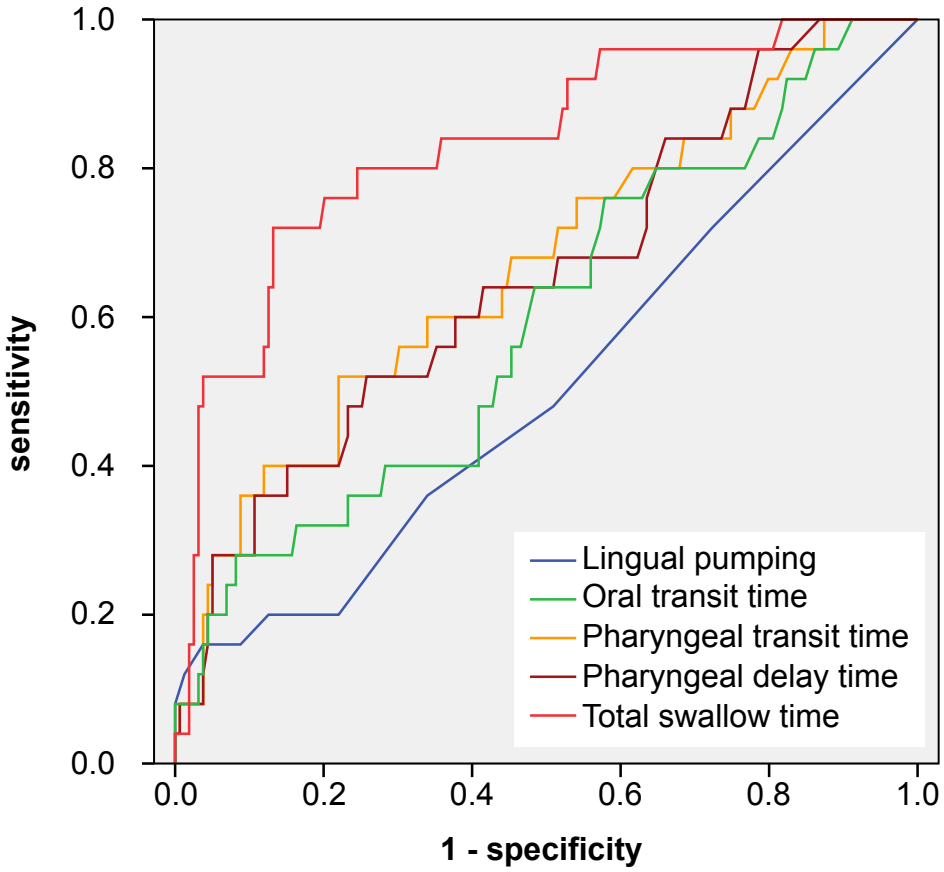
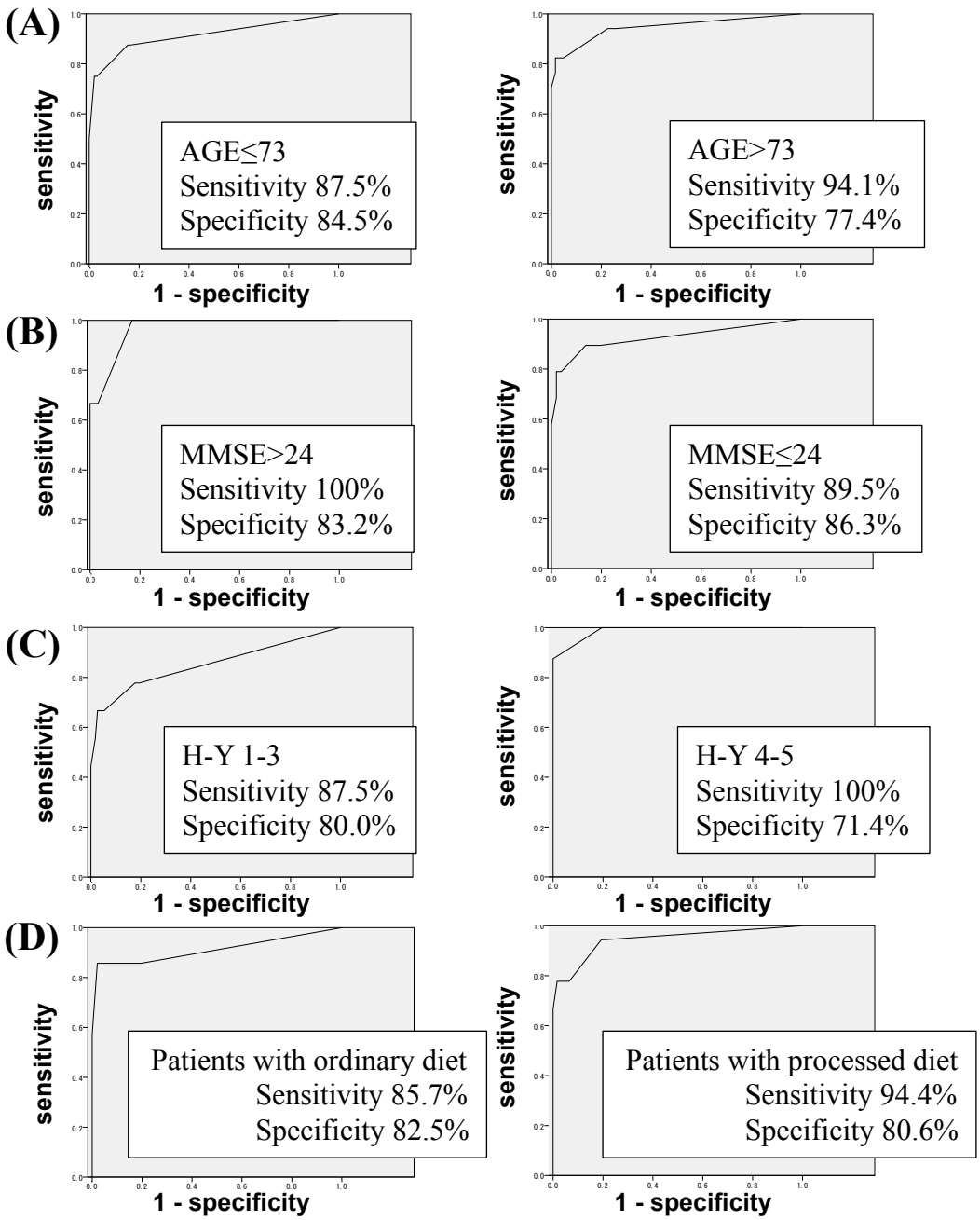


	AUC	Cut-off value	Sensitivity	Specificity
Lingual pumping	0.51	3	0.36	0.66
Oral transit time	0.60	5.0	0.28	0.91
Pharyngeal transit time	0.67	5.0	0.36	0.91
Pharyngeal delay time	0.65	4.0	0.36	0.89
Total swallow time	0.83	10.0	0.72	0.85

S1 Fig. ROC curve analysis and associated data of lingual pumping and four timed parameters.



S2 Fig. ROC curve analyzes of PDVFS stratified by (A) age (>73 or ≤73), (B) cognitive impairment (MMSE >24 or ≤24), (C) disease severity (Hoehn-Yahr stage (H-Y) 1–3 or 4–5), and (D) dietary interventions.

S1 Table List of selected studies on the abnormal VFSS features in PD

Article No.	Published articles (Author, Journal name, publication year, page)
1	Robbins JA, et al. Ann Neurol. 1986;19(3):283-7.
2	Feinberg MJ, et al. AJR Am J Roentgenol. 1991;156(2):293-6.
3	Bird MR, et al. Age Ageing. 1994;23(3):251-4.
4	Leopold NA, et al. Dysphagia. 1996;11(1):14-22.
5	Leopold NA, et al. Dysphagia. 1997;12(1):11-8; discussion 9-20.
6	Johnston BT, et al. Mov Disord. 1997;12(3):322-7.
7	Nagaya M, et al. Dysphagia. 1998;13(2):95-100.
8	O'Neil KH, et al. 1999;14(3):139-45.
9	Volonte MA, et al. Neurol Sci. 2002;23 Suppl 2:S121-2.
10	Pfeiffer RF, et al. Lancet Neurol. 2003;2(2):107-16.
11	Potulska A, et al. Parkinsonism Relat Disord. 2003;9(6):349-53.
12	Monte FS, et al. Mov Disord. 2005;20(4):457-62.
13	Troche MS, et al. Dysphagia. 2008;23(1):26-32.
14	Cappabianca S, et al. Radiol Med. 2008;113(6):923-40.
15	Menezes C, et al. J Clin Pharm Ther. 2009;34(6):673-6.
16	Yamamoto T, et al. Parkinsonism Relat Disord. 2010;16(8):503-6.
17	Baijens LW, et al. Gastroenterol Res Pract. 2011;2011:380682
18	Umemoto G, et al. Dysphagia. 2011;26(3):250-5.
19	Lin CW, et al. Arch Phys Med Rehabil. 2012;93(11):2080-4.
20	Londos E, et al. BMC Neurol. 2013;13:140.
21	Kim J, et al. Dysphagia. 2014;29(4):438-43.
22	Argolo N, et al. Int J Lang Commun Disord. 2015;50(5):659-64.
23	Kim YH, et al. Laryngoscope. 2015;125(2):389-95.
24	Rajaei A, et al. Adv Biomed Res. 2015;4:108.

S2 Table. Definitions of the 26 VFSS parameters

Parameter	Definitions	Coded value	Article No.*
Oral phase			
Pre-swallow anterior spill	Pre-swallow loss of bolus from the lips	0: absent, 1: present	17
Lingual pumping	Number of times the tongue pumps (rocks) while the bolus is in the oral cavity, resulting in posterior movement of the bolus and initiation of the swallow reflex	0: 1–3 times, 1: ≥4 times	7, 13, 22
Poor velopharyngeal closure	Failure of the velopharyngeal closure mechanism causes nasal regurgitation	0: absent, 1: present	8
Swallow hesitancy	Difficulty initiating swallowing, mainly trouble with bolus transfer	0: absent, 1: present	17
Piecemeal deglutition	Sequential swallowing of the bolus, which is fractionated into many swallowing units	0: absent, 1: present	1, 7, 10, 17, 18, 21, 22
Lip closure	Maintaining lip closure throughout the oral phase	0: intact, 1: inadequate	8, 9, 21
Mastication	Mastication is slow, hesitant, and delayed with ineffectual movements	0: intact, 1: inadequate	4, 6, 9, 21
Lingual motility prior to transfer	Tongue movement assisting mastication and bolus formation	0: intact, 1: inadequate	4
Bolus formation	Creating a cohesive bolus by mastication prior to the remaining phases of the swallow	0: intact, 1: inadequate	8, 10, 14, 20, 21
Premature bolus loss	Posterior bolus leakage prior to active transfer; because of impaired oral containment	0: absent, 1: present	2, 7, 21,
Palatal elevation	The tongue presses against the palate to transfer the bolus and prevent spillage	0: intact, 1: inadequate	9, 14, 21,
Poor bolus propulsion	Latent, uncoordinated, premature, and segmented lingual transfers of bolus	0: absent, 1: present	8
Residue in oral cavity	Oral retention of bolus	0: absent to mild, 1: moderate to severe	7, 10, 12, 17, 21
Pharyngeal phase			
Triggering of pharyngeal swallow	Delayed onset of the pharyngeal phase of swallow	0: intact, 1: delayed	9, 11, 21
Vallecular residue	Retention of bolus in one or both vallecular spaces	0: absent, 1: present	3, 5, 6, 7, 10, 17, 21
Laryngeal elevation	Insufficient movement or delayed onset of laryngeal elevation	0: intact, 1: inadequate	5, 7, 8, 21

Pyriform sinus residue	Retention of bolus in one or both pyriform sinus	0: absent, 1: present	5, 6, 7, 8, 12, 17, 20, 21
Reduced epiglottal tilt	Decreased epiglottic range of motion during the pharyngeal phase of swallow	0: intact, 1: inadequate	2, 8,
Coating of pharyngeal wall	Retention of bolus along the pharyngeal wall	0: absent, 1: present	14, 21
Repeated swallowing	Multiple swallows during the pharyngeal phase	0: absent, 1: present	14, 21
Aspiration	Entry of bolus into the lower respiratory tract	0: absent, 1: present	1, 2, 3, 5, 8, 12, 16, 17, 20, 21, 23, 24
Cricopharyngeal dysfunction	Impaired relaxation of the cricopharyngeal muscle (referred to as cricopharyngeal spasm or cricopharyngeal achalasia)	0: absent, 1: present	2, 8, 9, 10
Timed parameters			
Oral transit time	From onset of posterior movement by the bolus in the oral cavity, and point at which the tongue tip is raised and the bolus begins posterior movement toward the posterior aspect of the oral cavity to the point at which the tail of the bolus passes the level of the ramus of the mandible	0: ≤5 sec, 1: >5 sec	3, 7, 12, 15, 18, 19, 21, 23
Pharyngeal transit time	From a point at which the tail of the bolus passes the level of the ramus of the mandible to the point at which the bolus passes through the upper esophageal sphincter	0: ≤5 sec, 1: >5 sec	15, 18, 19, 21, 23
Pharyngeal delay time	From the arrival of the bolus head at the point where the shadow of the lower edge of the mandible crosses the tongue base until laryngeal elevation, indicating the onset of the pharyngeal swallow	0: ≤4 sec, 1: >4 sec	23
Total swallow time	From the initiation of mastication until the tail of the bolus passed through the upper esophageal sphincter	0: ≤10 sec, 1: >10 sec	23