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Objective vowel sound characteristics and their relationship with motor dysfunction in Asian Parkinson's disease patients

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ABSTRACT

Background: Speech impairments are very common in patients with Parkinson's disease (PD). However, knowledge of their objective characteristics and relationship to other motor symptoms amongst Asian PD patients is limited.
Objectives: To identify objective vowel sound characteristics in Thai PD patients and correlate with disease severity, as determined by UPDRS and various sub-scores.
Method: We evaluated 100 Thai PD patients, with a mean age of 66.56 years (±7.52) and HY of 2.7 (±1.08), and 101 age-matched controls. Phonatory evaluation, comprising of 15 objective parameters, was conducted using the Multi-Dimensional Voice Programme with a sustained /a/ phonation.
Results: PD patients exhibited significantly higher values of all dimensions of the phonatory parameters evaluated compared to controls (All, $p < 0.001$) except for duration of sustained phonation, which was significantly shorter in PD patients. When early- and advanced-stage patients were compared, significantly different parameters were limited to frequency perturbation parameters (Jitt, $p = 0.01$; RAP, $p = 0.013$; PPQ, $p = 0.01$; sPPQ, $p = 0.001$; vF0, $p = 0.011$), and NHR ($p = 0.028$). Several significant and moderate correlations were observed between both STD and frequency perturbation parameters and UPDRS-III, bradykinesia sub-score, and gait and postural instability sub-score. Both vF0, and STD significantly correlated with UPDRS-III and sub-scores in advanced stage patients.
Conclusion: Our study provides objective evidence of phonatory dysfunction in Asian PD patients with certain characteristics correlated with advanced stage or different motor dysfunction. Sustained vowel phonation is a promising digital outcome for global phenotyping a large number of PD patients.

1. Introduction

"In the great majority of cases of paralysis agitans, disorders of speech become obvious as the disease advances. The shades of inflection to emphasise a point disappear, the volume of the voice is reduced, pronunciation of consonants is defective and the sentence often ends in a mumble. From a monotonous, soft voice without variation in pitch, there is a gradual progression of the dysarthria until the patient's diction

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may become neither audible not intelligible. Whereas the general slowness of movements finds its expression also in the rate of speech in some cases, others talk fast, running words into each other as if they wanted to conserve their energies and get it over and done with. A few exhibit a progressive acceleration of words towards the end of a sentence similar to the festination of gait." [1].

This elegant description of a spectrum of speech impairments in Parkinson's disease (PD) by Selby [1] in his classic textbook on the basal ganglia and later quoted by Critchley is nowadays known to most neurologists who are involved in a daily care of PD patients as hypokinetic dysarthria. This collective description of a reduction in speech volume and pitch variability, breathy voice, tremor, hoarse voice quality, inconsistent rates of speech and imprecise articulation reflect the involvement of all dimensions of speech production, including respiration, phonation, resonance, articulation, and prosody in patients with PD [2,3]. Respiratory dysfunction, manifested by reduced vital capacity, amplitude of chest wall movements, and respiratory muscle strength and endurance could hinder the breath support required for patients to produce normal phrases and loudness variation [4]. Reduced vocal fold elongation and limited/unstable adduction significantly impacts phonatory function on voice quality and voice range profile. Impaired resonance reflects the inability of the pharyngeal and velopharyngeal muscles to transmit the voice through the oral cavity, leading to a perception of hypernasality. Articulation is primarily a function of lingual, facial, and jaw muscles, which are all affected by PD, resulting in low speech intelligibility. Lastly, prosody is a reflection of the combined activities of respiration, phonation, resonance, and articulation that manifests in PD individuals as alterations in speech rate, pause time, flattened pitch inflection (monopitch) and loss of stress (monoloudness) [5].

More than 90% of PD patients reported at least one symptom related to communication with the most common including weak voice, word-finding problems, imprecise articulation, off topic when speaking and strained-strangled voice [6]. In addition to patient's subjective reports, speech function can also be assessed by various subjective and objective methods. Perceptual analysis involves a clinical rating of speech by experienced listeners, which is representative of a patient's actual communication function, deficits and needs, but is prone to bias with limited capacity for longitudinal assessment and comparison [7]. Development of objective acoustic measures of vocal function that can provide quantitative non-invasive metrics that are sensitive to the severity of voice production, provide indirect inferences on underlying voice disorders, and can be utilised for different clinical purposes in PD [7,8]. Furthermore, identification of acoustic features that can be used as potential markers of early diagnosis, disease progression, and evaluation of treatment effects has been demonstrated [9–15].

Voice recordings can be obtained by asking subjects to perform sustained phonations, rapid repetition of syllables, variable speech reading, or freely speaking monologues to examine all five dimensions of speech production. When these methods were tested in early untreated PD patients, 78% of subjects showed some forms of vocal impairment [16]. However, how each dimension is affected in PD patients is rather individualised. While phonation was found to be the leading deficit, most frequently affected and more greatly impaired than other features in the early stage by the perceptual analysis involving 200 PD patients, a separate study using quantitative acoustic measurements was able to separate the involvement of each dimension in detail, supporting the view that prosodic insufficiency was most commonly affected in early untreated PD patients, accounting for 60.87% of patients, followed by lower ability of articulation (39.13%), and phonatory deficits (26.09%) [16,17]. However, 35% of early untreated PD patients were affected by more than one dimension of speech production. As the disease progresses, it is likely that PD patients will be affected by multiple dimensions as evident by several small longitudinal studies indicating progression of all speech dimensions in subsequent assessments [5,14,18,19]. Though it would also be informative if these acoustic parameters were correlated with various non-speech motor performances, current literature in this area is limited by very small datasets of usually less than 60 patients [12,13]. Moreover, very few studies have been conducted in Asian PD populations [20,21]. Therefore, our aim in this study is to conduct acoustic analysis in a large number of Thai PD patients with corresponding age-matched controls and to perform correlations with standard non-speech motor performances. In this study, we focus on the phonatory dimension as it is simple to perform providing the opportunity for us to recruit a large number of subjects, irrespective of educational background [7,11]. In addition, phonatory assessment by sustaining vowel prolongation is less likely to be influenced by native dialogues that can potentially affect other speech dimensions [22].

2. Methods

2.1. Study participants

A total of 100 PD patients (47 female and 53 male), with a mean age of 66.56 years (± 7.52), were recruited from the outpatient clinic of the Chulalongkorn Centre of Excellence for Parkinson's Disease and Related Disorders (www.chulapd.org) (Table 1). The diagnosis of PD was made according to the United Kingdom Parkinson's Disease Society Brain Bank clinical diagnostic criteria. Baseline clinical characteristics were evaluated in all patients by two independent movement disorders neurologists (RB and OP) with scale-based assessments, including the Unified Parkinson's Disease Rating Scale (UPDRS) sections II (Activities of Daily Living) and III (Motor), and the Hoehn and Yahr (HY) staging in

Table 1
Clinical demographics of study participants.

Characteristics	PD ($N = 100$)	HC ($N = 101$)	p-value
Gender			
Female N (%)	47 (47.00)	55 (54.50)	0.29
Male N (%)	53 (53.00)	46 (45.50)	
Age (years)	66.56 ± 7.52	65.13 ± 7.41	0.176
Female	66.83 ± 7.99	65.35 ± 7.24	0.327
Male	66.32 ± 7.14	64.87 ± 7.70	0.333
Disease duration (years)	7.90 ± 5.90		
Female	7.42 ± 4.59		
Male	8.32 ± 6.89		
HY stage	2.70 ± 1.08		
Early-stage: HY < 3: N (%)	48 (48.00)		
HY stage 1: N (%)	10 (10.00)		
HY stage 2: N (%)	38 (38.00)		
Advanced-stage: HY ≥ 3: N (%)	52 (52.00)		
HY stage 3: N (%)	33 (33.00)		
HY stage 4: N (%)	10 (10.00)		
HY stage 5: N (%)	9 (9.00)		
UPDRS score			
Total UPDRS-II (0–52)	21.81 ± 14.31		
Total UPDRS-III (0−132)	28.08 ± 27.52		
UPDRS-Bradykinesia (0–36)	9.00 ± 9.52		
UPDRS-Rigidity (0−20)	5.36 ± 5.56		
UPDRS-Tremor (0−32)	7.73 ± 8.34		
UPDRS-Gait and Postural instability (0–16)	4.52 ± 4.93		

PD: Parkinson's disease; HC: Healthy controls; HY: Hoehn and Yahr stage; UPDRS: Unified Parkinson's Disease Rating Scale. All statistics were performed using the Chi-Square test for categorical units and; Mann - Whitney U test for continuous units; P-value less than 0.05 was considered statistically significant; UPDRS Bradykinesia score is UPDRS III items 23–26 and 31; UPDRS Rigidity score is UPDRS III item 22; UPDRS Tremor is UPDRS II items 16, and UPDRS III items 20 and 21; UPDRS Gait and Postural instability score is UPDRS III items 27–30.

which both neurologists had to agree on their rating assessments. In the case of a discrepancy, both physicians assessed the evidence again, and arrived at a consensus. The following UPDRS sub-scores were calculated as the summation of specific UPDRS items as follows: 1) UPDRS bradykinesia (items 23, 24, 25, 26, and 31); 2) UPDRS rigidity (item 22); 3) UPDRS tremor (items 16, 20, and 21), and 4) UPDRS gait and postural instability (items 27, 28, 29, and 30) [23–25]. Forty-eight individuals were diagnosed with an early-stage PD (HY 1–2, mean age: 64.98 ± 7.17) and fifty-two individuals were in the advanced stage (HY 3–5, mean age: 68.33 ± 7.72). Each patient received clinically effective doses of dopaminergic medications, measured as the Levodopa Equivalent Daily Dosage (LEDD), and had been stable on their current dosage for at least four weeks. The evaluation was carried out in the morning, two hours after taking their medications, so the patients were all in the 'on' period.

Control subjects, comprising of 101 subjects (Mean age: 65.13 ± 7.41) were without known neurological or psychological disorders and were matched to PD patients with respect to sex and age (Table 1). All subjects had to be free from any acute respiratory tract infection at the time of entry. Exclusion criteria were as follows: age younger than 50 years, pregnancy, endotracheal intubation within three months before entry, current or ex-smokers, history of laryngeal neoplasms, history of laryngeal surgery or trauma, radiotherapy and/or chemotherapy at the head and neck region. Subjects with history of cerebrovascular disorders or focal neurological signs suspected for previous cerebrovascular events were also excluded. The study was approved by the Human Subjects Ethics Committee of the Faculty of Medicine, Chulalongkorn University (820/63) with certificate of approval (301/2021). All subjects gave their written informed consent before entering the study in accordance with the declaration of Helsinki.

2.2. Voice recordings and acoustic parameters

Voice recordings were set-up in accordance with the recommended protocols for instrumental assessment of voice by the American Speech-Language-Hearing Association and the most recent guideline for speech recording and analyses in dysarthrias of movement disorders [7,8]. Voice recordings for all PD subjects and controls were performed by the primary author (PS) and a speech and language pathologist (PL), who were blinded to all study subjects, between 09:00 and 12:00 h in a carpeted room with an ambient noise level < 45 dB. The participants sat on a fixed armchair wearing the Shure® unidirectional head-worn microphone (Model SM10-A), positioned at a distance of 4–5 cm from the lips at an angle of 45-90^{o} away from the front of the mouth. The voice signals were recorded directly to a 16-bit laptop computer running Adobe Audition CS6 software (Adobe Inc., San Jose, CA.) using a Presonus Audiobox 44VSL USB audio interface (Presonus Audio Electronics, Baton Rouge, LA.) with a sampling frequency of 44.1 kHz. Phonatory features characterise speech at the prearticulatory level, and were developed mainly to characterise the sustained phonation of vowels. Sustained phonation of a vowel is a standard measure used to assess quality of phonation and the advantage of this task in comparison with other commonly used vocal tasks is its independence from articulatory and other linguistic confounds [26]. Vowel /a/ was chosen as it is the most commonly used vowel [8,11,18]. All subjects were asked to phonate the /a/ vowel three times, each time for at least 5 s, at their most comfortable level to maintain steady frequency and amplitude. The entire duration of the vowel production was used for analysis. A 5-s long interval was used because this time span is sufficiently long to provide a reliable analysis of most parameters while sustaining the phonation of the vowel with a relatively stable effort and pitch, and it could be readily performed by PD patients at different disease stages. However, subjects were instructed to sustain their vowel as long as they feel comfortable in one breath at a comfortable pitch and loudness until they run out of air.

Voice analysis was performed using the Multi-Dimensional Voice Program™ Model 5105 (MDVP, Kay Elemetrics Corp., NJ, USA). This programme is most widely used for acoustic voice analysis in clinical applications of PD and provides several indices to assess voice quality [27]. 15 MDVP parameters that are achievable by sustained vowel phonation were selected for phonatory assessment according to previously published literature in PD patients [8,11,16,28]. Descriptions of select parameters with clinical relevance is provided in Supplementary Table 1. In speech pathology clinics, the majority of cases of hypokinetic dysarthria are the result of PD and these selected features, as a whole or in part, have been evaluated in PD, demonstrating clinical usefulness and reliability [29]. To describe a variety of phonatory disorders associated with PD, we quantified the following (Supplementary Table 1): a) fundamental frequency parameter: STD (standard deviation of fundamental frequency), PFR (phonatory fundamental frequency range in semitones); b) frequency perturbations: Jita (absolute jitter), Jitt (jitter percent), RAP (relative average perturbation), PPQ (pitch perturbation quotient), sPPQ (smooth pitch perturbation quotient), vF0 (fundamental frequency variation); c) amplitude parameters: Shim (shimmer percent), APQ (amplitude perturbation quotient), sAPQ (smooth amplitude perturbation quotient), vAm (peak-to-peak amplitude variation); d) voice irregularity: DUV (degree of voiceless); e) noise-related parameters: NHR (noise to harmonic ratio), VTI (voice turbulence index), SPI (soft phonation index); and f) duration parameter: Tsam [30]. According to a review article on the MDVP application, the most frequently occurring abnormal values are observed for the following parameters: vF0, vAm, SPI, sAPQ, sPPQ, and APQ, with the triad of vF0, vAm, and SPI considered to be the dominant pattern of voice disorders in PD [30]. STD is defined as the standard deviation of fundamental frequency (F0) using the period-to-period F0 values. Although significant differences were found between absolute and range values of F0 in PD patients compared to controls, F0 was not considered in our final analysis as it is affected by individual differences such as gender [31]. Previous study does recommend that STD is approximately the same for men and women if it is expressed in semitones (logarithmic tonal scale) [16]. vF0 represents the coefficient of F0 variation, reflecting the variation of F0 within the analysed voice sample [32]. vF0 can increase regardless of the type of pitch variation. As sustained phonation normative thresholds assume that F0 should not change, any variation in F0 is reflected in vF0, which could suggest frequency tremors, very high jitter, or rising or falling pitch over the analysed length [32]. DUV measures the ability of the subjects to sustain uninterrupted voicing, which is associated with stuttering and instability of speech [32]. NHR measures the proportion of 'noise' generated from the glottis against the vibration of the vocal cords, with its elevation correlating with incomplete vocal folds closure along with folds bowing during phonation, resulting in a rough or hoarse voice [33,34]. Therefore, NHR is affected by irregularities in the vibration patterns of the vocal folds such as voice break and frequency or amplitude perturbation. Jitter is a measure of frequency perturbation, representing the cycle-to-cycle variability in the fundamental frequency during steady phonation, with increased jitter indicating vocal fold vibration, associated with a harsh, hoarse, or rough voice quality [35]. On the other hand, shimmer measures the cycle-to-cycle variation in amplitude during steady phonation with an increased association with breathiness [35–37]. Both jitter and shimmer are measures that assess the micro-instability of vocal fold vibration, possibly reflecting reduced short-term neuromuscular control of laryngeal abduction and adduction [29].

2.3. Statistical analysis

Demographics and clinical data of all PD patients and control subjects, including UPDRS scores and speech parameters were summarised using either means and standard deviations (SD) for continuous variables, or frequencies and percentages for categorical variables. Chi-square test was used for a comparative analysis of difference between groups for categorical data. The Kolmogorov-Smirnov statistic was calculated to determine the normality of data to the p value. Larger

values for the Kolmogorov-Smirnov statistic indicates that the data does not follow a normal distribution (Supplementary Table 2). Mann-Whitney *U* test was used to compare continuous variables. Spearman's correlations were used to determine test-retest reliability between the first and third trial on all acoustic parameters and correlations between variables (Supplementary Table 3). The strength of correlation coefficient (r) was interpreted as very strong (≥ 0.70), strong (0.40–0.69), moderate (0.30–0.39), or weak (0.20–0.29) [38]. A $p < 0.05$ (two-tailed) was considered statistically significant. All statistical analysis was performed using SPSS version 23.0 software (SPSS Inc., Chicago IL).

3. Results

Demographic data and disease characteristics of all PD subjects are shown in Table 1. There were no significant differences between the age and gender between PD patients and control subjects. In PD patients, the mean disease duration was 7.9 years (SD = 5.9) with a mean HY staging of 2.7 (SD = 1.08) and a mean LEDD of 751.58 (SD = 451.6). The mean UPDRS-II and UPDRS-III during the 'on' period were 21.81 (SD = 14.31) and 28.08 (SD = 27.52) respectively. Results of individual UPDRS subscores were shown in Table 1. All participants were able to complete three trials of sustained phonation without any adverse events or major discomfort. Test-retest reliability of acoustic parameters between the first and third trial was calculated using Spearman's correlation coefficient, yielding moderate to very strong correlations in all parameters except weak correlation for sAPQ (Supplementary Table 3).

Comparisons of speech parameters between PD patients and normal subjects are shown in Table 2. Significant differences were observed in all acoustic parameters except for VTI. STD (1.26 ± 1.23 vs. 0.53 ± 0.41, $p < 0.001$), NHR (0.23 ± 0.17 vs. 0.15 ± 0.03, $p < 0.001$), SPI (14.48 ± 10.89 vs. 7.92 ± 6.33, $p < 0.001$), Jitt (2.60 ± 2.80 vs. 0.84 ± 0.49, $p < 0.001$), and Shim (9.19 ± 11.32 vs. 3.85 ± 2.05, $p < 0.001$) were all significantly higher in PD patients than control subjects. Compared to control subjects, Tsam was significantly shorter in PD patients (10.08 ± 5.79 vs. 12.20 ± 5.76, $p = 0.003$). When comparisons were made between early- and advanced stage PD patients, significant parameters were more limited to the parameters on frequency perturbation, including Jitt (1.99 ± 2.06 vs. 3/17 ± 3.25, $p = 0.01$), RAP (1.17 ± 1.20 vs. 1.90 ± 2.00, $p = 0.013$), PPQ (1.15 ± 1.28 vs. 1.85 ± 1.89, $p = 0.01$), sPPQ (1.93 ± 2.24 vs. 2.99 ± 2.58, $p = 0.001$), and vF0 (6.38 ± 7.40 vs. 8.37 ± 7.41, $p = 0.011$). In addition, NHR was also significant lower in early- compared to advanced stage patients (0.20 ± 0.12 vs. 0.26 ± 0.20, $p = 0.028$).

Correlations were performed between the acoustic parameters and clinical demographics, UPDRS-II, UPDRS-III, and various UPDRS subscores (Table 3). Significant and moderate correlations were mainly observed between STD and UPDRS-III ($r = 0.312$), bradykinesia subscore ($r = 0.329$), and gait and postural instability sub-score ($r = 0.349$). In addition, significant and moderate correlations were also demonstrated between the parameters on frequency perturbation and UPDRS-III, bradykinesia, and gait and postural instability sub-scores. In particular, sPPQ and vF0 significantly correlated with UPDRS-III ($r = 0.348, 0.314$), bradykinesia sub-score ($r = 0.370, 0.330$), sub-score on gait and postural instability ($r = 0.406, 0.347$) respectively. Interpretation of correlation coefficients indicated that there were also significant correlations of weak to moderate levels in advanced stage patients between both vF0, and STD and UPDRS-III ($r = 0.299, 0.297$), bradykinesia sub-score ($r = 0.311, 0.313$), rigidity sub-score ($r = 0.307, 0.297$), and gait and postural instability sub-score ($r = 0.328, 0.336$) respectively (Table 4).

4. Discussion

In this study, we have provided objective evidence of phonatory dysfunction in PD patients as demonstrated by the significant differences identified in 14 out of 15 phonatory parameters when compared to age-matched controls. With the exception of Tsam, these parameters significantly increase compared to healthy controls (Table 2) [19–21,36,37,39–41]. Specifically, STD expressed in semitones was significantly higher in our PD than control subjects, supporting a previous study by Rusz et al. suggesting that STD was the best method for separating healthy from PD subjects [16]. However, it should be stressed that sustained phonation alone is an inappropriate task for differentiating PD from control subjects [42]. Similar to previous studies, phonatory duration as expressed by Tsam was also significantly shorter in our PD than control subjects [41,43,44]. As heterogeneity of acoustic parameters was raised as one of the major concerns in a recent meta-analysis of acoustic analysis in PD, we also compare parameters with low risk of heterogeneity, evident by less than 25% on the Inconsistency tests (I^2), to published literature, and these include jitt and vF0 [12]. Consistent with previously published studies, our PD patients had significantly larger jitt and vF0 than neurologically normal controls [12,20,36,39,45,46]. However, we would like to caution on the interpretation of vF0 as it has been shown to be low in prodromal PD patients, but returns to 'normal' a few years after being symptomatic [47]. Still, our study provides further evidence on the continuum of vF0 findings in that it increased in the advanced stage and thus supports the early suggestion made by Harel et al. [48] that vF0 could potentially represent

Table 2
Comparison of phonatory parameters between Parkinson's disease patients and healthy controls, and between early-stage (HY <3) and advanced stage (HY ≥ 3) patients.

Dimensions of phonatory assessment	Phonatory parameters (unit)	PD (n = 100)	HC (n = 101)	p_a-value	Early-stage PD (n = 48)	Advanced-stage PD (n = 52)	p_b-value
Fundamental frequency	STD (Semitone)	1.26 ± 1.23	0.53 ± 0.41	<0.001*	1.06 ± 1.21	1.43 ± 1.24	0.133
Frequency perturbation	Jitt (%)	2.60 ± 2.80	0.84 ± 0.49	<0.001*	1.99 ± 2.06	3.17 ± 3.25	0.010*
	RAP (%)	1.55 ± 1.69	0.50 ± 0.30	<0.001*	1.17 ± 1.20	1.90 ± 2.00	0.013*
	PPQ (%)	1.51 ± 1.65	0.47 ± 0.29	<0.001*	1.15 ± 1.28	1.85 ± 1.89	0.010*
	sPPQ (%)	2.48 ± 2.47	0.83 ± 0.50	<0.001*	1.93 ± 2.24	2.99 ± 2.58	0.001*
	vF0 (%)	7.41 ± 7.43	3.08 ± 2.41	<0.001*	6.38 ± 7.40	8.37 ± 7.41	0.011*
Amplitude perturbation	Shim (%)	9.19 ± 11.32	3.85 ± 2.05	<0.001*	6.93 ± 5.92	11.27 ± 14.40	0.170
	APQ (%)	6.35 ± 6.72	2.85 ± 1.46	<0.001*	5.05 ± 3.72	7.55 ± 8.48	0.142
	sAPQ (%)	8.95 ± 6.78	4.59 ± 1.94	<0.001*	7.43 ± 4.10	10.35 ± 8.34	0.061
	vAm (%)	28.66 ± 11.67	21.40 ± 8.01	<0.001*	28.75 ± 13.47	28.57 ± 9.85	0.456
Voice irregularity	DUV (%)	13.95 ± 23.08	1.89 ± 4.26	<0.001*	10.26 ± 18.44	17.36 ± 26.38	0.241
Noise- related	NHR (−)	0.23 ± 0.17	0.15 ± 0.03	<0.001*	0.20 ± 0.12	0.26 ± 0.20	0.028*
	VTI (−)	0.07 ± 0.15	0.05 ± 0.01	0.889	0.06 ± 0.04	0.09 ± 0.21	0.754
	SPI (−)	14.48 ± 10.89	7.92 ± 6.33	<0.001*	13.54 ± 9.36	15.35 ± 12.17	0.654
Duration	Tsam (s)	10.08 ± 5.79	12.20 ± 5.76	0.003*	11.49 ± 6.67	8.79 ± 4.54	0.053

All statistics were performed using Mann-Whitney U test for equality of means difference; *: *p*-value less than 0.05 was considered statistically significant; p_a: *p*-value of comparison of speech parameters between PD patients and HC; p_b: *p*-value of comparison speech parameters between early- and advanced stage PD patients.

Table 3
Correlation between acoustic parameters and clinical demographics and UPDRS score and sub-scores.

Group of speech parameter measurement	Parameters (unit)	Age	Disease Duration	HY	Total UPDRS II	Total UPDRS III	UPDRS Bradykinesia	UPDRS Rigidity	UPDRS Tremor	UPDRS Gait & Postural instability
Fundamental frequency	STD (Semitone)	0.093	0.227*	0.257*	0.155	0.312*	0.329*	0.216*	0.279*	0.349*
Frequency perturbation	Jitt (%)	0.103	0.157	0.257*	0.100	0.255*	0.268*	0.068	0.177	0.313*
	RAP (%)	0.110	0.155	0.247*	0.091	0.247*	0.260*	0.066	0.172	0.302*
	PPQ (%)	0.095	0.167	0.256*	0.111	0.261*	0.279*	0.058	0.181	0.320*
	sPPQ (%)	0.093	0.249*	0.344*	0.192	0.348*	0.370*	0.163	0.261*	0.406*
	vF0 (%)	0.103	0.236*	0.253*	0.155	0.314*	0.330*	0.219*	0.284*	0.347*
Amplitude perturbation	Shim (%)	0.165	0.050	0.107	0.059	−0.003	0.059	−0.107	−0.074	0.099
	APQ (%)	0.147	0.059	0.120	0.066	−0.014	0.051	−0.125	−0.101	0.101
	sAPQ (%)	0.134	0.076	0.185	0.121	0.062	0.108	−0.050	−0.013	0.172
	vAm (%)	−0.062	0.014	0.086	−0.008	0.080	0.110	−0.037	−0.030	0.151
Voice irregularity	DUV (%)	0.041	0.050	0.074	−0.011	0.042	0.070	−0.017	−0.020	0.112
Noise- related	NHR (−)	0.110	0.098	0.172	0.052	0.152	0.198*	0.047	0.068	0.225*
	VTI (−)	−0.030	−0.113	−0.021	−0.110	−0.050	−0.018	−0.003	−0.067	−0.063
	SPI (−)	0.142	0.124	0.132	0.114	0.009	0.023	−0.163	−0.074	0.110
Duration	Tsam (s)	−0.251*	−0.081	−0.197	−0.139	−0.152	−0.151	−0.012	−0.130	−0.148

HY: Hoehn and Yahr; UPDRS: Unified Parkinson's Disease Rating Scale. All statistics were performed by Spearman correlation; *: A *p*-value less than 0.05 was considered statistically significant; UPDRS Bradykinesia score is UPDRS III items 23–26 and 31; UPDRS Rigidity score is UPDRS III item 22; UPDRS Tremor is UPDRS II items 16, and UPDRS III items 20 and 21; UPDRS Gait and Postural instability score is UPDRS III items 27–30.

Table 4
Correlations coefficient between phonatory parameters and UPDRS scores and sub-scores in early- and advanced-stage patients.

UPDRS	Early-stage PD (HY < 3)		Advanced stage PD (HY ≥ 3)	
	Speech parameter	*r*	Speech parameter	*r*
Total UPDRS II	VTI (-)	−0.297		
Total UPDRS III			vF0 (%)	0.299
			STD (semitone)	0.297
UPDRS Bradykinesia			vF0 (%)	0.311
			STD (semitone)	0.313
UPDRS Rigidity	SPI (-)	−0.535	vF0 (%)	0.307
			STD (semitone)	0.297
UPDRS Tremor				
UPDRS Gait and Postural			vF0 (%)	0.328
			STD (semitone)	0.336

PD: Parkinson's disease; HY: Hoehn & Yahr stage; UPDRS: Unified Parkinson's Disease Rating Scale. All statistics were performed using Spearman correlation; *: *p*-value less than 0.05 was considered statistically significant; UPDRS Bradykinesia score is UPDRS III items 23–26 and 31; UPDRS Rigidity score is UPDRS III item 22; UPDRS Tremor is UPDRS II items 16, and UPDRS III items 20 and 21; UPDRS Gait and Postural instability score is UPDRS III items 27–30.

a sensitive marker for disease progression as vF0 values are likely to continue to increase as the disease progresses. In a study involving 39 Japanese PD patients of four years disease duration, vF0 was also found to be significantly higher than their gender-matched controls [20]. A longitudinal study is needed to determine if vF0 and other acoustic parameters could be served as progression markers in PD. The interpretation of vF0 can be limited by its influence by gender as the extent of vF0 is related to the individual average voice pitch. This means subjects with naturally high-pitched voice (usually women) will have much larger vibrato and microtremor than persons with lower-pitched voices (usually men), thus causing a significant problem when these variations are measured on an absolute frequency scale in Hz [16]. However, our parameters were expressed as a percentage (not in Hz), which better reflects differences in gender [16]. Indeed, sub-analysis of these parameters demonstrated a significant difference of vF0 only in healthy subjects, but not STD in semitone sas suggested by Rusz et al. (Supplementary Table 4) [16]. One study that specifically determine Jitt, Shim, and NHR classification within gender only reported a significant difference only in Jitt parameter when expressed in μs, but not when expressed as a percentage [49]. To minimise the influence of gender, STD may be a reliable parameter if expressed in semitones. In our study, STD was significantly higher in PD patients compared to controls. Indeed, STD has been identified as the parameter that can also differentiate between PD, Huntington's disease and cerebellar ataxia [45]. In addition to STD, SPI was also an interesting parameter, found to be significantly higher in our PD patients compared to controls. It represents an average of the lower-frequency harmonic energy in the range 70–1550 Hz to the higher-frequency harmonic energy in the range 1600–4200 Hz and is considered an indicator of how completely, or tightly, the vocal fold adducts during phonation [50]. An increased value of SPI is generally an indicator of loosely or incompletely adducted vocal folds during phonation, associated with voice breathiness and asthenia [33,44,50,51]. To the best of our knowledge, this parameter has not been very well explored in PD patients.

The comparison of phonatory features between early and advanced stage PD patients in our study presents some further interesting findings. The significant differences were mainly observed in the frequency perturbation parameters (Jitt, RAP, PPQ, sPPQ, vF0) and NHR, further suggesting worsening incomplete vocal cord closure, producing hoarse voice quality in advanced stage patients. Perceptually, harshness, breathiness, monopitch and monoloudness were also found to be worse, corresponding to significantly worsening of Jitt in advanced stage patients [37]. The high value of vF0 can be attributed to the increased rigidity of the laryngeal and respiratory muscles, besides laryngopharyngeal tract hypomobility [43,52]. An impaired ability to keep laryngeal muscles in a fixed position for vowel production could also contribute to the increased vF0 in PD patients [29,53]. Indeed, PD patients were found to have more frequent abnormalities on videolaryngostroboscopy than normal controls with frequent findings including decreased mucosal wave, posterior glottal chink, irregular vocal fold edge, and aperiodicity [44]. Moreover, significant vocal fold bowing was identified in 87% of advanced PD patients who were candidates for deep brain stimulation [54]. Our findings should be further evaluated to determine the association between frequency perturbation parameters and vocal cord abnormalities in longitudinal studies involving a large number of PD patients.

In this study, we observe several significant correlations between both STD and frequency perturbation parameters and UPDRS-III, subscores on bradykinesia and gait and postural instability, and disease duration suggesting that phonatory dysfunction has a significant relationship with motor severity, bradykinesia and gait and postural dysfunction, and is likely to worsen with longer disease duration. When compared with previously published studies, a similar conclusion can be

drawn that phonatory disorders correlated with motor severity and disease duration but the association with individual parameters observed from our study and other published studies may not be identical or overall consistent [18,43,52,55–57]. However, vF0 and Jitt significantly correlated with disease duration and worsen in the advanced stage, which is consistent with previous studies [12,55]. Significant correlations between vF0 and STD and the advanced stage should be further explored in future studies as a possible marker for advanced disease. However, the issue of limited relationship between voice and motor disabilities has been raised by a recent review article which suggests that motor speech control system is different from other motor control mechanisms [12]. A high heterogeneity between studies limits further conclusions [12]. Some studies observed that progression of speech impairment may still occur whilst global motor impairment was overall stable, supporting a non-dopaminergic mechanism underlying motor speech control system [19,43]. Still, our correlations between phonatory and gait and postural dysfunction supports several clinical observations that speech and gait impairments may share a similar pathophysiological process, although the progression of these two dominant symptoms may not begin at the same onset or progress in parallel [58–60].

The main strength of our study was related to the relatively larger number of PD patients with age-matched control subjects included - most previously reported studies with acoustic analysis that usually recruited a maximum of 40–60 PD patients [12]. Careful clinical evaluation of PD patients was made by two movement disorder neurologists who had to agree on rating assessments and acoustic assessment was conducted by the PI, supervised by a speech and language pathologist to ensure that protocols were strictly followed according to American Speech-Language-Hearing Association expert panel recommendations [7]. We aimed to be comprehensive by selecting 15 acoustic parameters as recommended by previously published studies to be the phonatory features for analysis [8,9,11,16,28]. In addition, our study reports acoustic features of an Asian cohort, which is scant in the published literature. Acoustic features may be influenced by ethnicity as vocal tract dimensions have been shown to be different across races [61]. Moreover, normative values have been found to be different between Western and Indian young adults [62]. Interestingly, however, analysis of a small number of voice samples between Euro-American and African-American did not yield any significant differences [63]. Therefore, there is a need to develop a comprehensive dataset representing different ethnic populations with standardised methods to determine if race can potentially influence acoustic features. The limitations of our study were its cross-sectional design that requires a longitudinal follow-up to determine if the parameters with significant correlations are markers for advanced stage of PD. In addition, the assessment was limited to the phonatory dimension, not involving other dimensions of speech production, and the sustained phonation task alone cannot be used to differentiate PD from controls. However, our intention was to utilise a simple task as it is easy to elicit in a large number of subjects irrespective of educational background. In addition, measuring sustained vowel phonation is free from influences of phonetic context and thereby unaffected by intonation, stress, or speaking rate, and less affected by the dialect of subjects [22]. Acoustic analysis was performed only in the 'on' stage, so potentially adding an effect of medication on these acoustic parameters. However, a small study of only five patients did not identify significant differences of a small set of acoustic parameters (jitt, shim, NHR, and index of tremor) in PD patients between 'on' and 'off' stages [64]. Lastly, a lack of perceptual evaluation of standardised scales, such as the Voice Handicap Index or the Grade, Roughness, Breathiness, Aesthenia, Strain perceptual rating system, makes the correlation of voice quality not possible. However, our study utilised UPDRS-II, which has one item in activities of daily living on speech, but no significant correlation of acoustic parameters and UPDRS-II item 5 on speech was demonstrated.

In conclusion, our study demonstrated a range of phonatory parameters that were significantly different between PD patients and normal controls, and early and advanced disease stages. Several significant correlations were demonstrated between phonatory parameters and motor severity and sub-scores, providing the relationale for utilising these parameters as digital outcome measures. With the advances in digital technology, there has been an increased interest in developing patient-centred digital outcome (PDCO) measures in PD [65]. Digital phenotyping of acoustic parameters could potentially be selected as PDCO measures to determine disease progression or treatment response [66]. Indeed, sustained phonation was included as one of the six daily motor tasks in the recent mobile application for generating digital outcome measures in a 6-month phase I PD clinical trial and was shown to be feasible and reliable [67]. With the recent COVID-19 pandemic, it is likely that PDCO measures with voice parameters will play an increasing role in the management of PD.

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Authors' roles

1) Research project: A. Conception, B. Project administration, C. Methodology, D. Resources, E. Funding aquisition, F. Investigation, G. Project administration.

2) Statistical Analysis: A. Design, B. Data curation, C. Software, D. Execution, E. Formal analysis, F. Supervision.

3) Manuscript: A. Writing of the first draft, B. Review and editing.

PS: 1C, 1E, 2A, 2B, 2C, 2D, 2E, 3A.
OP: 1C, 2B, 2C, 2E, 2F, 3B.
NT: 1A, 2F, 3B.
AT: 1A, 2F, 3B.
PM: 2A, 2B.
PL: 2A, 2B.
RB: 1A, 1B, 1C, 1D, 1E, 1F, 1G, 2E, 2F, 3A, 3B.

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