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RESEARCH ARTICLE

Clinical Correlate of Dysphonia Measures in Patients with Parkinson's Disease

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ABSTRACT

In patients with Parkinson's disease (PD), the impairment of neurological control is frequently observed to affect the normal functioning of the muscles involved in speech production. In this study we propose to analyze a speech corpus from subjects with and without PD, with the aim of quantifying speech alterations. The data corpus was built in 2019 in collaboration with public hospitals and universities of Argentina, it contains 55 audio samples from patients with PD and 71 subjects without PD. The analysis was conducted from four perspectives: a) perceptual speech therapy evaluation of voice quality; b) estimation of acoustic disturbance through the integrated perturbance index; c) otorhinolaryngological clinical evaluation to identify structural and functional alterations; and d) acoustic analysis of the sustained phonation signal of the vowel /a/. In the latter, 339 measures of dysphonia were estimated, which were then reduced to 11 parameters using statistical feature selection methods. These parameters achieved a performance greater than 80% in the automatic binary classification task (PD or non-PD). In the otorhinolaryngological clinical evaluation analysis, the clinical findings were classified into four categories based on the presence or absence of the alteration: gastroesophageal reflux; tremor during phonation and rest; alterations in glottic closure; and other alterations.

We estimated the degree of correlation between the analyses from these four perspectives. The integrated perturbance index is more relevant than the perceptual analysis of the voice quality, however, no correlation is observed with the clinical evaluation. Nonparametric statistical tests were used to assess mean differences between the 11 measures of dysphonia and each of the four categories of clinical findings identified. Significant differences were observed for four of the 11 selected dysphonia measures. These results encourage us to continue our analysis of acoustic parameters. We are also beginning to build a new data corpus, in which other measures of interest will be added.

1. Introduction

The diagnosis of Parkinson's disease (PD) is primarily based on clinical criteria, with motor symptomatology serving as the basis for the diagnosis according to the criteria of the Movement Disorders Society (MDS). The highest incidence of PD is observed in people aged between 50 and 60 years. The clinical course of PD can be predominantly tremulous or mixed (rigid akinesia associated with axial symptoms)[1].

Regardless of the initial symptoms between 60 and 80% of PD patients will experience changes in their voice during the progression of the disease, ranging from mild hypophonia to severe symptoms that can lead to anarthria[2,3].

The loss of coordination, tone and posture of the pharyngolaryngeal respiratory and phono-articulatory muscles, produce alterations in all the functions of the larynx, being early recognized voice and speech disorders that lead to progressive social isolation[4].

As the disease progresses, the protective and swallowing function of the larynx are affected, increasing the risk of morbidity and mortality due to airway aspiration.

Hypokinetic dysarthria is a motor speech disorder that affects verbal expression, characterized by hypophonia, altered articulation leading to consonant inaccuracy, a monotonous and hoarse voice, dysprosody and vocal tremor.

In recent years, subjective and objective voice assessment has been considered as a potentially useful tool for the diagnosis of PD. It has been suggested to consider vocal changes in the early diagnosis, disease tracking and assessment of patient responses to ongoing treatments[4,5]. Acoustic analysis of voice and speech has been proposed as an objective and non-invasive diagnostic marker in PD[6,7].

Temporal variability in the fundamental frequency (jitter) and the amplitude (shimmer) in consecutive cycles show higher values in patients with PD compared to healthy controls[8,9]. These changes are believed to reflect patterns of the decreased ability of the laryngeal muscles to maintain a fixed position in the sustained vocal emission[10]. As well, in PD patients it can be seen an incomplete closure of the vocal folds, that produces a high noise level in the voice signal[8].

Some studies have analyzed levels of dysphonia that measure characteristics associated with four dysfunctional groups[11,15]. These measures quantify characteristics altered by the impairment of neurological control affecting the muscle movements involved in voice production. Later, those studies identify a small number of features that are relevant for the detection of PD.

In this work, we present the results of our attempts to correlate the analysis of acoustic features of the voice signal with perceptual, laryngoscopic and stroboscopic alterations that are related to the disease. The aim is to contribute to the understanding of the disease through speech analysis and measures of dysphonia and, in the process, to optimize automatic speech analysis and processing techniques to detect voice alteration degree in patients with PD.

2. Methods

In this study, we compared qualitative and quantitative analysis of voice alterations in people with PD through four different perspectives.
A corpus of voices from people with and without PD was built in 2019, through collaborative work by an interdisciplinary group of professionals from hospitals and public universities of Argentina. We compared the analysis from four perspectives: perceptual speech therapy analysis; analysis of the integrated perturbance index (IPI); clinical otorhinolaryngological study (ear, nose, and throat, ENT); and acoustic analysis of speech signals.

The following sections describe the construction of the data corpus and present the methodology to evaluate the incidence of the disease based on speech therapy, otorhinolaryngology, and study of dysphonia measures. First, we provide a description of the results of the corpus analysis from each perspective, and then we conduct cross-analyses between them.

2. 1. DATABASE

The speech corpus includes audios recorded from subjects with and without diagnosed PD. Specialists from two public hospitals, Hospital Nacional Profesor Alejandro Posadas and Hospital General de Agudos Bernardino Rivadavia, and the Universidad Nacional de La Matanza (UNLaM), participated in its construction.

Patients with PD were recruited at the Otorhinolaryngology service of HGABR, while subjects without PD (NPD) were enrolled at the UNLaM[16].

The scripts audios to be recorded were:
- Sustained vowels /a/, /i/, /u/ for an estimated time from 3 to 5 seconds.

- Three repetitions of the nonsense word “pataka”.
- The phrase “*¡Betty! ¡Qué inmensa alegría escucharte! Cuando vengas para fin de año, quiero llevarte a recorrer toda la Argentina.*” (“*Betty! What an immense joy to hear from you! When you come at the end of the year, I want to take you to sightseeing Argentina.*”). Phonetically rich phrase taken from[17].

Recordings were made in an acoustic chamber, using a permanently polarized, backplate, fixed-load, AT2020 cardioid condenser microphone.

All participants underwent a perceptual voice study. Patients with PD underwent neurological evaluations using the Spanish version of the Unified Parkinson's Disease Scale (UPDRS), which is sponsored by the MDS[18,19] and the YH scale[20]. After recording, the patients received laryngoscopy and stroboscopy examinations. These examinations were performed using the HENKE-SASS WOLF Gmbh flexible naso-fibroscope model: 6903003600; Stroboled stroboscope, 70° STORZ rigid optics with 80W high-power Led light source and PROCAM video camera. All patients with PD were assessed using the same diagnostic tools, equipment and staff.

Inclusion criteria specified that patients were included with a diagnosis of idiopathic PD disease duration ranging from 0 to 5 years and experiencing motor complications up to and including 15 years of evolution. As exclusion criteria, patients with PD who had more than 16 years of the disease, undergone basal ganglia surgery, experienced a stroke, had prior voice disorders, laryngeal pathology, or other neurodegenerative diseases were discarded.

2. 2. ANALYSIS PERSPECTIVES

The different analysis perspectives conducted on the data corpus described in the previous section are presented below.

a) Therapist perceptual evaluation of voice quality

The perceptual analysis was carried out by a speech therapy specialist, rating the stimuli in GRBAS (Dysphonia Grade, Roughness, Breathiness, Asthenia and Strain) scale with the help of the Audio-Perceptual Evaluation System (EVAPER)[21]

b) Integrated Perturbation Index acoustic analysis (IPI)

The voice perturbations are defined as any abnormality in the vocal quality, pitch, loudness or vocal effort that disturbs communication or generates a negative effect on the voice-related quality of life. IPI is a quantitative indicator that allows voice signals to be classified into levels of acoustic alteration: normal, risk zone and severe[22,23]. The Acoustic Analysis and Graphing of Speech Signals (ANAGRAF) software was used to estimate the IPI values.

c) Otorhinolaryngological clinical evaluation

The ENT clinical evaluation involved laryngeal stroboscopy to assess structural and functional alterations, excluding pathologies not related to PD ruling out pathologies not PD related. Identified alterations were grouped into four categories: signs compatible with gastroesophageal reflux (GERD); tremor on phonation and rest; alterations in glottic closure; and other alterations. This analysis was only performed over the PD subjects. Patients were also asked if they self-perceived changes in their voice[16,24].

d) Acoustic analysis of the signal

Due to its simplicity and acoustic richness, the 3 seconds sustained pronunciation of the vowel /a/ was chosen for this analysis. Its audio signal is quasiperiodic, characterized by its signal amplitude, fundamental frequency (F0), and its resonance frequencies in the vocal tract or formants (Fn). The F0 value corresponds to the vibration frequency of the vocal folds. For each audio signal, 339 acoustic measures of dysphonia proposed in Tsanas (2012)[12] were calculated.

In Giuliano et al (2020)[11] these measures were clustered in four groups that characterize the most common problems in the dysfunctional voices of PD patients. In group G1, jitter and periodicity perturbations; in group G2, shimmer and amplitude perturbations; in group G3, problems related to incomplete closure of vocal folds, linked to noise, measures like harmonic to noise ratio (HNR) and noise to harmonic ratio (NHR); and finally, in group G4, articulatory problems in the vocal tract, measures like mel frequency cepstral coefficients (MFCC), were included.

To complete the task, 11 of 339 features were selected using different statistical techniques: principal components (PCA), Analysis of Variance (ANOVA), logistic regression with penalty (RL). A final model was achieved with an accuracy of 80% in classifying subjects with and without Parkinson's, identifying relevant variables. Table 1 shows the selected variables, where the original names proposed in Tsanas (2012)[12] are indicated.

Table 1. Acoustic measurements according to classification groups. Names correspond to Tsanas (2012)[12] and groups to Giuliano et al (2020)[11].

Group according to Giuliano et al. (2020)[11]	Type of measure	Feature	Label	Name according to Tsanas (2012)[12]
G1	Jitter	V1	V1_G1	Jitter->F0_abs_dif
		V51	V51_G1	GQ->std_cycle_closed
G2	Shimmer	V34	V34_G2	Shimmer->F0_abs0th_perturb
G3	Relationship between HNR and NHR.	V338	V338_G3	DFA
		V59	V59_G3	VFER->std
		V70	V70_G3	IMF->NSR_entropy
G4	MFCC	V137	V137_G4	std_9th delta
		V141	V141_G4	std_delta delta log energy
		V152	V152_G4	std_10th delta-delta
		V71	V71_G4	mean_Log energy
		V75	V75_G4	mean_MFCC_3rd coef

Descriptive analysis, tables and boxplots were performed for each analysis perspective, according to PD patients and NPD subjects. The chi^2 test was used for the cross tables and the non-parametric Mann-Whitney U test was used for the difference in means. For all tests, standardized variables were used.

3. Results

Participants sociodemographic characteristics and clinical condition of PD patients are illustrated in Table 2. The average age of PD patients is 64.09 years, with 8.24 standard deviation, and the mean age of the disease of approximately 6 years. In the non-PD case, the average age is 61.58 years, not very different from the PD case.

According to the UPDRS scale, PD patients presented mean values of 30.35, with values between a minimum of 12 and a maximum of 53. Patients were also evaluated with the Hoehn & Yar (H&Y) scale and mean values of 1.59 were observed. At the time of the recording, they were on medication, in a state in which the symptoms are of low intensity.

Table 2. Sociodemographic characteristics of the participants and clinical condition of patients with PD. Mean (deviation) is indicated.

Condition	Frequency	Age (years)	Illness period (years)	UPDRS III	H&Y	Levadopa (mg)
PD	55	64.09 (8.24)	6.11 (3.89)	30.35 (11.17)	1.59 (0.59)	880.19 (479.22)
NPD	71	61.58 (11.61)				

3.1 SPEECH THERAPY EVALUATION

Results of perceptual analysis of the voice quality are shown in Figure 1. Mild categories present similar percentage values, close to 75%, for both groups, PD vs NPD (pvalue>0.05). Non severe instances are identified in NPD subjects, while in PD patients 9% were classified as this category.

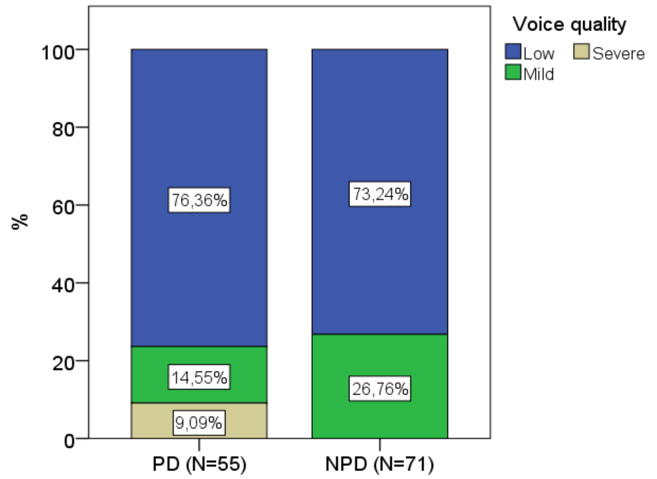


Figure 1. Results of perceptual analysis of voice quality, differentiated according to the disease condition.

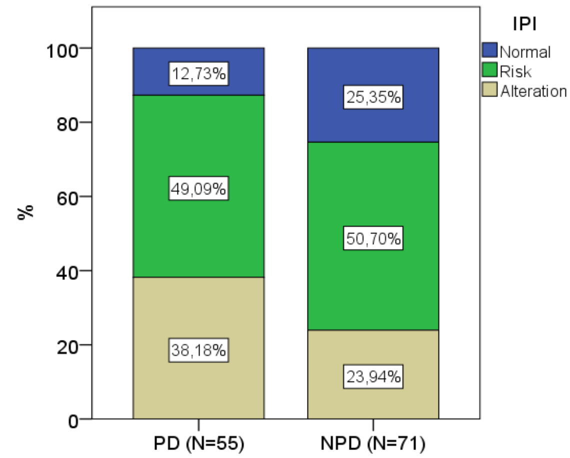


Figure 2. Results of integrated perturbation index (IPI), acoustic alteration classification, differentiated according to the disease condition.

3.2 ACOUSTIC ASSESSMENT WITH THE INTEGRATED DISTURBANCE INDEX

Results of IPI acoustic alteration classification are shown on Figure 2. Approximately 50% of instances belong to the risk zone, for both, PD and NPD subjects. Greater differences are seen in the normal and altered categories: PD patients get 50% more instances in the altered category.

3.3 OTORHINOLARYNGOLOGY ASSESSMENT OF PARKINSON'S DISEASE PATIENTS

When patients were asked if they perceived changes in their voice, 70% responded that they did not, 26% reported a decrease in vocal intensity, and the remaining 4% reported dysphonia, trembling voice or muffled voice.

Male patients showed higher F0 values than usual. Results of laryngeal stroboscope scans were reported in Giuliano et al (2021)[16] and Debas & Morales (2023)[24]. Alterations observed were clustered into four categories: GERD; chordal tremor in phonation and rest; alterations in glottal closure; and other alterations. Results show 71% of subjects present GERD compatible items, predominantly presenting mucosal congestion in the posterior arch. Vocal tremor was observed in 67% of patients, with predominance at rest status. An altered glottic closure was observed in 65% of instances, being incomplete in 14% of patients. Hyperfunction was found in 37% of patients due to supraglottic lateral contraction and ventricular band hypertrophy was observed in 11% of subjects.

Other alterations were observed in 40% of patients, for example: decreased muco-undulatory movement, hypotonic vocal folds, laryngeal asymmetry, vocal fold atrophy, ulcer, vocal fold edema, bilateral chordal sulcus and secretions retention. These may or may not be associated with the previous categories.

Table 3. Results of the ENT evaluation.

Discovery	Frequency	Percentage
Signs of GERD	39	71%
Alteration of the Glottis	36	65%
Tremor	37	67%
Other alterations	22	40%

The Table 4 shows the relationship between pairs of alterations and highlights the following issues:
- Among patients who do not self-perceive changes in their voice, 68% present GERD, 66% alterations in the glottis and also 66% tremor.
- Among patients who present GERD, 72% have glottis alterations and 69% have tremor.
- Among patients with alterations in the glottis, 78% have GERD and 72% have tremor.
- Among patients who present tremor, 68% self-perceive changes in their voice, 73% present GERD compatible items, and 70% show glottis alterations.

Table 4. Crosstable between self-perception of changes in voice and characteristics revealed by ENT.

		Self-perception		**GERD**		**Glottis alteration**		**Tremor**		**Other alteration**		**Total**
		Si	No	Si	No	Si	No	Si	No	Si	No	
Self-perception	Si	17	0	13	4	11	6	12	5	7	10	17
	No	0	38	26	12	25	13	25	13	15	23	38
GERD	Si	13	26	39	0	28	11	27	12	13	26	39
	No	4	12	0	16	8	8	10	6	9	7	16
Glottis alteration	Si	11	25	28	8	36	0	26	10	13	23	36
	No	6	13	11	8	0	19	11	8	9	10	19
Tremor	Si	12	25	27	10	26	11	37	0	15	22	37
	No	5	13	12	6	10	8	0	18	7	11	18
Other alteration	Si	7	15	13	9	13	9	15	7	22	0	22
	No	10	23	26	7	23	10	22	11	0	33	33

Table 5 shows the number of simultaneous alterations that were identified in the patients. Approximately half of all patients (53%), presented simultaneously between 3 and 4 alterations. Only 2 patients did not show any alteration.

Table 5. Number of alterations observed per patient, between none and four (N=55).

Number of clinical alterations	**Frequency**	**Percentage**	**Cumulative percentage**
0	2	3,6	3,6
1	7	12,7	16,4
2	17	30,9	47,3
3	23	41,8	89,1
4	6	10,9	100,0

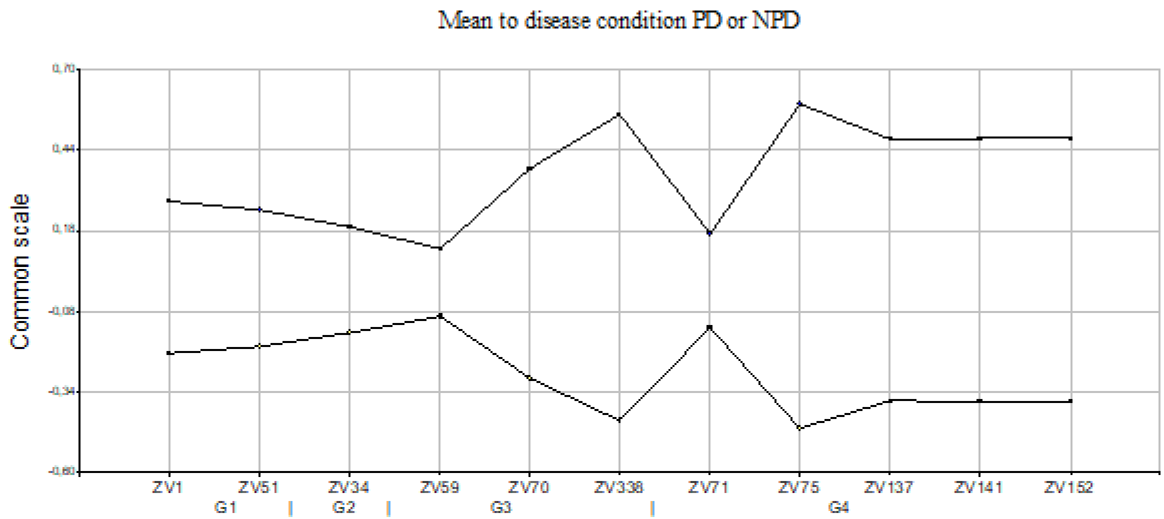
3.3 ANALYSIS OF DYSPHONIA MEASURES

The mean standardized values of the 11 selected features are shown in Figure 3, discriminated by the disease condition. All NPD values are lower than PD values. Wilcoxon tests were performed, obtaining significant differences ($p\text{-value} < 0.05$) for nine features, except for v51, v59, v71. Features V1 and V51, both from group G1, are two jitter measures and significant differences were found only for V1 (pvalue=0.0641). Feature V34 of group G2 is a shimmer measure where a significant difference in means is observed according to PD and NPD.

In group G3, the features related to noise V59, V70 and V338, measures of MFCC, only in V59 do not present significant differences (pvalue=0.8114).

In group G4, with features related to articulation problems, only V71 (pvalue=0.0974) does not present significant mean differences.

The results regarding the 11 features of dysphonia show significant mean differences for some measures of the 4 features groups: jitter, shimmer, harmonic noise and ceptral coefficients.



NPD down (N=126)

Figure 3. Mean of the 11 variables in standardized values according to disease condition, PD up and

Table 6. Comparison of IPI categories vs perceptual speech therapy evaluation (N=55)

		IPI			**Total**
		Normal	Risk	Alteracion	
Perceptual speech therapy evaluation	Low	6	24	12	42
	Mild	1	2	5	8
	Severe	0	1	4	5
Total		7	27	21	55

The eleven selected standardized acoustic features were compared with the otorhinolaryngological analysis. A comparison of mean values was carried out, for two independent samples, in pairs and according to the type of clinical alteration: GERD, tremor, glottis disorder. The results show significant mean differences, with p-value < 0.05, in the following variables and groups:

- G1: V1 average variation between the groups, with and without the presence of GERD.
- G3: V338 mean variation between groups, with and without the presence of alterations in the glottis.
- G4: V141 and V152 mean variation between groups, with and without the presence of tremor and GERD

To compare the distributions of the variables, a set of boxplots were performed. The IPI and one variable for each group were chosen: V1_G1, V34_G2, V338_G3 and V141_G4.

The greatest differences in the variables are observed in the cases according to GERD (Figure 4), where all the variables except for V34_G2 show values with greater intensity and greater variability for the cases with the presence of GERD (Yes).

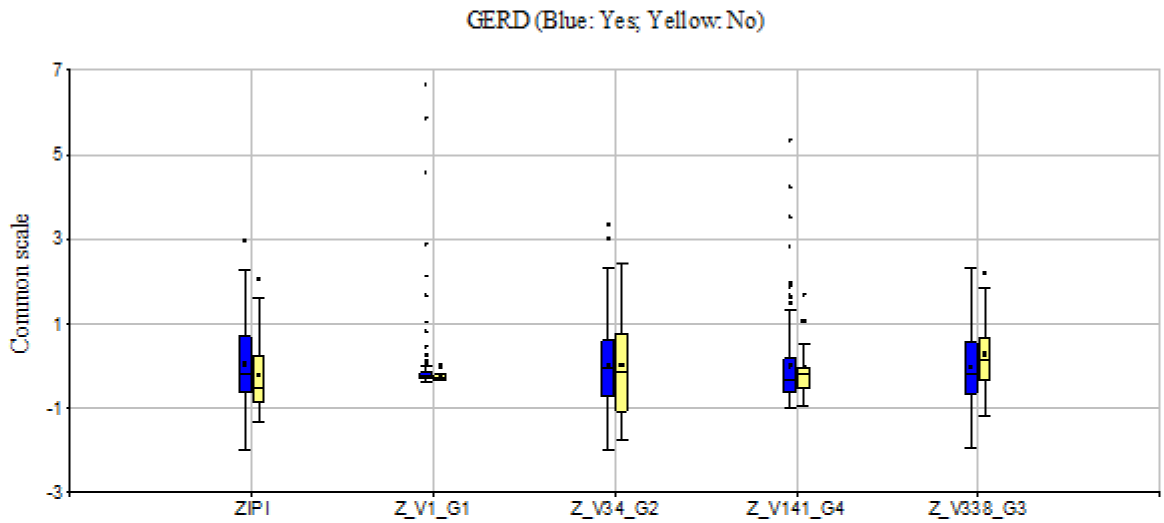


Figure 4. Variables IPI; V1_G1, V34_G2, V338_G3 y V141_G4, in standardized values according to the presence of gastroesophageal reflux, GERD (Yes/No, respectively Blue/Yellow). (N=55)

Regarding the presence of tremor (Figure 5), greater variations were observed in V1_G1 and V141_G4 with values of greater intensity, variability and a greater number of upper outliers.

Regarding the presence of alteration in the glottis (Figure 6), variation stands out in V338_G3 with values of greater intensity and variability.

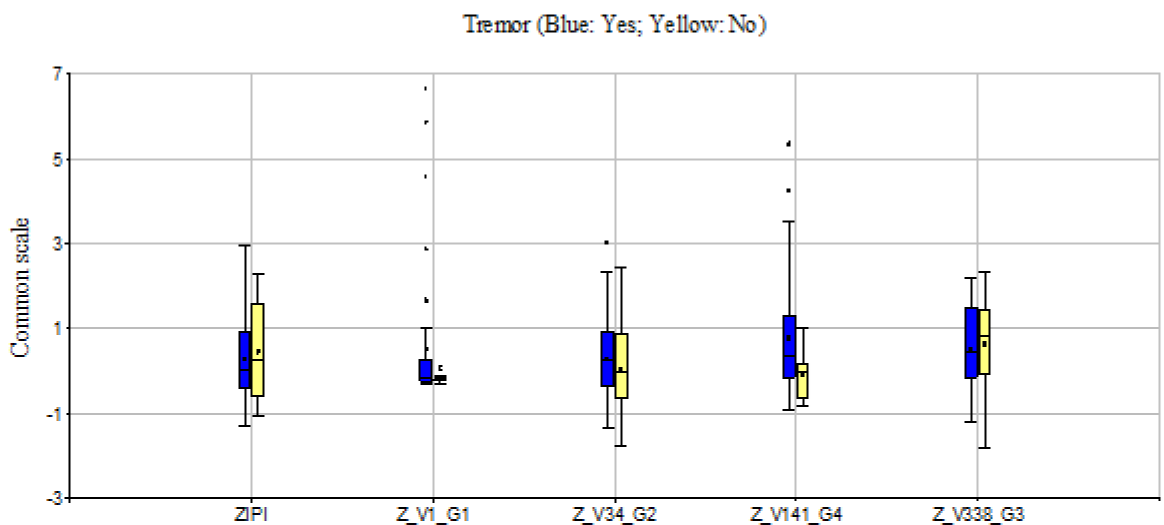


Figure 5. Variables IPI; V1_G1, V34_G2, V338_G3 y V141_G4, in standardized values according to the presence of tremor in phonation and repose (Yes/No, respectively Blue/Yellow) (N=55)

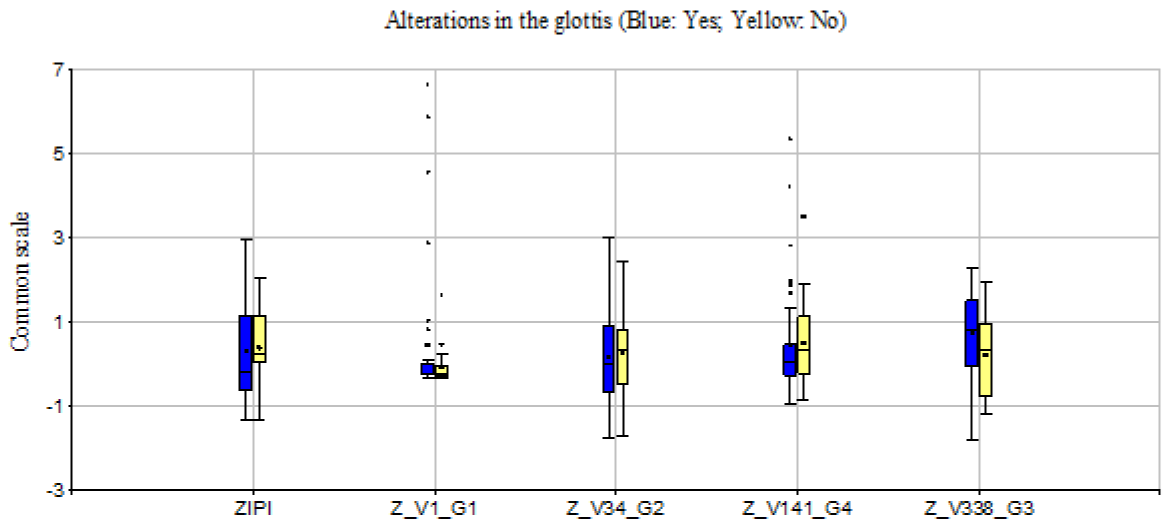


Figure 6: Variables IPI; V1_G1, V34_G2, V338_G3 y V141_G4, in standardized values according to the presence of alterations in the glottis (Yes/No, respectively Blue/Yellow) (N=55)

Laryngoscopic evaluation results showed information about the structural changes and the state of the larynx muscular function. The findings were chord tremor associated with altered voice disturbance indices, altered or incomplete glottic closure, and dysfunctions that the patient tries to compensate spontaneously with the hyperfunction of the others perilaryngeal and cervical muscles.

4. Discussion

In this work, a voice corpus was analyzed with samples from patients with PD and subjects without the diagnosed disease. This work was organized from three points of view: perceptual voice quality; acoustic parameters; and clinical characteristics of the larynx and vocal cords. The findings from the three analyzes were then correlated between them, in an attempt to find out how the patients' voices were affected. The corpus used is available for academic purposes[16,25]. Jitter and shimmer disturbance indices are identified in patients with PD, features which are related to alterations in the vocal muscles control. The general compromise of all muscles also impacts on other systems such as respiratory, phono-articulatory, and digestive, among others, which contributes to a greater vocal alteration. This can be observed more significantly in the disease progression[5,6,25,26,28].

The results of the meta-analysis carried out by Chiramonte[29] do not show consensus between some authors on the differences in means in jitter and shimmer measurements according to disease condition, PD or NPD. In our analysis of 11 dysphonia acoustic features, we found significant mean differences in only 7 of them. These involve 4 types of variables: jitter, shimmer, harmonic noise and cepstral coefficients, estimated with the algorithms proposed by Tsanas[4]. The mean differences do not show significant information, we assume that their values are affected by outliers, and it is proposed to observe the feature distribution in graphical representations such as boxplot graphs.

The patients underwent a synchronous evaluation using laryngoscopy with stroboscopy. Functional changes already reported in other studies were found, such as tremor[30,31,32], incomplete glottic closure[31,32] and rigidity of the global respiratory muscles[32]. In addition, other manifestations were observed that have not been reported associated with vocal alterations in PD, and can be explained from the pathophysiology associated with this disease. Gastroesophageal reflux disease (GERD) was found in 71% of the patients, resulting from a dysfunction of the enteric nervous system that causes gastroparesis with delayed gastric emptying, or from the consumption of antiparkinsonian medication. Furthermore, it was also found that 37% of the patients suffered from lateral supraglottic hyperfunction and in 11% hypertrophy of ventricular bands, both can be associated with compensatory manifestations to the previously described vocal alterations, present in the early stages of the disease.

Laryngeal muscles in PD patients have a decreased ability to sustain the emission of a vowel[10]. Incomplete closure of the vocal folds has also been observed, producing a higher noise level[8]. Deficiencies in the speech sound articulation are also observed[34].

The perceptual assessment of the voice through subjective scales dependents on the training of the speech therapist professional, even with computerized analysis tools like EVAPER[21]. The results don't show a relationship between voice quality measures and IPI, therefore the latter is preferred. However, IPI measures were originally calibrated for comparison with healthy young voices, and they may not be entirely suitable for differentiating older individuals with and without PD, given the voice changes with age. This suggests that the results obtained in this study should be revisited in future research in this respect.

UPDRS or Y&H disease progression scales are not analyzed here. In Giuliano et al (2020)[11] results do not show a relationship between the 11 variables and the disease progression degree according to these scales. There is no consensus among the authors on the relationship between voice alterations and the disease degree with UPDRS or Y&H scales[7].

5. Conclusions

This study contributes to understanding the correlation between various objective and subjective measures of voice dysphonia and alterations identified in laryngoscopy with laryngeal stroboscope in patients with PD. The results have implications particularly in disease monitoring in terms of vocal alterations that can manifest early on.

Mean differences non-parametric tests were made over 11 features of dysphonia with respect to 3 categories of clinical findings: presence or absence of GERD; alteration in the glottis; and chordal tremor. The category "other observed disturbances" is left aside as it brings together divergent alternatives for comparison with the acoustic measures.

These results show a correlation degree between the analyzed parameters and the clinical findings observed in the patients. In group G1 (jitter type), variable V1 presents mean differences according to the presence or absence of GERD. In group G3 (noise type), variable V338 presents mean differences according to the presence or absence of alterations in the glottis. Finally, in group G4 (MFCC), variables V141 and V152 present mean differences for both the presence or absence of GERD and tremor. Significant mean differences were observed, however, although the differences in means found, the study of the boxplots and of the measurements as a whole is considered more relevant.

The technology development has allowed us to access and integrate valuable clinical information about voice patients, for both voice pathologies detection and PD tracking. In future work, we will apply this knowledge to medical practice protocols and to development of a web application, both for physician and patient self-management[35,36].

The field is in the early stages of establishing a global consensus on the search for structural changes accessible by laryngeal stroboscopy and the subjective and objective perceptual evaluation of voice, which can be used as monitoring tools for Parkinson's Disease. The encouraging results obtained in this study underscore the importance of further parameter analysis.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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References

1. Postuma RB, Berg D, Stern M, Poewe W, Olanow CW, Oertel W, et al. MDS clinical diagnostic criteria for Parkinson's disease: MDS-PD Clinical Diagnostic Criteria. *Mov Disord.* 2015;30(12):1591–601. Available at http://dx.doi.org/10.1002/mds.26424
2. De Letter M, Santens P, Van Borsel J. The effects of levodopa on word intelligibility in Parkinson's disease. *J Commun Disord.* 2005;38(3):187–96. Available at: http://dx.doi.org/10.1016/j.jcomdis.2004.09.001
3. Törnqvist AL, Schalén L, Rehncrona S. Effects of different electrical parameter settings on the intelligibility of speech in patients with Parkinson's disease treated with subthalamic deep brain stimulation: DBS Electrical Settings and Speech in PD. *Mov Disord.* 2005;20(4):416–23. Available at http://dx.doi.org/10.1002/mds.20348
4. Karabayir I, Goldman SM, Pappu S, Akbilgic O. Gradient boosting for Parkinson's disease diagnosis from voice recordings. *BMC Med Inform Decis Mak.* 2020;20(1):228. Available at http://dx.doi.org/10.1186/s12911-020-01250-7
5. Yang S, Wang F, Yang L, Xu F, Luo M, Chen X, et al. The physical significance of acoustic parameters and its clinical significance of dysarthria in Parkinson's disease. *Sci Rep.* 2020;10(1). Available at: http://dx.doi.org/10.1038/s41598-020-68754-0
6. Suppa A, Costantini G, Asci F, Di Leo P, Al-Wardat MS, Di Lazzaro G, et al. Voice in Parkinson's disease: A machine learning study. *Front Neurol.* 2022;13. Available at http://dx.doi.org/10.3389/fneur.2022.831428
7. Chiaramonte R, Bonfiglio M. Análisis acústico de la voz en la enfermedad de Parkinson: revisión sistemática de la discapacidad vocal y metaanálisis de estudios. *Rev Neurol.* 2020;70(11):393–405. Available at: http://dx.doi.org/10.33588/rn.7011.2019414
8. Jiménez-Jiménez FJ, Gamboa J, Nieto A, Guerrero J, Orti-Pareja M, Molina JA, et al. Acoustic voice analysis in untreated patients with Parkinson's disease. *Parkinsonism Relat Disord.* 1997;3(2):111–6. Available at: http://dx.doi.org/10.1016/s1353-8020(97)00007-2
9. Jiang J, Lin E, Wang J, Hanson DG. Glottographic measures before and after levodopa treatment in Parkinson's disease. *Laryngoscope.* 1999;109(8):1287–94. Available at: http://dx.doi.org/10.1097/00005537-199908000-00019
10. Gallena S, Smith PJ, Zeffiro T, Ludlow CL. Effects of levodopa on laryngeal muscle activity for voice onset and offset in Parkinson disease. *J Speech Lang Hear Res.* 2001;44(6):1284–99. Available at http://dx.doi.org/10.1044/1092-4388(2001/100)
11. Giuliano M, Fernandez L, Perez S. Selección de Medidas de Disfonía para la Identificación de Enfermos de Parkinson [Not available in English]. In *Proceedings IEEE ARGENCON2020.* 2020, pp. 1-8, doi: 10.1109/ARGENCON49523.2020.9505554
12. Tsanas A. Accurate telemonitoring of Parkinson's disease symptom severity using nonlinear speech signal processing and statistical machine learning. [PhD thesis]. Oxford University, UK.; 2012.
13. Tsanas A, Little MA, Fox C, Ramig LO. Objective automatic assessment of rehabilitative speech treatment in Parkinson's disease. *IEEE Trans Neural Syst Rehabil Eng.* 2014;22(1):181–90. Available at http://dx.doi.org/10.1109/TNSRE.2013.2293575
14. Guatelli R, Giuliano M, Aubin V, Fernández L, Pérez S, Pepe L. Análisis comparativo entre CNN y Modelos Logísticos para detección de la Enfermedad de Parkinson utilizando la voz. In Proceedings X Congreso Nacional de Ingeniería Informática / Sistemas de Información. AJEA Ed. 2022;299-305. Available at: https://doi.org/10.33414/ajea.1146.2022
15. Giuliano M, Fernández L, Pérez S, Renato A. Evaluación de áreas del espacio vocal y formantes para caracterizar personas con y sin Enfermedad de Parkinson. In Proceedings IEEE ARGENCON2021. 917–24. Available at http://dx.doi.org/10.1109/ARGENCON55245.2022.9939816
16. Giuliano M, Adamec D, Debas MI. Construcción de una base de voz de personas con y sin enfermedad de Parkinson. *Rev Dig Departamento de Ingeniería e Investigaciones Tecnológicas (REDDI).* 2021;6-10. Available at https://reddi.unlam.edu.ar/index.php/ReDDi/article/view/141
17. Gurlekian JA, Colantoni L, Torres HM. El alfabeto fonético SAMPA y el diseño de córpora fonéticamente balanceados. Fonoaudiológica Editorial: ASALFA. 2001;3–58.
18. Goetz CG, Poewe W, Rascol O, Sampaio C, Stebbins GT, Counsell C, et al. Movement Disorder Society Task Force report on the Hoehn

and Yahr staging scale: status and recommendations the Movement Disorder Society Task Force on rating scales for Parkinson's disease. *Movement disorders*. 2004;19:1020–8.
19. Fahn S, Elton R. Members of the UPDRS Development Committee. En: Fahn S, Marsden CD, Calne DB, Goldstein M, editores. Recent developments in Parkinson's disease. Florham Park, NJ: Macmillan Health Care Information. 1987; 293–304.
20. Hoehn MM, Yahr MD. Parkinsonism: onset, progression, and mortality. 1967. *Neurology*. 1998;50(2):318-335. Available at http://dx.doi.org/10.1212/wnl.50.2.318
21. Gurlekian JA, Torres HM, Cediel MR. A perceptual method to rate dysphonic voices. *J Voice*. 2019;33(4):453–64. Available at http://dx.doi.org/10.1016/j.jvoice.2018.01.007
22. Gurlekian JA, Molina N. Índice de perturbación, de precisión vocal y de grado de aprovechamiento de energía para la evaluación del riesgo vocal. *Rev Logop Foniatr Audiol*. 2012;32(4):156–63. Available at http://dx.doi.org/10.1016/j.rlfa.2012.03.007
23. Sigal L, Gurlekian JA. Aplicación de los índices de perturbación integrado y de precisión articulatoria en pacientes con disfonía espasmódica. *Rev Investig Logop*. 2014;4(2):132–50. Available at http://dx.doi.org/10.5209/rlog.58665
24. Debas MI, Morales C. Base de habla de pacientes con EP: Características de las cuerdas vocales observadas. In Memoria del primer workshop de estudios del habla en pacientes con enfermedad de Parkinson. 2023;86–94. Available at: https://www.uno.edu.ar/eduno/publicaciones.html
25. Pérez SN, Giuliano M. Audios_vowel_A_PD. Figshare; 2022. Available at http://dx.doi.org/10.6084/M9.FIGSHARE.21453867.V1
26. Mamolar A, Santamarina Rabanal ML, Granda Membiela CM, Fernández Gutiérrez, MJ, Sirgo Rodríguez P, Álvarez Marcos C. Swallowing Disorders in Parkinson's Disease. *Acta Otorrinolaringológica Española*. 2017;68(1).
27. Wen P, Zhang Y, Wen G. Intelligent personalized diagnosis modeling in advanced medical systems for Parkinson's disease using voice signals. *Mathematical Biosciences and Engineering*. 2023;20(5):8085–102.
28. Moro-Velazquez L, Gomez-Garcia JA, Arias-Londoño JD, Dehak N, Godino-Llorente JI. Advances in Parkinson's Disease detection and assessment using voice and speech: A review of the articulatory and phonatory aspects. *Biomed Signal Process Control*. 2021;66 (102418):102418. Available at: http://dx.doi.org/10.1016/j.bspc.2021.102418
29. Chiaramonte R, Bonfiglio M. Análisis acústico de la voz en la enfermedad de Parkinson: revisión sistemática de la discapacidad vocal y metaanálisis de estudios. *Rev Neurol*. 2020 Jun; 70: 393-405. Available from https://doi.org/10.33588/rn.7011.2019414
30. Gamboa J, Jiménez-Jiménez FJ, Nieto A, Cobeta I, Vegas A, Ortí-Pareja M, et al. Acoustic voice analysis in patients with essential tremor. *J Voice*. 1998; 12: 444-52.
31. Bauer V, Aleric Z, Jancic E, Miholovic V. Voice quality in Parkinson's disease in the Croatian language speakers. *Coll Antropol*. 2011; 35 (Suppl 2): S209-12.
32. Midi I, Dogan M, Koseoglu M, Can G, Sehitoglu MA, Gunal DI. Voice abnormalities and their relation with motor dysfunction in Parkinson's disease. *Acta Neurol Scand*. 2008; 117: 26-34.
33. Santos García D, Deux TD, Tejera Pérez C, Expósito Ruiz I, Suárez Castro E, Carpintero P, Macías Arribi M. Gastroparesia y otros síntomas gastrointestinales en la enfermedad de Parkinson. *Rev neurol*. 2015;61:261-270.
34. Hirano M. Clinical examination of voice. New York: Springer Verlag; 1981.
35. Giuliano M, Pérez SN, Berduc A. Memoria del primer workshop de estudios del habla en pacientes con enfermedad de Parkinson. EDUNO. 2023. Available at: https://www.uno.edu.ar/eduno/publicaciones.html
36. Giuliano M, Pérez SN, Mangiarua N. Estudio del habla de pacientes con enfermedad de Parkinson y desarrollo de aplicación web. In Actas XXIV WICC 2022 – Workshop de Investigadores en Ciencias de la Computación. FUSMA Ed. 2023 [accessed October 30, 2023]. Available at https://wicc2022.uch.edu.ar/