Voice Quality Changes After Laryngopharyngeal Reflux Disease Treatment: A Systematic Review☆

*Guangjin Chen, and *,†,‡,§Jérôme R. Lechien, *Mons, §Brussels, Belgium, †Paris, and ‡Poitiers, France

SUMMARY: Objective. To review the current literature dedicated to the voice quality changes throughout laryngopharyngeal reflux disease (LPRD) treatment.

Methods. Two independent investigators conducted a literature search for studies investigating the voice quality changes after treatment in LPRD patients through PubMED, Scopus, BioMed Central, Biological Abstracts, and Cochrane Library databases according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statements.

Results. Twenty-seven studies (1470 patients, 48.0% females) were included. Most LPRD diagnoses were based on symptoms and findings, with only three studies using 24-hour hypopharyngeal-esophageal multichannel intraluminal impedance-pH testing. Treatment regimens primarily involved proton pump inhibitors, with adjunctive therapies in 10 studies and diet/lifestyle modifications in 15 studies. Post treatment voice quality reported improvements in subjective parameters, such as the Voice Handicap Index and grade of dysphonia, roughness, breathiness, asthenia, strain, instability, regardless of study design. Acoustic parameters (percent jitter, percent shimmer, and harmonic-to-noise ratio) consistently improved throughout treatment, while aerodynamic measurements yielded controversial results. Quality assessment revealed methodological limitations, with only three studies combining objective LPRD diagnosis with multidimensional voice quality assessment.

Conclusion. Voice quality is an interesting biomarker of therapeutic changes in LPRD patients with perceived or self-reported dysphonia. Future studies are needed to correlate the voice quality impairment with microscopic vocal fold changes.

Key Words: Laryngopharyngeal reflux–Gastroesophageal reflux–Voice–Laryngology–Otolaryngology–Head neck surgery.

INTRODUCTION

Laryngopharyngeal reflux disease (LPRD) is defined as a disease of the upper aerodigestive tract resulting from the direct and/or indirect effects of gastroduodenal content reflux, inducing morphological and/or neurological changes in the upper aerodigestive tract.[1] Dysphonia is one of the most prevalent symptoms in LPRD patients, accounting for up to 61.0% of cases.[2] The mechanisms underlying the development of dysphonia without objectifiable lesions (eg, nodules, polyps) may include the occurrence of epithelial microtrauma, thickening, mucosal and submucosal inflammations, and the development of dryness; all of them leading to a modification of the biomechanical properties of the vocal folds.[3–5] The high prevalence of dysphonia, the significant impact on quality of life of patients,[1,2,6,7] and the related micro- and macroscopic changes in the vocal folds[7] have led some authors to use voice quality evaluations (eg, subjective patient-reported outcome questionnaires, perceptual voice evaluation, aerodynamic, and acoustic measurements) as indicators of treatment effectiveness.[1,6,8] Currently, proton pump inhibitors (PPIs) are considered the standard for LPRD treatment in most world regions. However, pharmacologically, PPIs reduce H+ secretion in the stomach without changing the number of pharyngeal reflux events in the upper aerodigestive tract,[3] which may be ineffective on the backflow of gastroduodenal content into the vocal cords.[1,3] Among alternative therapeutic options, alginates form a raft over the stomach content, which prevents gastroesophageal reflux events.[3]

This systematic review aimed to update the current literature dedicated to voice quality changes throughout LPRD treatment.

METHODS

Two independent investigators (GJC and JRL) conducted this systematic review with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist.[9] The criteria for considering studies were based on population, intervention, comparison, outcome, timing, and setting framework.[10]

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From the *Department of Surgery, Faculty of Medicine, UMONS Research Institute for Health Sciences and Technology, University of Mons (UMons), Mons, Belgium; †Department of Otolaryngology - Head and Neck Surgery, Foch Hospital, School of Medicine, UFR Simone Veil, Université Versailles Saint-Quentin-en-Yvelines (Paris Saclay University), Paris, France; ‡Department of Otolaryngology, Polyclinic of Poitiers, Elsan Hospital, Poitiers, France; and the §Department of Otolaryngology-Head and Neck Surgery, CHU Saint-Pierre (CHU de Bruxelles), Brussels, Belgium.

Address correspondence and reprint requests to: Jerome R. Lechien, Department of Surgery, University of Mons, Mons, Belgium. E-mail: Jerome.Lechien@umons.ac.be

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Types of studies

The literature search included randomized controlled trials, prospective studies, or retrospective chart reviews of prospective data collection studies published between January 1990 and April 2025 in English-language peer-reviewed journals investigating voice quality changes throughout LPRD therapeutic regimens. In the present review, controlled studies were defined as studies comparing pretreatment to post treatment findings of at least two treatment groups of LPRD patients. Case reports, letters to the editor, comments, and studies focused on human biopsy specimens or in vitro cell lines were excluded.

Population

Populations consisted of patients with suspected or confirmed LPRD. Consistent to European and IFOS consensus guidelines, the LPRD diagnosis was considered confirmed only for patients with more than one acid, weakly acid, or nonacid pharyngeal reflux event detected by 24-hour hypopharyngeal-esophageal multichannel intraluminal impedance-pH monitoring (HEMII-pH).[1,11] Patients with more than one pharyngeal reflux event at the 24-hour dual- or triple-probe pH monitoring with pharyngeal sensor but without impedance system were considered as patients with an acid LPRD. Given the lack of full column before documentation of pharyngeal reflux event, patients with a positive diagnosis at the 24-hour Dx-pH system (oropharyngeal pH monitoring, Restech) were considered as subjects with a suspected LPRD.[1,11] Patients selected according to the use of patient-reported outcome questionnaires (eg, reflux symptom index (RSI),[12] reflux symptom score[13]) and validated sign instruments (eg, reflux finding score (RFS),[14] reflux sign assessment[15]) were considered as patients with a suspected LPRD. Similar consideration was made for patients with symptoms, findings, or gastroesophageal reflux disease without 24-hour HEMII-pH diagnosis.

Outcomes

The primary outcomes were the pretreatment to post treatment voice quality changes in patient populations. The voice quality assessment may include patient-reported outcome questionnaires, perceptual analyses, (video)laryngostroboscopy evaluations, aerodynamic, and acoustic measurements.[16] The combination of subjective and objective voice quality evaluations was considered ideal (multidimensional voice quality evaluation).[16] The secondary outcomes included demographics, gender ratio, mean/median age, and therapeutic outcomes (medication, duration, and follow-up). The inclusion and exclusion criteria were collected for conducting a bias analysis.

Intervention and comparison

Only conventional medical interventions were considered, including PPIs, alginates (Gaviscon), antacids (Magaldrate), and histamine blockers. Data related to recommendations for an antireflux diet were collected. Studies evaluating voice quality outcomes after nonconventional treatments (eg, Chinese herbs, acupuncture, and mucolytics) or surgical interventions were excluded.

Time and setting

There were no strict criteria for time and setting.

Search strategy

The two investigators independently conducted the PubMED, Scopus, BioMed Central, Biological Abstracts, and Cochrane Library databases for relevant peer-reviewed publications related to the voice quality change throughout treatment in LPRD populations. The following keywords were used: Larynx; Laryngeal; Reflux; Laryngopharyngeal; Gastroesophageal; Voice; Vocal Fold; Cord; Acoustic; Aerodynamic; Change; Perceptual; and Outcomes. The authors considered studies reporting database abstracts, available full texts, or titles with the search terms. The research findings were reviewed for relevance and the reference lists of state-of-the-art or systematic reviews were examined for additional references. Precisely, data from a 2016 systematic review conducted by the senior author (JRL)[8] were included and retrieved for the present updated review.

Bias analysis

The bias analysis was carried out with the Methodological Index for Non-Randomized Studies (MINORS) tool.[17] The MINORS tool includes items related to the analysis of methodological points of comparative studies, which is particularly important for review, including studies with potential methodological issues (eg, diagnosis of LPRD, multidimensional voice quality assessment methodology). Each item was rated as 0 if absent or not mentioned; 1 when reported but inadequate or unclear; and 2 when reported and adequate. The MINORS outcome score was calculated. Among MINORS outcomes, the endpoints were considered as fully appropriate for studies evaluating multidimensional voice quality outcomes, including subjective, perceptual, and objective evaluations, in patients with an objective LPRD diagnosis at the 24-hour HEMII-pH. The consideration of either multidimensional voice quality evaluation or objective diagnosis was considered as not fully adequate. Concerning voice quality evaluation, only studies considering patient-reported dysphonia, perceptual voice evaluations, aerodynamic, and acoustic evaluations were considered as fully adequate. A period of 6 weeks or more was considered as adequate to observe significant voice quality changes.

RESULTS

Of the 1048 identified papers, 27 studies met the inclusion criteria (1470 patients) (Figure 1).[18–44] There were 706 (48.0%) females and 548 (37.3%) males. Gender was unspecified in 216

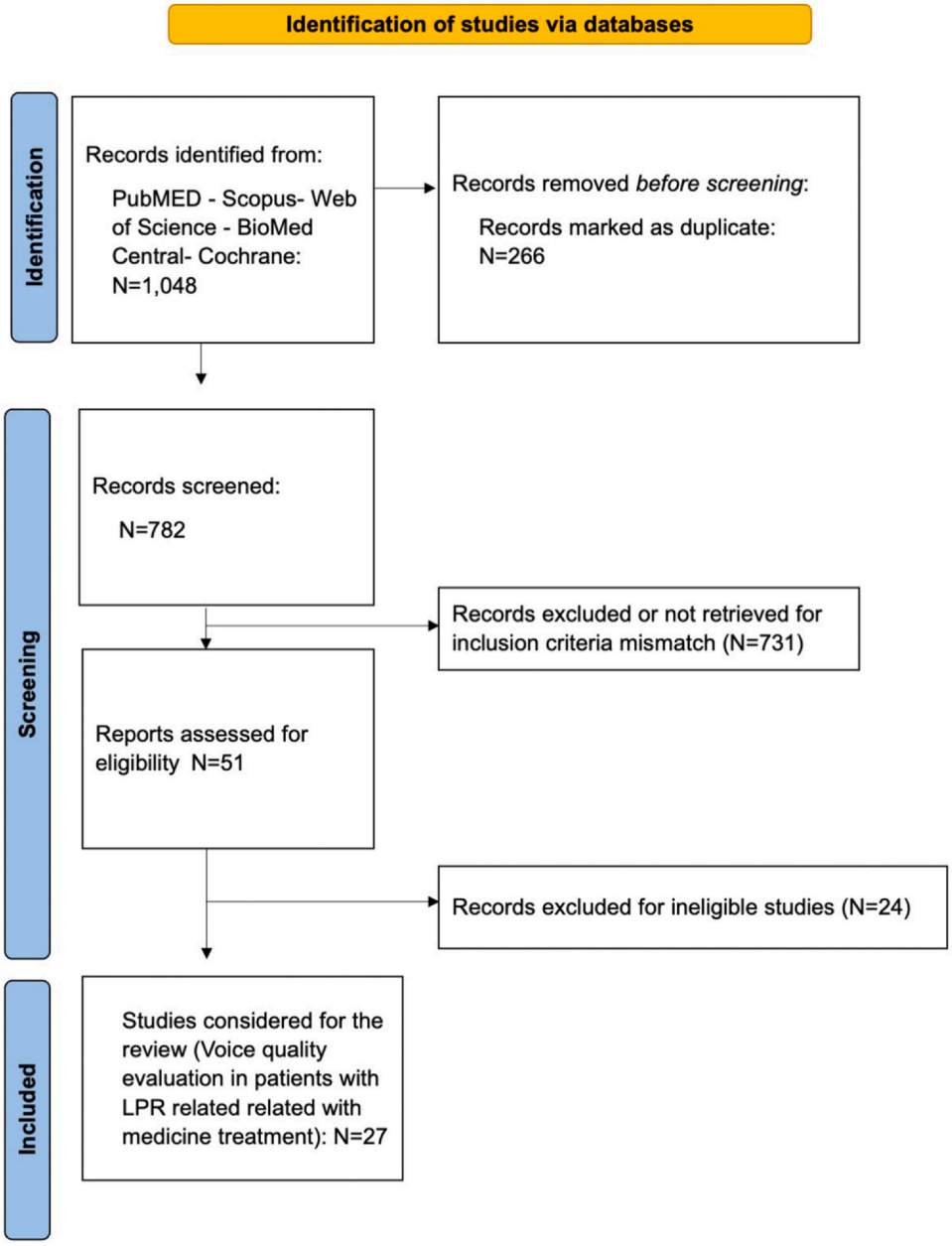

FIGURE 1. Chart flow.

(14.7%) cases (Table 1). The weighted mean age was 39 years. Most authors included patients with suspected LPRD according to symptoms and findings (n = 7),[18,22–26,30] including dysphonia as a primary inclusion criterion in five studies.[19,28,29,35,39] Validated patient-reported outcome questionnaires and clinical instruments were used in 10 studies.[31–34,36–38,41,43,44] The 24-hour HEMII-pH was used to confirm the diagnosis in three studies.[40–42] Two studies supported the LPRD diagnosis based on GERD findings (Table 2).[20,32] Numerous therapeutic regimens have been considered, most of them based on PPIs once or twice daily (Table 3). Alternative medications to PPIs were considered in 10 studies, associating PPIs with alginates/antacids,[40,42] prokinetics,[18,20,27,39] or voice/speech therapy.[22,29,31,41] Diet and lifestyle changes were recommended in 15 studies (Table 3).[20–23,25,28,33,34,36–38,40–43] In 10 investigations, the authors did not mention the recommendations regarding diet and lifestyle changes (Table 3). The duration of treatment substantially varied across studies, with most teams prescribing a 12-week duration of treatment.

Voice quality outcomes

Table 4 summarizes the pretreatment to post treatment voice quality results of included studies. Most studies demonstrated significant improvement in subjective evaluations, including reduction of Voice Handicap Index, Voice Symptom Scale, and most items of grade of dysphonia, roughness, breathiness, asthenia, strain, instability scale

TABLE 1.
Demographic, Clinical, and Voice Quality Outcomes of Included Studies

References	Design	*N*	F/M	Age	Diagnosis	Treatment Outcomes	Results	Treatment Type	Diet	DT (w)
Studies including all patient types										
Shaw et al[18]	UP	96 sLPRD	57/39	45	Symptoms/ signs	Jitter, shimmer, and STD	Pre > post-tt (dysphonia patients)	PPIs (2/d), alginate (3/d)	NP	12
						F0	Post > Pre (dysphonia patients)	Bloating: GP (4/d)		
Hamdan et al[20]	UP	22 sLPRD	NP	NP	Symptoms/ signs	Voice breaks, fatigue, and dysphonia	Pre > post-tt	Pantoprazole 40 mg (2/d)	+	4
					GERD	F0, RAP, Shim%, NHR, VTI, and MPT	Pre = post-tt	Cisapride 20 mg (2/d)		
Noordzij et al[21]	RCT	15 sLPRD	7/8	52	Symptoms/ signs	Dysphonia score (RSI)	Pre > post-tt; sLPRD > CT	Omeprazole 40 mg (2/d)	+	8
		15 CT	7/8	45	Esophageal pH metry			Placebo (2/d)		
Selby et al[22]	UP	13 sLPRD	7/6	19-68	Symptoms/ signs	HNR—Jitt%, Shim%	Post > pre-tt-pre = post-tt	PPIs, VT	+	8-10
Siupsinskiene and Adamonis[23]	CP	120 sLPRD	NP	NP	Symptoms/ signs	Vocal dysfunction degree (5 we)	sLPRD/ CT=Pre > post-tt	PPI (1-2/d)	+	5
		113 CT	NP	NP				CT = diet		
Williams et al[24]	UP	20 sLPRD	11/9	55	Symptoms/ signs	Perceptual dysphonia	Pre > post-tt	Omeprazole 20 mg (3/d)	NP	12
Sereg-Bahar et al[25]	UP	43 sLPRD	25/18	44	Symptoms/ signs	F0, Jitt%-Shim%, NHR, and VHI	Pre = post-tt-Pre > post-tt	Esomeprazole 40 mg	+	8
Siupsinskiene et al[26]	CP	100 sLPRD	75/25	39-44	Symptoms/ signs	VHI	sLPRD > CT	PPI (1-2/d)	-	12
Jin et al[27]	UP	40 LPRD	23/17	54	Symptoms/ signs	Jitt%, Shim%	Pre > post-tt	Lansoprazole 30 mg 1/d	NP	20
					Dual-probe pH metry	HNR	Post > Pre	GP (1-3/d)		
Fass et al[30]	RCT	41 sLPRD	17/24	63-68	Symptoms/ signs	STD, F0, and voice intensity	PPI = placebo (post-tt)	Esomeprazole 20 mg (2/d) Placebo (2/d)	NP	12
Park et al[31]	UP	100 sLPRD	52/48	53-57	RSI > 13 and RFS > 7	VHI (≥15 change)/ GRBAS (≥1 change)	PPI and VT > PPI (post-tt)	Omeprazole 20 mg (2/d)	NP	12
						Jitt%, Shim%	PPI and VT = PPI (post-tt)	Omeprazole 20 mg (2/d) and VT		
Beech et al[32]	UP	74 sLPRD	NP	NP	RSI > 13 and GI GERD	Voice Symptom Scale	Pre > post-tt	Lansoprazole 30 mg b.i.d.	NP	12

TABLE 1 (*Continued*)

References	Design	*N*	F/M	Age	Diagnosis	Treatment Outcomes	Results	Treatment Type	Diet	DT (w)
Wan et al[33]	UP	58 sLPRD	21/37	NP	RSI > 13 and RFS > 7	Jitter%, Shimmer%, and HNR	Pre > post-tt-Post > pre-tt	Esomeprazole 20 mg b.i.d.	+	4
		58 CT	30/28		pH monitoring	F0, MPT	Pre = post-tt			
Lechien et al[34]#	UP	41 sLPRD	23/18	50	RSI > 13 and RFS > 7	VHI, GRBASI, Jitt%, and Shim%	Pre > post-tt	Pantoprazole 20 mg (2/d)	+	12
						NHR, VTI, and SPI	Pre = post-tt			
Lechien et al[36]#	UP	41 sLPRD	23/18	50	RSI > 13 and RFS > 7	VHI, Jitt%	Pre > post-tt (all)	Pantoprazole 20 mg (2/d)	+	12
		Dysph (15)/				GRBASI, Shim%	Pre > post-tt (dysph group)			
		no dysph (26)				STD, NHR	Pre = post-tt (all)			
Lechien et al[37]*	UP	80 sLPRD	40/40	51	RSI > 13 and RFS > 7	GRSI, MPT, Jitt%, and Shim%	Pre > post-tt	Pantoprazole 20 mg (2/d)	+	24
Lechien et al[38]*	UP	80 sLPRD	40/40	51	RSI > 13 and RFS > 7	VHI, GRS, Jitt%, and Shim%	Non-resp > resp (post-tt)	Pantoprazole 20 mg (2/d)	+	12
		Resp (59)/ non-resp (21)								
Lechien et al[40]**	UP	109 LPRD	59/50	50	HEMII-pH	Jitt%, Shim%, and NHR (12 we)	Pre > 12-we post-tt	Alginate/ magaldrate ± P-PI	+	12
		Dysph (49)/				Jitt%, Shim%, and NHR (12-24 we)	12 = 24-we post-tt			
		no dysph (60)								
Barillari et al[41]	RCT	52 LPRD	32/20	43	RSI > 13 and RFS > 7	GR, VHI, and B (VT group)	Pre > post-tt	Pantoprazole 20 mg (2/d) and	+	12

TABLE 1 (*Continued*)

References	Design	*N*	F/M	Age	Diagnosis	Treatment Outcomes	Results	Treatment Type	Diet	DT (w)
		PPI/ alginate (26)/ PPI/ alginate + VT (26)			HEMII-pH	VHI pre-to-post-tt decrease	VT > medication group	alginate (3/d) ± VT		
Lechien et al[42]**	UP	160 LPRP	90/70	50	HEMII-pH	Jitt%, Shim%, MPT, NHR, VHI, and GR	Pre > post-tt (all)	Alginate/ magaldrate ± PPI	+	12
		Acid (60)				VHI, MPT, and G	Pre > post-tt (acid)			
		Weakly acid (52)				G, Shim%	Pre > post-tt (weakly acid)			
		Alkaline (48)				Jitt%, Shim%, MPT, NHR, VHI, and GR	Pre > post-tt (alkaline)			
Suda et al[43]	CP	100 sLPRD	43/57	44	RSI > 13	Jitt%, Shim%, MPT, and F0-HNR	Pre > post-tt- Pre < post-tt	PPIs (2/d)	+	8
Studies including patients with dysphonia only										
Habermann et al[19]	UP	29 sLPRD	4/25	49	Symptoms/ signs	Hoarseness (RSI)	Pre > post-tt	Pantoprazole 40 mg	-	6
					Dysphonia	Videostroboscopy alterations	Pre > post-tt			
Sala et al[28]	UP	22 sLPRD	16/6	41	Symptoms/ signs	GRBAS	Pre > post-tt- pre = post-tt	PPI (1/d)	+	12
					Dysphonia	Erythema and edema of vocal folds	Pre > post-tt			
Vashani et al[29]	CP	32 sLPRD	18/14	> 18	Symptoms/ signs	Perceptual G, B, Shim%, and HNR	Pre > post-tt- Post > pre-tt (VT > PPI)	Omeprazole 20 mg (2/d)	NP	6
					Dysphonia	Jitt%, NNE	Pre > post-tt	Omeprazole 20 mg (2/d) and VT		
Batıoğlu et al[35]	UP	84 sLPRD	66/18	43	Symptoms/ signs	SNR-HNR	Pre > post-tt- Post > pre-tt	Lansoprazole 30 mg (2/d)	NP	12
					Dysphonia	MPT, Jitt%, Shim%, NHR, and F0	Pre = post-tt			
Jain et al[39]	UP	50 sLPRD	32/18	41	RSI > 10 and dysphonia	GRBAS, F0, Jitt%, and S/Z (F vs M)	Pre > post-tt (F/M)	Pantoprazole 40 mg (2/d)	NP	24
						Shim%	Pre > post-tt (F)	and Mosapride 5 mg (3/d)		

TABLE 1 (*Continued*)

References	Design	*N*	F/M	Age	Diagnosis	Treatment Outcomes	Results	Treatment Type	Diet	DT (w)
Zhang et al[44]	UP	78 sLPRD	47/31	NP	RSI > 13 and RFS > 7 Dysphonia	VHI, GRBAS Jitt%, Shim%, and MPT	Pre > post-tt Pre > post-tt	Omeprazole 20 mg (2/d)	NP	8

*/# Overlap but different group analyses. *Abbreviations*: MII-pH metry, 24-hour multichannel intraluminal impedance and pH monitoring; CP, controlled prospective; CT, control; DT, duration of treatment; Dysph, dysphonia; F, female; F0, fundamental frequency; G.R.B.A.S.I., Grade, Roughness, Breathiness, Asthenia, Strain, Instability; GI, gastrointestinal; GP, gastroprokinetic; Gr, group; HNR, harmonics-to-noise ratio; Jitt%, percent jitter; (s)LPR, (suspected) laryngopharyngeal reflux; M, male; md, median; MPT, maximum phonation time; N, number; NP, not provided; Resp, responder; RFS, Reflux Finding Score; RSI, Reflux Symptom Index; RSS, Reflux Symptom Score; S/Z, S/Z ratio; Shim%, percent shimmer; SNR, signal-to-noise ratio; SPI, Soft Phonation Index; STD, F0 standard deviation; tt, treatment; UP, uncontrolled prospective study; VHI, Voice Handicap Index; VT, voice therapy; VTI, Voice Turbulence Index; We, week.

(Table 4). Among objective evaluations, the results are inconsistent for aerodynamic measurements, particularly for maximum phonation time that significantly increased in four studies,[37,42–44] but did not change in three.[20,33,35] The analysis of acoustic measurement results revealed that cues highlighting F0 and intensity perturbations primarily improved from pretreatment to post treatment in most studies, particularly percent jitter, percent shimmer, and harmonic-to-noise ratio (Table 4). The significant improvements of both subjective and objective voice quality evaluations were particularly relevant in studies reporting specific findings of hoarse LPRD patients (Table 1).[18,19,28,29,35,36,39,40,44]

Bias analysis

The mean MINORS was 9.74 ± 2.10 (Table 5). There were only three studies with both 24-hour HEMII-pH objective LPRD diagnosis and multidimensional voice quality evaluations.[40–42] The LPRD diagnosis was mainly based on laryngopharyngeal symptoms and findings (Table 1) without exclusion of comorbidities that can be associated with nonspecific laryngopharyngeal symptoms and findings. Concerning the appropriateness of voice quality evaluation, only nine studies reported a voice quality assessment based on the combination of patient-reported outcome questionnaires, perceptual analysis, and objective evaluations (aerodynamic and acoustic measurements).[20,31,34,36,37,39–42] In five studies, the voice quality evaluation was based on only one dimension, which was considered inadequate.[21,23,24,26,32]

DISCUSSION

The number of studies investigating voice quality as an outcome of therapeutic regimens in LPRD has progressively increased over the past two decades. The findings of the present review support the usefulness of voice quality evaluations, including patient-reported voice questionnaires, perceptual evaluations, and acoustic measurements. Among objective assessments, there is no clear trend for aerodynamic measure changes, voice turbulence index, and F0 increase. However, compared with the previous systematic review published in 2016,[8] the present one suggests that most acoustic parameters highlighting instability of F0 (eg, STD, percent jitter), harmonics (eg, HNR, NHR), and intensity (eg, percent shimmer) significantly improved from pretreatment to post treatment. Interestingly, a substantial number of studies exploring pretreatment to post treatment voice quality outcomes in patients with dysphonia versus those without dysphonia suggested that voice quality assessment can be particularly relevant in patients with self-reported or perceptual dysphonia,[18,36,40] which was strengthened by investigation, including only patients with LPRD symptoms, findings, and voice disorders.[19,28,29,35,39,44] These data suggest a variable degree of voice quality impairment in patients with suspected or confirmed LPRD, with some patients experiencing low

TABLE 2.
Demographics and Clinical Summary

	N (%)	References
Total number of patients (*N*)	1470	
Gender		
Female (*N*, %)	706 (48.0)	
Male (*N*, %)	548 (37.3)	
Unspecified (*N*, %)	216 (14.7)	
Age		
Weighted mean age (years)	39	
Range of mean age (years)	41-55	
Diagnostic LPRD		
Symptoms/findings	7	18, 22-26, 30
Symptoms/findings and voice disorders	4	19,28,29,35
Symptoms/findings and GERD	1	20
Symptoms/findings and pH testing	2	21,27
RSI > 13 and RFS > 7	5	31, 34, 36-38
RSI > 13 and RFS > 7 and dysphonia	1	44
RSI > 13 and RFS > 7 and pH testing	1	33
RSI > 13 and GI GERD findings	1	32
RSI > 13	1	43
24-hour HEMII-pH testing	2	40, 42
24-hour HEMII-pH testing, RSI > 13, RFS > 7	1	41
RSI > 10 and dysphonia	1	39

Abbreviations: GERD, gastroesophageal reflux disease; GI, gastrointestinal; HEMII-pH, hypopharyngeal-esophageal multichannel intraluminal impedance-pH monitoring; LPRD, laryngopharyngeal reflux disease; N, number; RFS, Reflux Finding Score; RSI, Reflux Symptom Index.

TABLE 3.
Therapeutic Outcomes

Therapeutic approaches	*N*	References
Pantoprazole/(eso)meprazole 20 mg 2/d	10	24, 29-31, 33, 34, 36-38, 44
Unspecified/multiple PPIs 1 or 2/d	4	23, 26, 28, 43
Combination of medications and voice therapy	4	22, 29, 31, 41
Combination of PPIs and gastroprokinetic	4	18, 20, 27, 39
Lansoprazole 30 mg 2/d	2	32, 35
Combination of PPIs, alginates, and antacids	2	40, 42
Pantoprazole/esomeprazole 40 mg 1/d	2	19, 25
Omeprazole 40 mg 2/d	1	21
Diet and lifestyle recommendations		
Yes	15	20-23, 25, 28, 33, 34, 36, 37, 38, 40-43
No	2	19, 26
Information not provided	10	18, 24, 27, 29, 30, 31, 32, 35, 39, 44
Treatment durations		
4 weeks	2	20, 33
5 weeks	1	23
6 weeks	2	19, 29
8 weeks	5	21, 22, 25, 43, 44
12 weeks	14	18, 24, 26, 28, 30-36, 38, 40-42
20 weeks	1	27
24 weeks	2	37, 39

Abbreviations: d, day; *n*, number; PPI(s), proton pump inhibitor(s).

LPRD impact on vocal fold function and others experiencing moderate to high impact.

It is well-known that subtle voice changes can be even more difficult to detect by the current perceptual assessment of the practitioner, especially in mild or moderate dysphonia related to reflux.[7] In these patients, the use of acoustic measurements can be relevant to study the vibratory process of the vocal folds, highlighting, as demonstrated in this review, potential treatment efficiency for voice quality. Regarding recent human vocal fold tissue

TABLE 4.
Summary of Voice Quality Change Throughout Treatment Regimen

Voice quality outcomes	Pretreatment to post treatment changes	*N*	References		*N*	References
Subjective voice quality						
Patient-reported dysphonia	Pretreatment to post treatment significant improvement of scores	3	19-21	-	-	-
Voice Symptom Scale (VSS)	Pretreatment to post treatment significant reduction of scores	1	32	-	-	-
VHI	Pretreatment to post treatment significant reduction of scores	9	25, 26, 31, 34, 36, 38, 41, 42, 44	-	-	-
Perceptual evaluations						
Perceptual dysphonia	Pretreatment to post treatment significant reduction of scores	1	24	-	-	-
GRBASI (sub)scores						
Grade of dysphonia	Pretreatment to post treatment significant reduction of scores	11	28, 29, 31, 34, 36-39, 41, 42, 44	-	-	-
Roughness	Pretreatment to post treatment significant reduction of scores	10	28, 31, 34, 36-39, 41, 42, 44	-	-	-
Breathiness	Pretreatment to post treatment significant reduction of scores	8	28, 29, 31, 34, 36, 39, 41, 44	-	-	-
Asthenia	Pretreatment to post treatment significant reduction of scores	6	28, 31, 34, 36, 39, 44	-	-	-
Strain	Pretreatment to post treatment significant reduction of scores	7	31, 34, 36-39, 44	No pretreatment to post treatment change	1	28
Instability	Pretreatment to post treatment significant reduction of scores	3	34, 36, 37	-	-	-
Videostroboscopy findings	Pretreatment to post treatment significant decrease of alterations	1	19	-	-	-
Objective voice quality						
Aerodynamic features						
Maximum phonation time	Pretreatment to post treatment significant increase of duration	4	37, 42, 43, 44	No pretreatment to post treatment change	3	20, 33, 35
S/Z ratio	Pretreatment to post treatment significant decrease of measure	1	39	-	-	-
Voice intensity	-	-	-	No pretreatment to post treatment change	1	30
Acoustic measurements						
Vocal dysfunction degree (VDD)	-	-	-	No pretreatment to post treatment change	1	23
Fundamental frequency (F0)	Pretreatment to post treatment significant increase of values	3	18, 39, 43	No pretreatment to post treatment change	5	20, 25, 30, 33, 35
F0 standard deviation (STD)	Pretreatment to post treatment significant decrease of measure	1	18	No pretreatment to post treatment change	2	30, 36
Absolute jitter	Pretreatment to post treatment significant decrease of measure	1	18	-	-	-
Percent jitter (Jitt%)	Pretreatment to post treatment significant decrease of measure	12	27, 29, 33, 34, 36-40, 42-44	No pretreatment to post treatment change	4	22, 25, 31, 35

TABLE 4 (*Continued*)

Voice quality outcomes	Pretreatment to post treatment changes	*N*	References		*N*	References
Absolute shimmer	Pretreatment to post treatment significant decrease of measure	1	18	-	-	-
Percent shimmer (Shim%)	Pretreatment to post treatment significant decrease of measure	13	25, 27, 29, 33, 34, 36-40, 42-44	No pretreatment to post treatment change	4	20, 22, 31, 35
Noise-to-harmonics ratio (NHR)	Pretreatment to post treatment significant reduction of values	3	25, 40, 42	No pretreatment to post treatment change	4	20, 34, 35, 36
Harmonics-to-noise ratio (HNR)	Pretreatment to post treatment significant increase of values	6	22, 27, 29, 33, 35, 43	-	-	-
Signal-to-noise ratio (SNR)	Pretreatment to post treatment significant decrease of measure	1	35	-	-	-
Normalized noise energy (NNE)	Pretreatment to post treatment significant decrease of measure	1	29	-	-	-
Voice Turbulence Index (VTI)	-	-	-	No pretreatment to post treatment change	2	20, 34
Soft Phonation Index (SPI)	-	-	-	No pretreatment to post treatment change	1	34

Abbreviations: GRBASI, grade of dysphonia, roughness, breathiness, asthenia, strain, instability; VHI, Voice Handicap Index.

specimen analysis of LPRD patients,[5] the documentation of objective voice quality alterations in untreated LPRD patients and the related pretreatment to post treatment improvements can all support an LPRD-related alteration of vocal fold function. However, to the best of our knowledge, there is no study investigating in patients both multidimensional voice quality alterations and vocal fold tissue lesions, such as microtrauma, epithelium thickening, and dryness.

Given the high heterogeneity across studies for treatment medication, doses, diet recommendation, and duration, it is difficult to identify the best therapeutic approach for patients with LPRD and related voice quality impairments. The occurrence of different patterns in pretreatment to post treatment voice quality evolution in patients with acid, alkaline versus weakly acid LPRD at the 24-hour HEMII-pH[42] may suggest the use of alginate or antacid to act on both acid and nonacid pharyngeal reflux events.[3,45] Indeed, LPRD is primarily an upright, gaseous, and weakly acid/alkaline disease,[46,47] requiring a combination of PPIs, alginate, or antacids (personalized treatment) to reach a higher therapeutic success rate.[48] The determination of potential superiority of one medication over others requires future controlled studies considering the HEMII-pH profile and digestive enzyme profiles of LPRD hoarse patients. The minimal duration of treatment is another key point for interpreting the data of the present review.[49] In the study of Hamdan et al,[20] most objective parameters did not report significant change after 4 weeks of treatment, while Vashani et al[29] and Habermann et al[19] observed subjective and objective improvements at 6 weeks post treatment. Note that Vashani et al recommended voice therapy in some patients in addition to the PPI therapy, which can accelerate voice recovery.[29] In the study of Lechien et al, both subjective and objective voice quality evaluations significantly improved from baseline to 3 months post treatment, but there were no additional improvements for 3-6 months post treatment.[40]

Although an overall trend of pretreatment to post treatment voice quality change emerges from this review, a substantial number of heterogeneities across studies limits the drawing of valid conclusions. First, as aforementioned, a high number of therapeutic regimens was identified in the review, including medication variability, doses, adherence to diet, and duration of treatment. The majority of authors used PPI therapy[19,21,23–26,28–38,43,44] without consideration of alginate and antacid drugs, which may significantly impact the pretreatment to post-therapeutic voice quality evaluations. PPIs do not influence the number of pharyngeal reflux events because they only reduce H+ secretion in the stomach. Alginate forms a raft over the stomach content and reduces the backflow of gastroduodenal content into the vocal folds, which may theoretically lead to fewer enzyme injuries in the tissue and better post treatment voice quality. Indeed, there would exist some significant differences across patients according to the type of LPRD (acid, weakly acid, or alkaline), with better post

TABLE 5.
Bias Analysis

References	Clearly Stated Aim	Consecutive Patients	Prospective Data Collection	Endpoints Appropriate to Study	Unbiased Endpoint Assessment	Follow-Up Adequate Period	<5% Lost to Follow-Up	Study Size Population Calculation	Total MINORS Score
Shaw et al[18]	2	0	2	1	1	2	0	0	8
Habermann et al[19]	2	2	2	1	1	2	0	0	10
Hamdan et al[20]	2	0	2	1	2	2	0	0	9
Noordzij et al[21]	2	0	2	1	0	1	0	0	6
Selby et al[22]	2	0	2	1	1	2	0	0	8
Siupsinskiene and Adamonis[23]	2	0	2	1	0	1	0	0	6
Williams et al[24]	2	2	2	1	0	2	2	0	11
Sereg-Bahar et al[25]	2	0	2	1	1	2	0	0	8
Siupsinskiene et al[26]	2	0	2	1	0	2	0	0	7
Jin et al[27]	2	2	2	1	1	2	0	0	10
Sala et al[28]	2	1	2	1	1	2	0	0	9
Vashani et al[29]	2	0	2	1	1	2	0	0	8
Fass et al[30]	2	0	2	1	1	2	0	0	8
Park et al[31]	2	2	2	1	2	2	2	0	13
Beech et al[32]	2	1	2	1	0	2	0	0	8
Wan et al[33]	2	2	2	1	1	1	2	0	11
Lechien et al[34]#	2	2	2	1	2	2	2	0	13
Batıoğlu et al[35]	2	0	2	1	1	2	0	0	8
Lechien et al[36]#	2	2	2	1	2	2	2	0	13
Lechien et al[37]*	2	2	2	1	2	2	0	0	11
Lechien et al[38]*	2	2	2	1	1	2	0	0	10
Jain et al[39]	2	2	2	1	2	2	0	0	11
Lechien et al[40]**	2	2	2	2	2	2	0	0	12
Barillari et al[41]	2	2	2	2	2	2	0	0	12
Lechien et al[42]**	2	2	2	2	2	2	0	0	12
Suda et al[43]	2	2	2	1	1	2	0	0	10
Zhang et al[44]	2	2	2	1	1	2	0	0	10

treatment voice quality outcome improvements in patients with acid and alkaline LPRD as compared with those with weakly acid reflux.[42]

Second, the literature investigation reported that the methods of acoustic measurements substantially varied from one study to another. Although there is a common trend of significant improvement in most acoustic measurements of variability of both F0 and intensity, the comparison across studies can be limited due to methodological inconsistencies.

The importance of methodology in acoustic measurements was highlighted in a recent prospective study where the acoustic measurements (eg, percent jitter, percent shimmer) carried out on the 1-, 2-, 3-, 4-, or 5-s middle intervals of the sustained vowel /a/ reported significantly different values from one interval to another.[50] Thus, it has been demonstrated that the potential effect of the treatment on acoustic parameters may or may not be statistically demonstrated depending on the time interval over which the acoustic parameters are measured.[50] Other studies reported significant impact of variation in equipment, recording conditions, analysis settings, and software[16] on the acoustic measurements, which may explain the variability observed across studies in this review. The adoption of a consensus for the assessment of voice quality is therefore strengthened by the findings of this review, which may improve the quality of further reviews dedicated to voice quality outcomes in laryngeal disorders.

Third, there was a substantial heterogeneity across studies for the diagnostic method of LPRD, with most investigations using clinical evaluation without objective testing. Because LPRD is associated with nonspecific symptoms and findings,[51,52] the lack of objective testing (HEMII-pH) or the lack of exclusion of some confounding conditions (eg, active allergy, chronic rhinosinusitis, and tobacco- or inhaled-drug-induced laryngitis) can lead to biased results in patients without LPRD but a confounding condition.[53–55] In this way, RSI and RFS were found to be high and falsely positive for LPRD in patients with chronic rhinitis,[54] rhinosinusitis,[56] or tobacco-induced laryngopharyngitis.[55] Only two teams[40–42] have used 24-hour HEMII-pH for confirming the diagnosis, while a few

others used single- or dual-probe pH testing, which cannot detect weakly acid or alkaline pharyngeal reflux events.[21,27,33] The laryngopharyngeal symptoms, including dysphonia related to LPRD, may involve different pathophysiological mechanisms affecting the vocal fold mucosa compared with laryngopharyngeal symptoms associated with these confounding conditions, which may influence voice quality measurements.

This systematic review of the literature has identified a substantial number of limitations, which challenge the design of future studies. The consideration of an objective LPRD diagnosis, subgroup analyses regarding the types of LPRD (acid, weakly acid, and alkaline) and enzyme profiles (pepsin, elastase, trypsin, and bile salts), evaluation of the effectiveness of several therapeutic regimens, multidimensional voice quality evaluation adhering to recommendations,[16] and correlation between voice quality evaluations and tissue sample biopsies represent numerous important points for improving the quality of research.

CONCLUSION

Voice quality may be considered an interesting biomarker of therapeutic changes in LPRD patients with perceived or self-reported dysphonia. Future studies are needed to correlate the multidimensional voice quality impairment with microscopic vocal fold changes in patients with an objective LPRD diagnosis. The exploration of emerging machine learning technology's value in the identification of baseline voice quality disorders and for voice pattern tracking could be an additional important future direction.

CRediT Authorship Contribution Statement

Guangjin Chen: Design, acquisition of data, data analysis and interpretation, drafting, final approval, and accountability for the work; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Jerome R. Lechien: Design, acquisition of data, data analysis and interpretation, drafting, final approval, and accountability for the work; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Declaration of Competing Interest

The author has no financial interest in the subject under discussion. All authors have read and approved the paper.

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