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Systematic Review
Revisão Sistemática

Impact of levodopa treatment in the voice pattern of Parkinson's disease patients: a systematic review and meta-analysis

O impacto do tratamento com levodopa na voz de pacientes com doença de Parkinson: revisão sistemática e meta-análise

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Keywords

Levodopa
Parkinson's Disease
Systematic Review
Meta-analysis
Voice

ABSTRACT

Purpose: Investigate the association between levodopa therapy and vocal characteristics in Parkinson's disease patients. **Search strategy:** Studies published at MEDLINE, LILACS, and SciELO, from 1960 to December 2016. A systematic review and meta-analysis was performed using the following keywords: Parkinson's disease; levodopa; L-dopa; voice; speech disorders; dysphonia; dysarthria. After analyzing titles and abstracts, two independent reviewers selected all clinical trials that met the eligibility criteria and selected the articles and the data recorded in a previously standardized table. **Selection criteria:** Trials published in English between 1960 and December 2016 individuals with clinical diagnosis of Parkinson's disease; use of levodopa therapy in stable doses; acoustic analysis combined or not with auditory-perceptual analysis to evaluate the vocal parameters under investigation. **Data analysis:** The following vocal parameters were analyzed: fundamental frequency (*F*0), jitter, and vocal intensity. Standardized mean differences (SMD) were calculated using the Comprehensive Meta-analysis V2 software. **Results:** Nine articles met the eligibility criteria and were selected, with a total of 119 individuals. From these, six articles with 83 individuals were included in the meta-analysis. During the levodopa therapy "on" state, modifications in *F*0 (SMD=0.39; 95% CI - 0.21-0.57) and jitter (SMD=0.23; 95% CI - 0.02-0.45) were observed. Vocal intensity was not affected (SMD=0.09; 95% CI - 0.22-0.39) by levodopa ingestion. Data of the included studies were controversial in the auditory-perceptual analysis of voice. **Conclusion:** Levodopa therapy modifies *F*0 and jitter. No changes in vocal intensity were observed in either the "on" or "off" states of levodopa therapy.

Descritores

Levodopa
Doença de Parkinson
Revisão Sistemática
Metanálise
Voz

RESUMO

Objetivo: investigar a associação entre o uso da levodopa e as características vocais em pacientes com doença de Parkinson. **Estratégia de pesquisa:** estudos publicados nas bases MEDLINE, LILACS e SciELO, de 1960 a dezembro de 2016. Uso dos descritores: doença de Parkinson; levodopa; L-dopa; voz; distúrbios do discurso; disfonia e disartria. Depois de analisar os títulos e os resumos, dois revisores independentes selecionaram todos os ensaios clínicos que atendiam aos critérios de seleção, selecionaram os artigos e registraram os dados em uma tabela padronizada anteriormente. **Critérios de seleção:** ensaios publicados em inglês entre 1960 e dezembro de 2016 assuntos com diagnóstico clínico de doença de Parkinson; uso de terapia com levodopa em doses estáveis; análise acústica combinada ou não com a análise auditiva-perceptiva para avaliar os parâmetros vocais sob investigação. **Análise dos dados:** os parâmetros vocais analisados foram: frequência fundamental (F0), Jitter e intensidade vocal. As diferenças de médias padronizadas (SMD) foram calculadas com o software Metanálise Abrangente V2. **Resultados:** 9 artigos preencheram os critérios de elegibilidade e foram selecionados, com um total de 119 indivíduos. Desses 9 artigos, 6, com 83 indivíduos, foram incluídos na metanálise. Durante a fase "on", houve uma modificação no F0 (SMD = 0,39; IC 95% 0,21-0,57) e Jitter (SMD = 0,23; IC 95% 0,02-0,45). A intensidade vocal não foi afetada (SMD = 0,09; IC 95% -0,22-0,39) pela ingestão da levodopa. Ao considerar a análise auditiva-perceptiva, os dados foram controversos entre os estudos incluídos. **Conclusão:** a terapia com levodopa modifica F0 e Jitter. Não houve alteração na intensidade vocal nas fases "on" e "off" da terapia com levodopa.

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INTRODUCTION

Parkinson's disease (PD) is characterized by bradykinesia, rigidity, tremor, and postural instability, associated with non-motor symptoms such as dementia, mood disorders, and pain[1]. Among the non-motor symptoms, dysarthria, sialorrhea, dysphagia[2], and dysphonia[3] impair social interaction and reduce the quality of life of patients[4,5]. The described symptoms are usually neglected by caregivers and health professionals in the treatment of these patients. A large number of characteristics have been described as vocal disorders in PD patients, including hoarseness, vocal tremor, loudness reduction, mono-pitch, and mono-loudness[3,6-9].

In the past years, some studies have addressed rehabilitation of vocal symptoms in PD patients[4], including the Lee Silverman Voice Treatment (LSVT®), which provides improvement in vocal intensity after 16 daily sessions of exercises[10].

Levodopa, which is considered the gold standard therapy drug for PD since 1960, reduces rigidity and bradykinesia of striated muscles, and its efficacy in motor symptoms is irrefutable. In this way, voice production could be modified by its action on the laryngeal and respiratory muscles. However, there are controversial data about its action in vocal parameters in this group of patients[7,11-13].

PURPOSES

Investigate whether levodopa modifies vocal characteristics in Parkinson's disease patients.

SEARCH STRATEGY

This systematic review and meta-analysis was performed by two independent reviewers at the following electronic databases: MEDLINE, LILACS, and SCIELO. The search was conducted using a combination of the following keywords: Parkinson's disease; levodopa; L-dopa; voice; speech disorders; dysphonia; dysarthria.

SELECTION CRITERIA

After a previous analysis of the titles and abstracts of articles retrieved from the electronic databases, clinical trials were selected according to the following inclusion criteria: published in English between 1960 and December 2016; individuals with confirmed diagnosis of Parkinson's disease (PD); prescription of levodopa combined or not with other antiparkinsonian agents, in stable doses; results of acoustic analysis and/or auditory-perceptual analysis on vocal evaluation and presentation of the vocal parameters analyzed.

After that, the references of the selected articles were verified in order to identify articles not found in the electronic search. All selected articles were analyzed by two investigators and were excluded from the review if they did not present the outcomes of interest. Quality of the included trials was assessed by the Methodological Index for Non-randomized Studies (MINORS)[14]. This protocol is composed of 12 items. Eight of them were applied to all studies and the other four were applied only to those with comparative groups.

Evaluations of vocal characteristics through auditory-perceptual and acoustic analyses were the outcomes considered. Hoarseness, roughness, vocal tremor, loudness, and pitch were considered in the auditory-perceptual analysis, whereas standardized mean differences (SMD) of the following variables were considered in the acoustic analysis: fundamental frequency (*F*0), vocal tremor, vocal intensity, jitter, and shimmer.

DATA ANALYSIS

The standardized mean differences (SMD) were obtained for every study included in the review. The SMD were considered at 95% CI and 5% significance level. Heterogeneity was calculated and confirmed by the χ^2 and I^2 tests, respectively. As there were no inconsistencies between the selected articles, the Fixed Effects Model was used to estimate the effect sizes. As it is known that gender may interfere with the vocal parameters analyzed, a subgroup analysis by gender was performed to verify the existence of effect-size variations. Publication biases were verified by a funnel plot graph. All calculations were processed using the Comprehensive Meta-analysis V2 software.

RESULTS

The search yielded 503 articles, but 494 were excluded: 318 for not meeting the inclusion criteria and 167 for being in duplicate (Figure 1). Nine articles were included in this systematic review with a total of 119 individuals. Their data are summarized in Table 1. From these, six articles with 83 individuals were included in the meta-analysis. To accomplish the meta-analysis, only the studies that performed acoustic analysis with comparative data were included.

In this context, three studies were excluded from the meta-analysis. Two of them used analogue scale to assess vocal

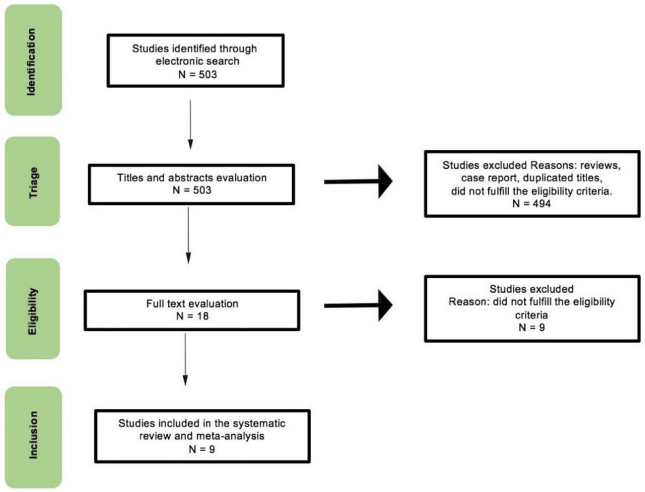


Figure 1. Flowchart

Table 1. Characteristics of the studies included in the meta-analysis

Article	Sample	Age (years)	Time to disease	Hoehn & Yarh	Voice assessment	Investigated Outcomes
Jiang et al.[15]	10 males 5 females	47-82	5 months-10 years	02/apr	Cspeech 4.0	fundamental frequency, jitter, shimmer
Sanabria et al.[16]	10 males 10 females	53-73	------	02/mar	Kay Elemetrics	fundamental frequency, jitter, shimmer voice tremor, harmonics
Goberman et al.[17]	6 males 3 females	57-84	3-19 years	-----	Kay CSL – 4300b	fundamental frequency, intensity
Letter et al.[18]	5 males 5 females	63-80	-----	02/mar	Escala analógica	variations in loudness, variations in pitch
Ho et al.[19]	8 males 1 female	52-80	3-18 years	-----	Kay Elemetrics	fundamental frequency, intensity
Plowman-Prine et al.[20]	12 males 4 females	43-81	1-15 years	1.5-5	Escala analógica	loudness, pitch reduce stress harsh voice
Letter et al.[21]	3 males 4 females	37-69	5-21 years	4	Kay CSL – 4300 Praat	fundamental frequency, jitter, shimmer
Skodda et al.[22]	9 males 14 females	42-78	0.5-5 years	1.5-2.5	Praat	fundamental frequency, intensity
Azevedo et al.[23]	5 males 5 females	59-88 ages	------	02/mar	WinPitch version 1.8 VoxMetria version 2.0	prosody (fundamental frequency and intensity)

parameters from auditory-perceptual analysis[18,20]. In one study conducted with ten individuals, analysis was performed with a scale ranging from zero to ten[18]. The authors found increased variation in pitch and loudness during the "on" state of levodopa therapy. In the other study[20] conducted with 16 individuals, the authors used a scale ranging from zero to seven and verified no improvements in the investigated parameters (sound imprecision, mono-loudness, mono-pitch, reduced stress, and harsh voice after medication use). In the third study, which analyzed the acoustic of prosody, no modifications in fundamental frequency (*F*0) and vocal intensity after levodopa therapy were found in ten individuals with Parkinson's disease (PD)[23].

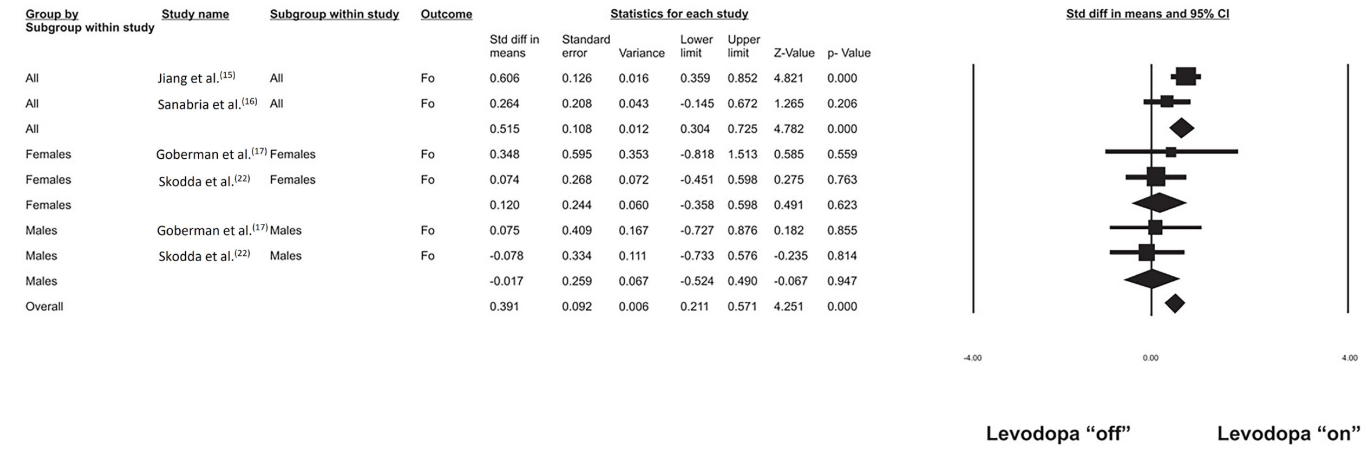
The meta-analysis included six articles that used acoustic analysis to evaluate the vocal outcomes through the following analytical programs: Kay Elemetrics, Cspeech 4.0, and Praat. *F*0 was investigated in five studies[15-17,21,22], and four of them presented comparative outcomes that could be pooled in a meta-analysis[15-17,22].

In the analysis of 67 individuals with PD, the effect size showed modification of the *F*0 after levodopa use (SMD=0.39; p=0.00; I^2=31.3). In a subgroup analysis, two studies with 30 individuals showed no modifications in *F*0 after levodopa therapy (Figure 2). Vocal intensity was analyzed in three studies[17,19,22] with 41 individuals, and no significant modification in this parameter were observed after levodopa ingestion (SMD=0.09; p=0.58; I^2=0) (Figure 3). Jitter was investigated in three studies[15,16,21]; however, only two presented data that could be pooled in a meta-analysis[15,16,21]. The evaluation of jitter in 35 individuals with PD showed significant modification in this parameter after levodopa therapy (SMD=0.23; p=0.03; I^2=0) (Figure 4).

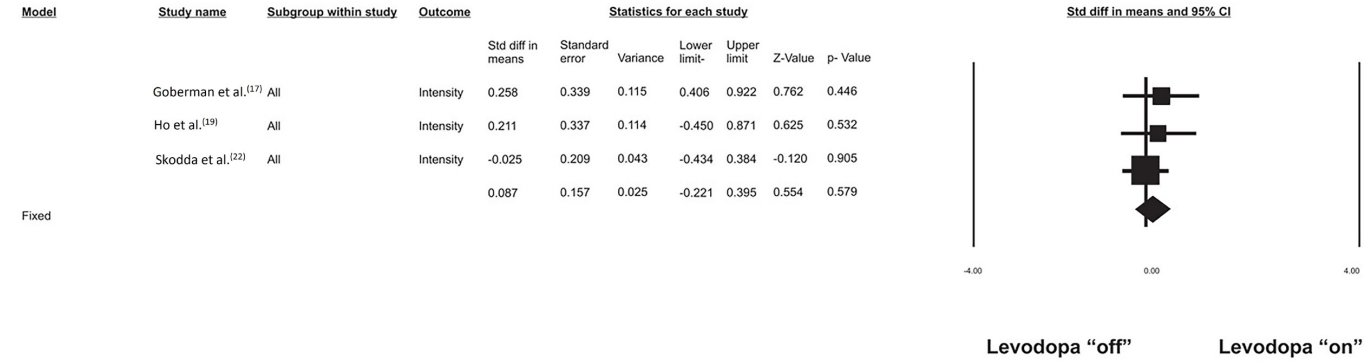
Shimmer was analyzed in two studies with 22 participants[15,21]. Both showed significant reduction in the "on" state of levodopa therapy, but one of them did not present comparative data that could be pooled in a meta-analysis. Tremor intensity investigated in one study conducted with 20 individuals and showed a smaller variation through subjective evaluation of the spectrogram[16].

According to the MINORS, the quality of nine included studies ranged from ten to 22 points (Table 2). Publication biases were investigated by funnel plot graph analysis, and the results demonstrated that the included studies tended to favor levodopa therapy (Figure 5).

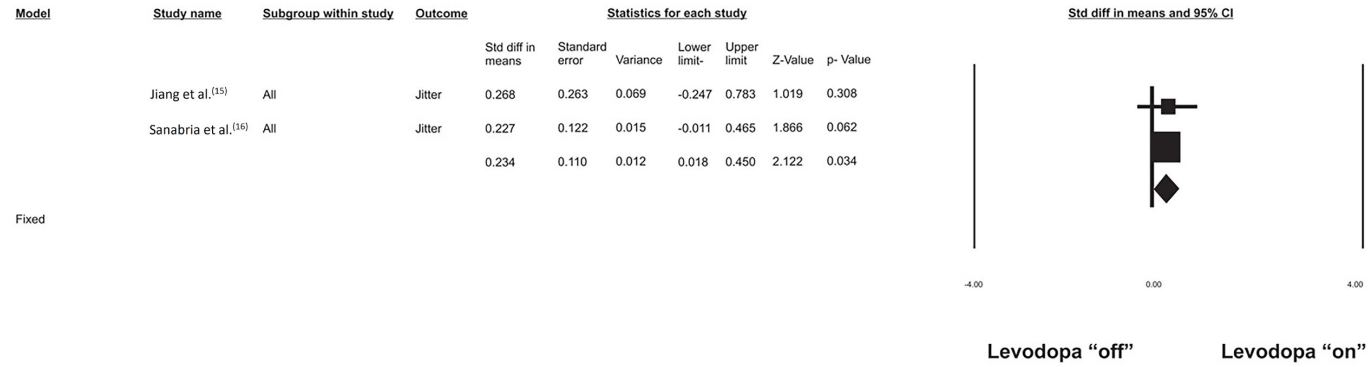
It is worth emphasizing that the modification found in *F*0 after levodopa therapy should be seen with caution. A subgroup analysis by gender would be required to qualify this modification as a better or worse outcome promoted by the drug, as there are differences in the *F*0 between males and females. Meanwhile, the studies that performed the analysis by gender did not find differences in the *F*0 between males and females after levodopa ingestion.



Caption: Levodopa and Fundamental Frequency. SMD: standard mean difference
Figure 2. Subgroup analysis and pooled SMD of levodopa for fundamental frequency in Parkinson's disease



Caption: Levodopa and Fundamental Frequency. SMD: standard mean difference
Figure 3. Pooled SMD of levodopa for vocal intensity in Parkinson's disease

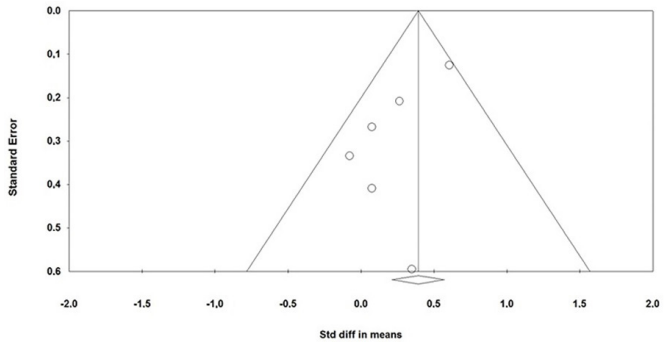


Caption: Levodopa and Fundamental Frequency. SMD: standard mean difference
Figure 4. Pooled SMD of levodopa for jitter in Parkinson's disease

Curiously, according to the data of this study, changes in vocal intensity in the "on" state of the medication were not observed. Although pulmonary dysfunction is frequent in PD patients and its prevalence varies between 28 and 85%[24], improvement in restrictive respiratory parameters and decrease of larynx intrinsic muscle rigidity promoted by ingestion of levodopa in PD patients have been described[24,25]. However, according to a review study, there is no evidence that levodopa therapy enhances laryngeal function[22], promoting better glottic coaptation. In the same way, previous reports have demonstrated that reduction of lip muscle rigidity and improvement of tongue strength with levodopa therapy do not ameliorate the mobility of these oral structures[26-29].

Table 2. Quality assessment using the methodological index for non-randomized studies (MINORS)

	MINORS								
	Jiang et al.[15]	Sanabria et al.[16]	Goberman et al.[17]	Letter et al.[18]	Ho et al.[19]	Plowman-Prine et al.[20]	Letter et al.[21]	Skodda et al.[22]	Azevedo et al.[23]
1. A clearly stated aim	2	2	2	2	2	2	2	2	2
2. Inclusion of consecutive patients	2	1	2	2	1	2	2	2	1
3. Prospective collection of data	2	1	2	2	2	2	2	2	2
4. Endpoints appropriate to the aim of the study	2	1	2	2	2	2	2	2	2
5. Unbiased assessment of the study endpoint	0	0	0	2	0	2	0	2	2
6. Follow-up period appropriate to the aim of the study	2	2	2	2	2	2	2	2	2
7. Loss to follow-up <5%	2	2	2	2	2	2	2	2	2
8. Prospective calculation of the study sample size	0	0	0	0	0	0	0	0	0
Additional criteria in the case of comparative studies									
9. Adequate control group	--	--	2	--	--	--	--	2	2
10. Contemporary groups	--	--	0	--	--	--	--	2	2
11. Baseline equivalence of groups	--	--	2	--	--	--	--	2	2
12. Adequate statistical analyses	--	--	2	--	--	--	--	2	2
Total	12	10	18	14	12	14	12	22	21



Caption: Standard Error (vertical). SMD: standard mean difference (horizontal). Standard difference in means (horizontal)
Figure 5. Funnel chart

Therefore, despite the reduction in rigidity of oral and laryngeal structures and enhancement of chest wall mobility[17,25], there is no evidence that treatment with levodopa could improve laryngeal function or articulatory movements[29], interfering with vocal intensity in the "on" state of treatment. In addition, prolonged treatment with levodopa can lead to complications such as oromandibular and laryngeal dystonia and respiratory dyskinesia, resulting in shortness of breath and tachypnea[30,31]. These factors could also contribute to reduced vocal intensity and voice projection, frequently observed in these individuals.

In the population studied in this review, reduction in voice tremor was observed while the patients were in the "on" state of treatment, as well as greater vibration amplitude of the vocal cords, with more harmonic vibratory cycles and decrease in short-term (cycle-to-cycle) perturbation in voice *F*0 (jitter)[19,22].

Decreased laryngeal rigidity and increased amplitude of glottic cycles could contribute to reduction of shimmer and vocal tremor in the "on" state of therapy; however, these data were not analyzed due to absence of comparative outcomes between the included studies.

It was not possible to compare data in the studies that used auditory-perceptual analysis of the vocal parameters due to their different analogue scales and outcomes. As this is a subjective analysis, it was difficult to conduct a homogeneous quantitative analysis.

Auditory-perceptual analysis has been considered the gold standard for vocal evaluation[32,33]. However, data generated from these tests are completely dependent on the subjective impressions of the evaluator. In contrast, acoustic analysis provides objective data and assesses different vocal parameters. Thus, an improvement in acoustic parameters may not correspond to a better vocal perception by the evaluator. Therefore, a joint analysis of the vocal characteristics by the two methods can provide better and more consistent results.

There are a few important potential sources of bias in the outcomes assessed in the present review. First, diversity in voice recording protocols and different outcomes limit data comparison and hamper study replication. A second source of bias is the small number of primary studies found in this review. This can be justified by the paucity of studies in the literature on the theme and lack of comparative data in some of the articles.

Other limitations are associated with the drugs used by the participants of primary studies. Previous reports have suggested that concomitant PD medications in addition to levodopa therapy, such as biperidene, tolcapone, and selegiline, may provide better performance in PD patients' communication[29,34]. There were no references in the included studies whether other dopaminergic therapies used by PD patients were discontinued during the evaluations, making it difficult to assign the effects achieved on vocal parameters exclusively to levodopa. Neither the time of exposure to levodopa, nor the doses used by participants were found in the analyzed studies, which precluded the analysis of the impact of these variables on the outcomes investigated.

Nevertheless, although levodopa acts as a dopamine precursor[35], vocal disorders observed in PD may not be caused only by dopaminergic depletion of the nigrostriatal circuit[36]. Hypokinetic dysarthria observed in PD presents a strong correlation with axial symptoms that do not show significant response to dopaminergic replacement therapy[37].

According to the results of this systematic review, further studies should be conducted with larger samples and combination of acoustic and auditory-perceptual analyses of voice parameters. Care to control the time of action of other dopaminergic drugs should also be observed.

CONCLUSION

Results suggest that the use of levodopa improves vocal parameters such as fundamental frequency (*F*0) and jitter; however, vocal intensity remains reduced in both the "on" and "off" states of therapy.

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Author contributions

PP participated in the study design, collection, analysis and interpretation of data, and writing of the manuscript; LM participated in the statistical analysis and discussion of data; MFPS and AM participated in the interpretation and discussion of data; LT participated in the process of construction of the project, search for articles, and assembly of results; ACN was the study adviser, and participated in the analysis and interpretation of data and writing of the manuscript.