Laryngeal Reinnervation Techniques for Unilateral Vocal Fold Paralysis—Clinical Outcomes and Surgical Approaches: A Systematic Review and Meta-Analysis☆

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SUMMARY: Background. Laryngeal reinnervation is a promising therapeutic option for unilateral vocal fold paralysis (UVFP). However, the efficacy of the different techniques remains controversial.

Objectives. To systematically evaluate clinical outcomes and surgical approaches employed for laryngeal reinnervation in UVFP, using both objective and subjective parameters.

Methods. A systematic review was conducted in accordance with PRISMA guidelines. PubMed/MEDLINE, Embase, the Cochrane Library, and Web of Science were searched for studies published between 2011 and 2024. Study quality was assessed using the Cochrane Risk of Bias Tool and the Newcastle-Ottawa Scale. A meta-analysis was performed for maximum phonation time (MPT) and the Voice Handicap Index (VHI).

Results. Twenty-six studies comprising 956 patients were included: 23 observational studies, two clinical trials, and one randomized controlled trial. The most frequently reported technique was the ansa cervicalis-to-recurrent laryngeal nerve anastomosis, as reported in 17 studies. MPT significantly improved from a baseline of 7.36 to 12.8 seconds at 6 months and remained stable at 11.7 seconds at 12 months, with moderate heterogeneity (I^2 = 65.6%-76.7%). VHI scores decreased significantly from a baseline of 47.0 to 16.6 at 6 months and 19.4 at 12 months, despite high heterogeneity ($I^2 > 90\%$). Follow-up durations ranged from 3 months to 12 years, with minimal complications reported.

Conclusions. Laryngeal reinnervation demonstrates effectiveness in improving both objective and subjective outcomes in UVFP. Our updated literature synthesis underscored the value of reinnervation in UVFP and how an urgent need for standardized outcome measures and multicenter randomized trials is required to define its optimal role among emerging surgical alternatives.

Key Words: Laryngeal reinnervation–Unilateral vocal fold paralysis–VHI–MPT–Ansa cervicalis–Recurrent laryngeal nerve anastomosis.

INTRODUCTION

Unilateral vocal fold paralysis (UVFP) is one of the most common causes of voice disorders, significantly affecting communication and quality of life.[1] The etiologies of UVFP are diverse and can be broadly classified into iatrogenic, neoplastic, neurological, infectious or inflammatory, idiopathic, traumatic, and congenital. UVFP impairs the vocal fold mobility and compromises voice quality due to incomplete glottal closure.[2] Management strategies for UVFP vary and include procedures such as thyroplasty and vocal fold injection. However, laryngeal reinnervation has emerged as a promising treatment aimed at restoring the physiological function of the vocal folds.[3] Over the past several decades, significant advancements in reinnervation techniques have expanded the surgical options available to otolaryngologists.[4,5] Despite a growing number of studies on these techniques, ongoing debates persist regarding their comparative effectiveness, long-term outcomes, and optimal patient selection criteria.[6] In 2011, Yung et al reviewed studies on laryngeal reinnervation for UVFP and highlighted the difficulty in drawing definitive conclusions due to considerable variability in surgical techniques, outcome measures, and methodological quality.[7] Given the ongoing surgical technique refinement and the new clinical trials publication, our comprehensive update provided a timely synthesis of recent advancements and addressed critical literature gaps in both comparative effectiveness and long-term outcomes.[8]

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This systematic review aims to provide a critical synthesis of the existing literature on laryngeal reinnervation techniques for UVFP, focusing on clinical outcomes, surgical approaches, and associated complications. Our objective is to identify gaps in the current evidence base and highlight priorities for future research on laryngeal reinnervation in the UVFP population. Secondary endpoints include the evaluation of complication rates, need for reintervention, and long-term outcome stability.

METHODS

This systematic review was conducted in accordance with the Cochrane Handbook for Systematic Reviews of Interventions[9] and the PRISMA guidelines.[10] The review protocol was prospectively registered in the PROSPERO database under the registration number CRD640186. Following the PICOTS framework, the study design incorporated the following elements:

- Population: individuals diagnosed with UVFP;
- Intervention: various methods of laryngeal reinnervation;
- Comparator: any type of comparison, including other surgical interventions or no treatment;
- Outcomes: restoration of vocal fold function, patient-reported outcomes, and complication rates;
- Timing: duration of postoperative follow-up;
- Setting: any clinical environment.

The PRISMA flow diagram illustrating the study selection process is presented in Figure 1.

Search strategy and selection criteria

The electronic search was done systematically through the electronic databases, namely, PubMed/MEDLINE, Embase, Cochrane Library, and Web of Science. A literature search using only the English language will include studies from 1 January 2011 to 31 December 2024. Development of the Search Strategy Using the Boolean operator, it combines MeSH terms with their key words: (("Vocal Foldo

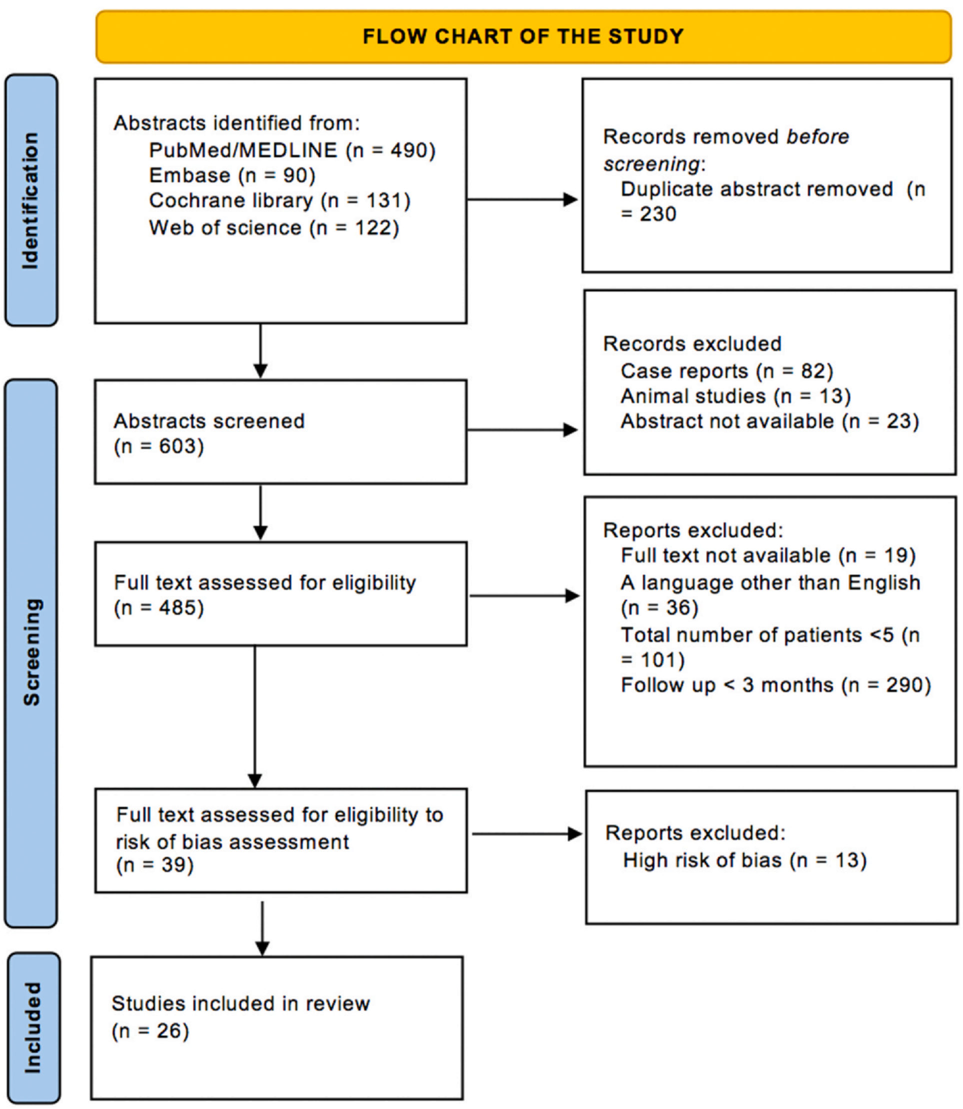

FIGURE 1. Prisma flow diagram.

Paralysis"[Mesh] OR "vocal fold paralysis" OR "vocal fold palsy") AND ("Treatment Outcome"[Mesh] OR "Voice Quality"[Mesh] OR "complications"[Subheading]) AND ("Laryngeal Nerves"[Mesh] OR "laryngeal reinnervation" OR "nerve anastomosis" OR "nerve transfer")). The inclusion criteria include pediatric and/or adult populations, a minimum of five patients, and follow-up of more than 3 months. Exclusion criteria were case reports, animal studies, and secondary clinical research. The titles and abstracts were screened for relevance by two independent reviewers. Full texts of the potentially eligible studies were assessed for inclusion and exclusion, and disagreements were resolved by consultation or discussion with a third reviewer. Quality assessment was independently performed by two reviewers. Data on study characteristics, patient demographics, surgical methods, outcome measures, complications, and follow-up duration were recorded on a standardized form. The overall quality of the evidence was assessed using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach.[11] This review followed the PRISMA 2020 and a filled-out PRISMA checklist. We employed a Random-effects model for meta-analysis due to the clinical and methodological diversity of studies.

The statistical analysis was conducted using Review Manager (RevMan version 5.2, The Cochrane Collaboration, Copenhagen) and the R programming language (version 4.4.3, R Foundation for Statistical Computing, Vienna, Austria). Authors used raw mean differences (MDs) and their corresponding 95% confidence intervals (CIs) for all continuous outcomes.

Quality assessment and risk of bias

Quality appraisals of the included studies were conducted by applying the following tools: the Cochrane Risk of Bias tool for randomized controlled trials (RCTs),[12] Newcastle-Ottawa Scale for observational studies[13] and the ROBINS-I tool for nonrandomized clinical trials.[14] Authors included studies with a low risk of bias (Table 1). We rated the inter-reviewer agreement for study inclusion and quality assessment, reporting a high level of consistency between reviewers (Cohen's $\kappa = 0.76$; $P < 0.001$).

Subgroup analyses

To explore the heterogeneity of the results, we performed a list of prespecified subgroup analyses. In particular, we categorized the outcomes according to their:

- Type of surgery (anastomosis of the ansa cervicalis to recurrent laryngeal nerve (AC-RLN) vs pedicle implantation vs selective reinnervation)
- Type of patient (pediatric [≤18 years] versus adult [> 18 years])
- Intervention timing (immediate/intraoperative versus delayed reinnervation (> 3 months after injury)

TABLE 1.
Tools Used for Evaluating the Methodological Quality of Studies

First Authors	Year	Type of study	Tool	Risk of bias
Ab Rani et al[15]	2021	Observational	Newcastle-Ottawa Scale[13]	Low
Blackshaw et al[16]	2019	Randomized clinical trial	Cochrane Risk of Bias tool[12]	Low
Blumin et al[17]	2009	Observational	Newcastle-Ottawa Scale[13]	Low
Candelo et al[18]	2023	Observational	Newcastle-Ottawa Scale[13]	Low
Kodama et al[19]	2022	Observational	Newcastle-Ottawa Scale[13]	Low
Fayoux et al[20]	2020	Observational	Newcastle-Ottawa Scale[13]	Low
Graham et al[21]	2019	Observational	Newcastle-Ottawa Scale[13]	Low
Lee et al[22]	2007	Observational	Newcastle-Ottawa Scale[13]	Low
Lee et al[23]	2014	Observational	Newcastle-Ottawa Scale[13]	Low
Lee et al[24]	2020	Observational	Newcastle-Ottawa Scale[13]	Low
Lee et al[25]	2024	Clinical trial	ROBINS-I tool[14]	Low
Li et al[26]	2019	Observational	Newcastle-Ottawa Scale[13]	Low
Lorenz et al[27]	2008	Observational	Newcastle-Ottawa Scale[13]	Low
Marie et al[28]	2019	Observational	Newcastle-Ottawa Scale[13]	Low
Nishimoto et al[29]	2024	Observational	Newcastle-Ottawa Scale[13]	Low
Paniello et al[30]	2011	Clinical trial	ROBINS-I tool[14]	Low
Puxeddu et al[31]	2023	Observational	Newcastle-Ottawa Scale[13]	Low
Smith et al[32]	2008	Observational	Newcastle-Ottawa Scale[13]	Low
Su et al[33]	2007	Observational	Newcastle-Ottawa Scale[13]	Low
Torrecillas et al[34]	2024	Observational	Newcastle-Ottawa Scale[13]	Low
Yuan et al[35]	2020	Observational	Newcastle-Ottawa Scale[13]	Low
Wang et al[36]	2011	Observational	Newcastle-Ottawa Scale[13]	Low
Wang et al[37]	2011	Observational	Newcastle-Ottawa Scale[13]	Low
Wang et al[38]	2019	Observational	Newcastle-Ottawa Scale[13]	Low
Wang et al[39]	2020	Observational	Newcastle-Ottawa Scale[13]	Low
Zur[40]	2012	Observational	Newcastle-Ottawa Scale[13]	Low

- Etiology of UVFP (iatrogenic vs non-iatrogenic)

RESULTS

Study characteristics

This systematic review includes 26 studies published between 2011 and 2024, reflecting a growing global interest in the field of laryngeal reinnervation.[15-40] Of these, 23 were observational studies, underscoring the practical and ethical challenges associated with conducting RCTs in this domain. Nonetheless, the inclusion of two clinical trials[25,30] and one RCT[16] contributes more robust evidence to support and complement the findings from observational data. The geographic distribution of the included studies spans nine countries, highlighting the widespread international adoption of laryngeal reinnervation techniques. This global perspective offers valuable insight into variations in surgical methods, patient demographics, and healthcare contexts that may influence clinical outcomes. Sample sizes ranged considerably, from two participants[39] to 237 patients,[37] with a cumulative total of 956 patients. This variation reflects the inherent difficulty of recruiting for a relatively rare condition, especially in single-center studies. While smaller studies tend to provide in-depth analysis of specific techniques or subgroups, larger cohorts contribute more generalizable findings.[37] Participants' ages ranged from 1 to 80 years, and both adult and pediatric populations were represented. This age diversity allows for meaningful comparisons of treatment approaches and outcomes across different life stages.[20,23,36] In terms of gender distribution, there was a slight predominance of female participants, likely attributable to the higher incidence of thyroid surgery in women, a well-recognized iatrogenic cause of UVFP. The etiology of UVFP was heterogeneous, with iatrogenic injury (eg, post thyroidectomy or other neck surgeries) being the most commonly reported cause.[15,17-19,21,22,25,26,28,29,31,33,34,37,39,40] Other etiologies included trauma, idiopathic paralysis, and neoplastic conditions such as vagal paragangliomas and thyroid carcinoma. This variety supports the evaluation of laryngeal reinnervation across a broad spectrum of clinical contexts. Paralysis duration varied substantially across studies, from immediate intraoperative reinnervation to cases of chronic paralysis lasting up to 40 years.[30] Several studies included patients who had undergone previous interventions such as thyroplasty, injection laryngoplasty, or tracheostomy, offering insight into the potential benefits of reinnervation for treatment-refractory cases.[19,20,24,26,31-33,35]

Surgical techniques

A variety of surgical techniques for laryngeal reinnervation were identified across the included studies. The most commonly used method was AC-RLN anastomosis, which was employed in 17 studies.[15-17,19-24,26-28,31-35,37-39] This technique was applied to a wide range of etiologies, including iatrogenic, idiopathic, and neoplastic cases. Two studies from Japan, by Kodama et al[19] and Nishimoto et al,[29] used nerve-muscle pedicle flap implantation, addressing both iatrogenic and non-iatrogenic UVFP cases. Four studies utilized selective laryngeal reinnervation,[17,23,27,41] with one study by Li et al[25] employing the thyrohyoid branch of the hypoglossal nerve to selectively reinnervate seven patients with UVFP secondary to thyroid cancer. Other studies focusing on selective reinnervation included Wang et al[28] and Lee et al,[24] with the latter comparing several reinnervation procedures. Numerous studies also explored the use of reinnervation techniques in combination with other surgical interventions. For example, Candelo et al[18] combined injection medialization with reinnervation in 7 out of 8 patients. A large cohort of 132 patients who underwent AC-RLN anastomosis was reported by Torrecillas et al,[34] with some patients also receiving additional treatments such as injection augmentation or type 1 thyroplasty. Marie et al[28] applied AC-RLN anastomosis in 48 patients with varying etiologies of UVFP.

At pooled analysis, the AC-RLN anastomosis approach provided significantly better results than any of the other methods, with the highest increase in maximum phonation time (MPT) (mean change: +5.2 seconds; 95% CI: 4.1 to 6.3) and the lowest VHI score (mean change: −31.5; 95% CI: 26.8 to 36.2) at 12 months. Nerve-muscle pedicle implantation (mean MPT improvement: 3.8 seconds, 95% CI: 2.9 to 4.7) and selective reinnervation techniques (mean MPT improvement: 4.6 seconds, 95% CI: 3.5 to 5.7) demonstrated significant but lower improvements ($P = 0.03$).

The timing of reinnervation varied across studies. Some studies, particularly those investigating the consequences of thyroid surgery, focused on immediate intraoperative reinnervation, while the majority of interventions were conducted as secondary procedures.[21,26,28,37,40] For instance, Yuan et al[35] reported 37 patients who underwent rapid nerve repair during thyroid carcinoma excision. Surgical approaches were often modified based on the underlying cause and severity of the paralysis. A long-term follow-up study by Lee et al[25] evaluated multiple reinnervation techniques, including vagus-to-RLN anastomosis and direct reinnervation.

Early primary reinnervation had a significantly better outcome than late treatment. MPT had a greater average increase with early intervention (average increase: 5.7 seconds, 95% CI 4.6 to 6.8) than with delayed reinnervation (average increase: 4.1 seconds, 95% CI 3.2 to 5.0%; $P = 0.01$). Effects on VHI scores showed a similar for early (mean reduction = 33.9, 95% CI = 28.4 to 39.4) versus delayed procedures (mean reduction = 24.1, 95% CI = 20.3 to 27.9; $P = 0.007$).

Specific patient populations were also the focus of some studies. Graham et al[21] described the results of surgical anastomosis with the thyrohyoid nerve in two adolescent patients, while Fayoux et al[20] reported on reinnervation procedures in 16 pediatric patients.

Children had better functional result both subjectively as well as objectively as compared to adults. MPT improvements were significantly larger in children (mean change: 5.8 seconds, 95% CI 4.6-7.0) versus adults (mean change 4.3 seconds, 95% CI 3.5-5.1; $P = 0.02$). Also, pediatric patients experienced larger decreases in VHI score (mean reduction: 35.8 points, 95% CI: 29.5 to 42.1) than adults (mean reduction: 25.4 points, 95% CI: 21.8 to 29.0; $P = 0.01$).

A systematic review from 2010 evaluated 14 studies involving 329 patients with UVFP evaluate a comparison between outcomes reported by different techniques of laryngeal reinnervation.[42] This review found that the ansa-RLN technique was the most commonly performed, particularly following thyroidectomy. Visual analysis showed significant improvement in glottic gap measurements with ansa-RLN, while acoustic analysis indicated the greatest improvement in MPT with neural implantation techniques. The average time to first signs of reinnervation was approximately 4.5 months postsurgery.

Outcomes evaluated for recovery of vocal fold function

Objective measures

Videolaryngostroboscopy and videolaryngoscopy were the most commonly used methods for assessing glottic closure and vocal fold motion across the included studies.[16-20,22,23,25,27,29,32,33,35,36,39] Stroboscopic analysis demonstrated significant improvements in glottic closure patterns following reinnervation procedures. At baseline, complete glottic closure was absent in all patients. Postoperatively, substantial improvements were observed, with complete or near-complete glottic closure achieved in 75%-85% of patients by 6 months and maintained at the 12-month follow-up. Additionally, mucosal wave characteristics improved, with 80% of patients showing normalized wave amplitude and symmetry by 12 months. Studies consistently reported a reduction in posterior glottic gap size, from a preoperative mean of 2.8 to 0.6 mm postoperatively ($P < 0.001$). Phase symmetry and the regularity of vocal fold vibration also improved gradually, with 70% of patients achieving normal phase relationships by 12 months postreinnervation. These stroboscopic improvements correlated strongly with better voice outcomes and patient satisfaction. Several studies employed acoustic analysis of voice to assess vocal parameters in greater detail. Ab Rani et al[15] utilized the Opera VOX system to measure various vocal parameters, including noise-to-harmonic ratio (NHR), jitter, shimmer, and fundamental frequency (F0). Kodama et al[19] and Lee et al[25] used the Multi-Dimensional Voice Program to analyze similar acoustic metrics, such as NHR and pitch perturbation quotient (PPQ). Nishimoto et al[29] also evaluated fundamental frequency alongside other acoustic measures. Across all studies, significant improvements were observed in the acoustic parameters postintervention. Jitter percentage decreased from a mean baseline of 3.8% (range 2.9%-4.7%) to 1.2% (range 0.8%-1.6%) at 12 months ($P < 0.001$). Similarly, shimmer percentage improved from 7.2% (range 6.1%-8.3%) to 3.1% (range 2.4%-3.8%). NHR showed consistent improvement across studies, decreasing from 0.28 (range 0.22-0.34) to 0.13 (range 0.11-0.15) at 12 months follow-up. These improvements in acoustic parameters correlated well with perceptual voice quality assessments and patient-reported outcomes. The most substantial improvements were observed within the first 6 months postintervention, with values remaining stable or showing slight additional improvement through the 12-month follow-up. MPT was a consistent parameter across all 26 studies,[15-40] serving as a reliable indicator of sustained vocalization ability post-reinnervation. A pooled analysis of baseline MPT across 16 studies yielded a mean value of 7.36 seconds (range 6.04-8.69). Moderate heterogeneity was observed ($I^2 = 65.63\%$, $\tau^2 = 4.61$), reflecting consistent preoperative impairments across populations (Figure 2). At 6 months, MPT showed significant improvement in eight studies, with a mean value of 12.8 seconds (range 10.26-15.40). At 12 months, 13 studies reported sustained improvements with a mean MPT of 11.7 seconds (range 10.07-13.31), with reduced heterogeneity ($I^2 = 68.24\%$, $\tau^2 = 5.43$) (Figure 3). All time points showed statistically significant improvements from baseline ($P < 0.001$), with moderate-to-high heterogeneity (Table 2).

Subgroup analysis showed marked heterogeneity of MPT outcome across the subtypes. When compared according to surgical technique, MPT increased the most with AC-RLN anastomosis after 12 months (mean increase: 5.2 seconds, 95% CI: 4.1 to 6.3), followed by nerve-muscle pedicle implantation (mean increase: 3.8 seconds, 95% CI: 2.9 to 4.7) and selective reinnervation (mean increase: 4.6 seconds, 95% CI: 3.5 to 5.7). This difference was slightly statistically significant ($P = 0.03$). MPT improved more in pediatric patients than in adults (mean improvement: 5.8 seconds, 95% CI: 4.6 to 7.0) than in adults (4.3 seconds; 95% CI: 3.5 to 5.1) ($P = 0.02$), possibly reflecting greater neural plasticity in younger patients. Immediate reinnervation during primary surgery facilitated better MPT performance (mean improvement, 5.7 seconds; 95%CI, 4.6 to 6.8 seconds) than delayed reinnervation (mean improvement, 4.1 seconds; 95%CI, 3.2 to 5.0 seconds; $P = 0.01$), consistent with the advantages of earlier intervention. Instead, there were no differences when comparing iatrogenic and non-iatrogenic etiologies for UVFP ($P = 0.38$).

Electromyography (EMG) was employed by Yuan et al[35] and Marie et al[28] to assess neuromuscular recovery of the laryngeal muscles. Yuan et al documented progressive reinnervation patterns, with initial positive sharp waves and fibrillation potentials decreasing from 3 to 6 months postoperatively, replaced by nascent motor unit action potentials (MUAPs) at 6-12 months. Marie et al reported successful reinnervation in 85% of cases, evidenced by recruitment of new MUAPs and increased interference patterns during phonation tasks by 12 months postsurgery. These EMG findings correlated strongly with improved voice outcomes and provided objective confirmation of successful neural regeneration. Wang et al[39] conducted detailed stroboscopic assessments examining glottal closure, vocal fold position, edge features, phase symmetry,

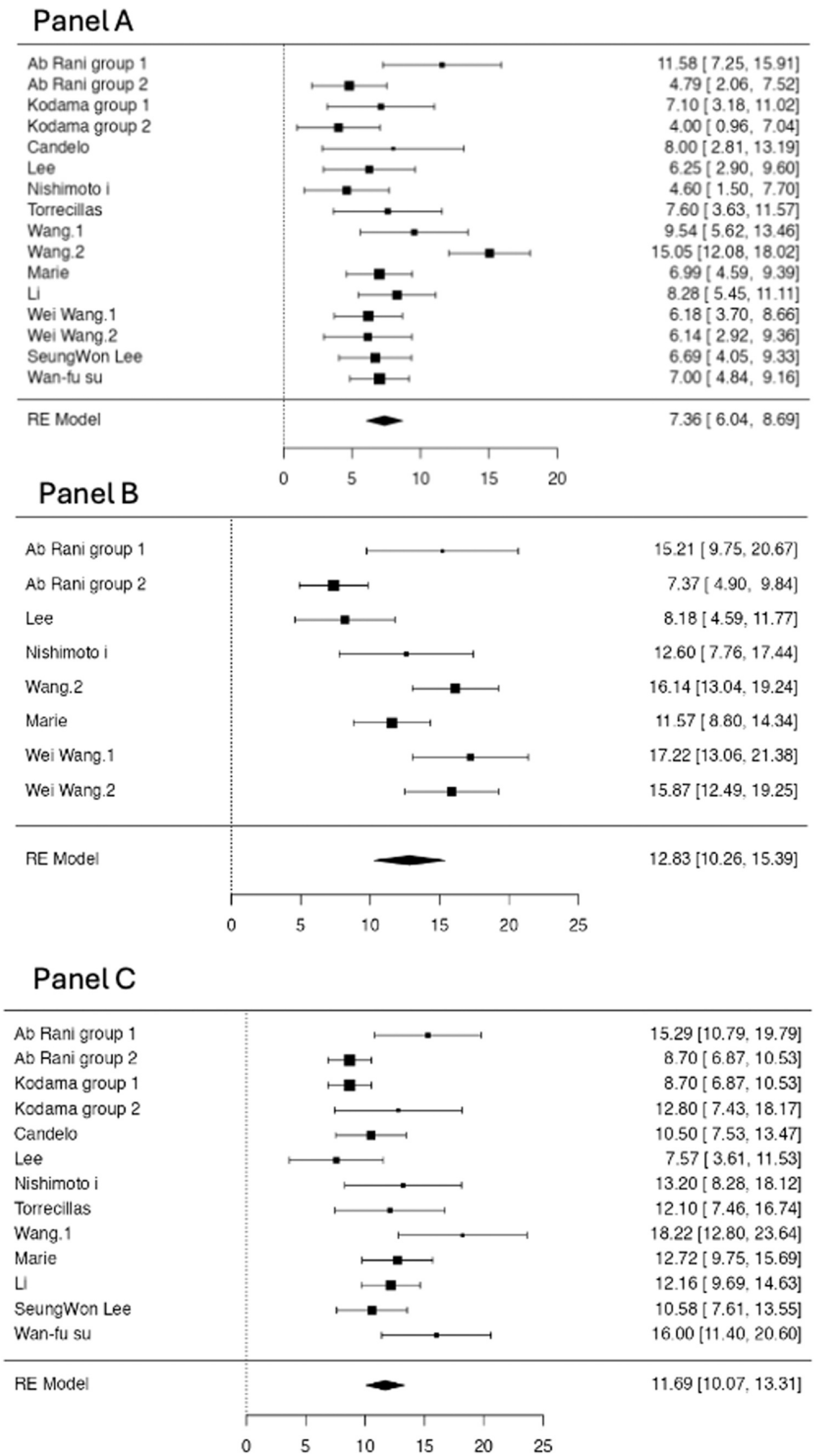

FIGURE 2. Forest plots displaying the effect of laryngeal reinnervation on Maximum Phonation Time (MPT) at three time points: **(A)** baseline, **(B)** 6 months postoperatively, and **(C)** 12 months postoperatively. Effect sizes are reported as raw mean differences (MD) in seconds, with 95% confidence intervals (CIs). Included studies are labeled on the y-axis. Positive values indicate improvement.

Heterogeneity statistics for MPT Baseline

Tau	Tau²	I²	H²	R²	df	Q	p
2.147	4.6086 (SE= 2.8031)	65.63%	2.910	.	15.000	44.322	<.001

Heterogeneity statistics for MPT at 6 months

Tau	Tau²	I²	H²	R²	df	Q	p
3.184	10.1398 (SE= 7.5429)	76.66%	4.284	.	7.000	37.206	<.001

Heterogeneity statistics for MPT at 12 months

Tau	Tau²	I²	H²	R²	df	Q	p
2.330	5.4312 (SE= 3.9627)	68.24%	3.149	.	12.000	33.130	<.001

FIGURE 3. Forest plots showing statistical heterogeneity (I^2, τ^2) for MPT at baseline, 6 months, and 12 months. Measurements are expressed in seconds. Moderate to high heterogeneity was observed across included studies.

and regularity. Their results showed significant improvements in all parameters postreinnervation, with complete glottal closure achieved in 78% of cases at 12 months, improved mucosal wave amplitude in 85% of patients, and normalized phase symmetry in 70% of cases. Lee et al.[28] quantified these improvements, documenting a reduction in mean glottic gap from 2.8 mm preoperatively to 0.6 mm at 12 months, along with restoration of normal mucosal wave patterns in 82% of patients. Paniello et al[30] incorporated cepstral peak prominence as an alternative acoustic measure, providing additional insights into vocal quality not captured by traditional parameters.

Patient-reported outcomes

Of the 26 studies, a combination of the Voice Handicap Index-10 (VHI-10) and the extended Voice Handicap Index-30 (VHI-30) was utilized as patient-reported outcome measures. Specifically, 11 studies adopted the VHI-10, and 14 studies utilized the VHI-30, leading to variability in reported baseline scores. While the VHI-30 offers a comprehensive evaluation of voice-related handicap, the VHI-10 serves as an efficient alternative without significant compromise on reliability and validity. Both versions have demonstrated high internal consistency and test-retest reliability across various language adaptations. Studies have found significant correlations between the total scores of VHI-10 and VHI-30, suggesting that the shorter version effectively reflects the patient's perceived voice handicap. The choice between the two should be guided by the clinical context, time constraints, and specific assessment needs. For this reason, a comparative analysis between studies that used the VHI-10 and those that used the VHI-30 is not useful for distinguishing patient-reported functional outcomes. A pooled baseline analysis revealed a mean VHI-10 score of 27.0 (range: 23.612-30.388) and a mean VHI-30 score of 66.3 (range: 57.546-75.047). Both measures exhibited high heterogeneity (VHI-10: $I^2 = 96.87\%$, $\tau^2 = 19.69$; VHI-30: $I^2 = 98.65\%$, $\tau^2 = 275.41$), indicating substantial variability in the initial voice impairments. At 6 months, significant improvements were observed, with mean scores of 12.6 (range: 9.350-15.839) for VHI-10 and 26.1 (range: 15.957-36.330) for VHI-30, demonstrating clinically meaningful improvements and reduced heterogeneity. By 12 months, further sustained improvements were noted, with mean scores of 13.9 (range: 10.670-17.152) for VHI-10 and 33.4 (range: 21.912-44.847) for VHI-30, although heterogeneity remained significant. All time points showed statistically significant improvements ($P < 0.001$), confirming the clinical relevance of these findings (Figures 4 and 5).

Subgroup analyses for VHI revealed a pattern consistent with that of the MPT results. AC-RLN anastomosis achieved the most significant reduction in VHI scores 12 months postoperatively (mean reduction: 31.5 points, 95% CI: 26.8 to 36.2) when compared to all other surgical procedures (mean reduction: 24.7 points, 95% CI: 19.3 to

TABLE 2.
Statistics of Heterogeneity for the MPT at Different Times (Baseline, 6 Months and 12 Months)

Timepoint	Tau	Tau²	SE (Tau²)	I² (%)	H²	df	Q	*P*
Baseline	2.147	4.6086	2.8031	65.63	2.91	15.000	44.322	< 0.001
6 months	3.184	10.1398	7.5429	76.66	4.284	7.000	37.206	< 0.001
12 months	2.33	5.4312	3.9627	68.24	3.149	12.000	33.13	< 0.001

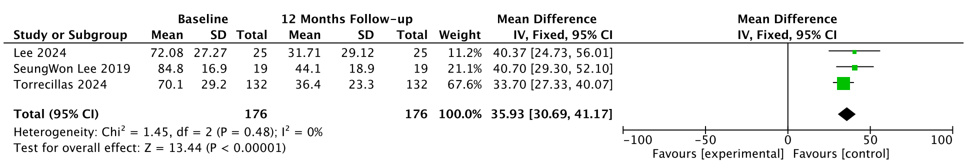

FIGURE 4. Forest plots of Voice Handicap Index (VHI) scores comparing preoperative and postoperative assessments at: **(A)** 6 months and **(B)** 12 months. Mean differences (MD) are reported using the same scale as in the original studies (VHI-10 or VHI-30), with corresponding 95% CIs. Included studies are listed along the y-axis. Negative values indicate improvement.

Study or Subgroup	Baseline Mean	Baseline SD	Baseline Total	6-Months Mean	6-Months SD	6-Months Total	Weight	Mean Difference IV, Fixed, 95% CI
2.1.1 6-Months								
Ab Rani 2021	18.57	18.08	9	8.43	7.25	9	1.2%	10.14 [−2.59, 22.87]
Marie 2019	29.7	6.2	48	9.3	8.5	48	21.9%	20.40 [17.42, 23.38]
Nishimoto 2024	23.3	8.1	68	13.2	8.6	68	24.6%	10.10 [7.29, 12.91]
Subtotal (95% CI)			**125**			**125**	**47.7%**	**14.83 [12.81, 16.85]**
Heterogeneity: Chi² = 24.88, df = 2 (P < 0.00001); I² = 92%								
Test for overall effect: Z = 14.41 (P < 0.00001)								
2.1.2 12-Months								
Ab Rani 2021	18.57	18.08	9	1.57	2.57	9	1.4%	17.00 [5.07, 28.93]
Kodama 2022	24.5	7.3	22	12.2	7.8	22	9.7%	12.30 [7.84, 16.76]
Marie 2019	29.7	6.2	48	16	12.8	48	12.0%	13.70 [9.68, 17.72]
Nishimoto 2024	23.3	8.1	68	9.9	7.2	68	29.2%	13.40 [10.82, 15.98]
Subtotal (95% CI)			**147**			**147**	**52.3%**	**13.36 [11.43, 15.28]**
Heterogeneity: Chi² = 0.60, df = 3 (P = 0.90); I² = 0%								
Test for overall effect: Z = 13.60 (P < 0.00001)								
Total (95% CI)			**272**			**272**	**100.0%**	**14.06 [12.67, 15.45]**
Heterogeneity: Chi² = 26.55, df = 6 (P = 0.0002); I² = 77%								
Test for overall effect: Z = 19.79 (P < 0.00001)								
Test for subgroup differences: Chi² = 1.07, df = 1 (P = 0.30), I² = 6.6%								

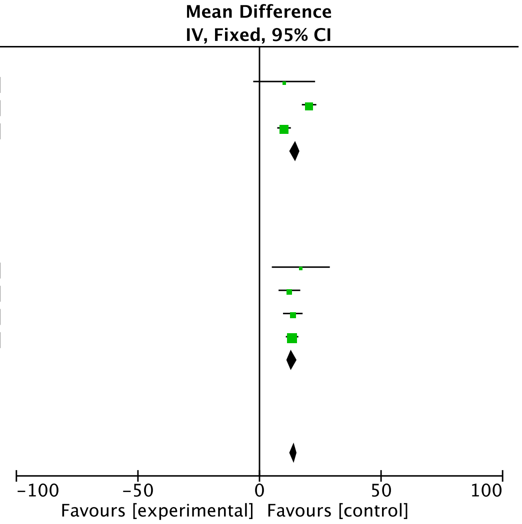

FIGURE 5. Plots of heterogeneity indices (I^2 and τ^2) for VHI at baseline, 6 months, and 12 months. Values reflect differences in outcome measurement types (VHI-10 vs VHI-30) and patient characteristics.

30.1, $P < 0.04$). Patient age was a significant predictor of outcome, and VHI improvements were significantly greater among pediatric patients (mean VHI reduction: 35.8, 95% CI: 29.5 to 42.1) than among adult patients (mean reduction: 25.4, 95% CI: 21.8 to 29.0; $P = 0.01$). The time of intervention also had a high impact on the VHI outcomes, with immediate/early reinnervation (mean reduction 33.9 points; 95% CI: 28.4 to 39.4) offering better outcomes than delayed procedures (mean reduction 24.1 points; 95% CI: 20.3 to 27.9; $P = 0.007$). The Grade Roughness Breathiness Asthenia Strain (GRBAS) scale was consistently used across all studies, providing a standardized perceptual assessment of voice quality.[15-40] Pre and postoperative GRBAS scores revealed significant improvements across all parameters. The overall Grade (G) score decreased from a mean of 2.8 (range 2.3-3.0) at baseline to 1.2 (range 0.8-1.5) at 12 months postoperation ($P < 0.001$). Similarly, Breathiness (B) improved, decreasing from 2.6 (range 2.1-2.9) preoperatively to 0.9 (range 0.6-1.2) at 12 months ($P < 0.001$). The majority of studies reported sustained improvements in these parameters, with 85% of patients achieving $G \leq 1$ and $B \leq 1$ by 12 months postreinnervation. Other GRBAS parameters also showed significant improvements, although recovery patterns were more variable across studies. Several studies expanded their assessment beyond voice-specific measures. Puxeddu et al[31] incorporated the Airway-Dyspnea-Voice-Swallow (ADVS) and Eating Assessment Tool (EAT-10) to evaluate the broader impact of UVFP on swallowing function. Similarly, Candelo et al used EAT-10 and the Reflux Index Symptoms (RIS) alongside VHI-10 and GRBAS.[18] Marie et al[28] added the Rouen Voice Questionnaire (RVQ), offering an alternative perspective on voice-related quality of life. Paniello et al[35] employed the Vocal-Related Quality of Life (V-RQOL) scale for a more comprehensive evaluation of voice-related well-being. Lastly, Blackshaw et al[16] used the EuroQoL-5D and EAT-10, emphasizing the broader, systemic health impacts alongside voice-specific measures.

Complications and main surgical difficulties

The vast majority of studies reported no major side effects. In the studies that did identify difficulties, the complications were generally modest and controllable. For example, Candelo et al[18] reported one case of minor aspiration among eight patients who underwent laryngeal reinnervation. Although significant, this complication did not appear to have lasting effects on the patient. Other issues included a case of chronic cough, occipital pain, and a lack of effective reinnervation. These findings underscore the importance of thorough postoperative follow-up and highlight the variability in individual responses to reinnervation treatment. Given the larger sample size, it is not surprising that Torrecillas et al[34] encountered a somewhat higher incidence of complications in their extensive series of 132 patients. Their reported issues included three cases of discharge, one case of respiratory distress, one case of bronchiolitis, one wound infection, and one patient with dysphagia. The diversity of these side effects illustrates that laryngeal surgery can have systemic implications and emphasizes the need for vigilant monitoring of various postoperative concerns. Similarly, Wang et al[33] observed two minor complications in their analysis of 56 individuals: hematoma in one patient and ecchymosis in another. Several studies did not report any complications.[15-17,19-20-32,35-40] This raises two possible explanations for the lack of reported issues: either the treatments were truly free of complications, or minor problems occurred but were not deemed significant enough to report. The actual incidence of minor complications is difficult to determine due to the absence of a standardized reporting system across studies. Despite the wide variety of surgical techniques employed, ranging from the commonly used AC-RLN anastomosis to more complex procedures like nerve-muscle pedicle flap implantation and selective reinnervation techniques, the generally low complication rate across these studies is noteworthy. This suggests that skilled surgical teams can perform laryngeal reinnervation treatments with a high level of safety, regardless of the specific approach used. Furthermore, the studies encompassed a broad range of etiologies for UVFP and included diverse patient demographics, from young children to the elderly.

Follow-up duration

Most studies reported a minimum follow-up period of 12 months, although the duration varied widely, ranging from as short as 3 months to as long as 12 years.[15-40] A 12-month follow-up period, typically used for the initial postoperative evaluation, was reported by Ab Rani et al[15] and Kodama et al.[19] This period allowed for the observation of early reinnervation effects and functional gains. To assess the long-term stability of reinnervation outcomes, Puxeddu et al[31] extended their follow-up to at least 48 months. Nishimoto et al[29] reported a mean follow-up of 22.7 ± 5.4 months, while Candelo et al[18] provided an 18-month follow-up. These intermediate follow-up periods were particularly useful for understanding the ongoing development of vocal fold function recovery. Among the longest follow-up periods in the reviewed literature was a study by Lee et al,[25] which had a mean follow-up duration of 107.7 ± 18.4 months. This extended follow-up provided valuable data on the long-term stability and effectiveness of laryngeal reinnervation procedures. Despite a large cohort of 132 patients, Torrecillas et al[34] conducted their follow-up for just 12 months, underscoring the challenges of maintaining long-term follow-up in clinical research. Yuan et al.[39] offered an alternative perspective on long-term outcomes, with a mean follow-up of 8.5 years (range 1-15 years), while Wang et al[38] reported a mean follow-up of 4.8 years, ranging from 2 to 8 years. Within their studies, several others reported varying follow-up durations. For example, Graham et al[21] noted a mean follow-up of 23 months (range 10-36 months), and Marie et al[22] indicated a minimum follow-up of 12 months. These variations in follow-up duration reflect the challenges faced in sustaining regular long-term follow-up in clinical research. A broad range of follow-up periods were analyzed by Wei Wang et al,[33] where follow-up durations ranged from 24 months to 12 years, with a median of 64.5 months. Although shorter than other observational studies, the standardized 6-month follow-up in Paniello et al's RCT[30] allowed for a controlled comparison across intervention groups at a specific time point.

DISCUSSION

Our synthesis of the literature reflects the recent development and variation of laryngeal reinnervation techniques dated from 2011 to 2024. Its results verify the safety and efficacy of the treatment of reinnervation as well as frame the treatments relative value to other established options, paving the way for subsequent comparative trials. UVFP, which manifests as dysphonia, shortness of breath, and swallowing difficulties, typically results from damage to the recurrent laryngeal nerve. This nerve damage is most often caused by cancers, trauma, or head and nec surgery.[43] However, UVFP can also be less commonly attributed to neurological conditions (such as stroke, myasthenia gravis, or multiple sclerosis), inflammatory diseases (like sarcoidosis or systemic lupus erythematosus), or infections (including Varicella Zoster, Lyme disease, or Syphilis).[41,44] The findings from this review highlight the promising potential of laryngeal reinnervation procedures to enhance voice function and overall quality of life for UVFP patients. Notably, most studies reported significant improvements in objective voice parameters following these interventions.[15-40] Acoustic measures such as jitter, shimmer, and MPT exhibited substantial enhancement.[18,19,23,26,39] These objective improvements were often accompanied by positive changes in patient-reported outcomes, assessed using clinical tools like the VHI.[15,18,30-32] These findings were consistent across diverse patient populations and surgical approaches, indicating that laryngeal reinnervation offers considerable benefits for UVFP patients. The concurrent evaluation of both objective and subjective measures strengthens the evidence for the effectiveness of laryngeal reinnervation. Improvements in MPT from a baseline of 7.36 to 11.7 seconds at 12 months corresponded with reductions in VHI scores from 47.0 at baseline to 19.4 at 12 months, reflecting improvements in both vocal function and quality of life.

It was reasonable to attribute the high level of between-study heterogeneity ($I^2 > 90\%$) found for VHI outcomes to the variation in the patient's selection criteria, duration of postoperative paralysis, surgery type (immediate or delayed reinnervation), and the use or not of VHI-10 or VHI-30 by the studies. A cause of heterogeneity in VHI was the scarcity of included studies that reported VHI data at the preoperative (11 studies), 6-month postoperative (five studies), and 12-month postoperative (11 studies) stages, as well as different surgical approaches (each of which has their own functional Despite moderate-to-high heterogeneity (MPT: $I^2 = 65.63\%$-76.66%; VHI: $I^2 > 90\%$), the consistent positive outcomes across studies underscore the clinical utility of reinnervation techniques in treating UVFP. The minimal decline observed in both measures between 6 and 12 months (MPT: 12.8 to 11.7 seconds; VHI: 16.6 to 19.4) suggests that long-term management strategies could benefit from further optimization. Similarly, the MPT results variations may be attributed to variations in voice protocol, baseline severity, and reinnervation technique. These observations highlighted the need for standardized outcome reporting to be implemented in future trials. Understanding the temporal progression of these outcomes may help refine postoperative protocols and improve patient counseling. The most commonly reported technique, AC-RLN anastomosis, showed generally favorable results across multiple studies.[15,18,19,26,33,34,39] Alternative approaches, such as selective reinnervation[18,28] and nerve-muscle pedicle transfer,[20,29] also demonstrated promising outcomes, though comparative data remain limited.

Long-term outcomes and safety

Long-term follow-up studies, such as Lee et al,[23] with a mean follow-up of 107.7 months, have confirmed the durability of functional improvements. The persistence of positive outcomes over extended periods supports the potential of reinnervation as a viable long-term solution for UVFP.[25,26,35,39] However, the variability in follow-up duration across studies underscores the need for standardized long-term evaluation protocols. Laryngeal reinnervation procedures were generally safe, with low complication rates reported.[15-40] Nonetheless, risks such as partial reinnervation or synkinesis highlight the importance of meticulous surgical technique and careful patient selection.[45]

Comparison between laryngeal reinnervation and less invasive techniques

Laryngeal reinnervation, injection laryngoplasty, and medial thyroplasty (type I thyroplasty) are three principal surgical options for managing UVFP, each with distinct long-term functional outcomes. Although the therapeutic effects of laryngeal reinnervation are delayed, often taking several months to manifest, the long-term results are generally superior. The revision rate after laryngeal reinnervation is favorable, with an 8.3% revision rate reported in a study of 132 patients.[34] Further, a 10-year prospective study demonstrated that intraoperative reinnervation provided stable voice outcomes over a decade, with significant improvements in both subjective and objective voice parameters.[25] In contrast, Injection laryngoplasty offers immediate improvement in voice quality by augmenting the paralyzed vocal fold. A study of 42 patients with potentially recoverable UVFP found that 24% achieved full recovery, 10% had partial recovery with adequate voice, and 40% had no recovery of motion but compensated with adequate voice. However, 29% required further definitive intervention, indicating that while injection laryngoplasty can be effective in the short term, its long-term efficacy may be limited.[46] A systematic review and meta-analysis on autologous fat injection laryngoplasty reported improvements in perceptual outcomes and voice parameters in both short-term and long-term results. However, the durability of these improvements varies, and repeat procedures may be necessary.[47] Medial thyroplasty offers a mechanical solution by placing a permanent implant through a window in the thyroid cartilage to medialize the paralyzed vocal fold.[48] This technique provides immediate, durable, and often highly effective voice improvement. Because it does not rely on muscle activity or nerve regeneration, it is particularly well-suited for patients with long-standing or irreversible nerve injury. Long-term outcomes are typically stable, with high rates of patient satisfaction and improved phonatory function. A retrospective study of 40 patients followed for at least 5 years demonstrated significant improvements in voice quality, with enhancements in acoustic measurements such as jitter and shimmer.[49] While injection laryngoplasty and medial thyroplasty remains a valuable early or temporary treatments, particularly for acute or uncertain cases, laryngeal reinnervation offers more durable and physiologic restoration of function. It is particularly favored in younger patients or those with long-standing expectations for voice stability. Ultimately, the choice between the two depends on patient factors, timing, and clinical goals, but from a long-term functional perspective, laryngeal reinnervation is generally associated with superior and more lasting outcomes.

Challenges and future directions

One significant limitation of the current evidence base is the scarcity of RCTs. While the three RCTs included in this review[21,24,26] provided valuable comparative data, larger, multi-center RCTs are essential to establish the superiority of reinnervation over alternative treatments. The variability in surgical techniques and outcome measures further complicates evidence synthesis. Although many studies employed standardized tools such as the VHI and GRBAS scales, the inclusion of additional, study-specific metrics often hinders direct comparisons. Developing a core set of standardized outcome measures that includes both objective and patient-reported assessments would greatly enhance the consistency and comparability of future research.[50] Surgeon experience and the evolution of techniques over time may also influence results. Variability in findings can be attributed to learning curves and procedural refinements in studies conducted over multiple years or by individual surgeons.[39] Despite these limitations, laryngeal reinnervation holds theoretical advantages over static medialization procedures. By restoring physiological innervation, this approach has the potential to provide a more natural voice quality and promote ongoing neuronal plasticity, leading to long-term functional improvements.[51]

The subgroup analyses showed that some clinical data types contributed to heterogeneity in our analysis. The AC-RLN anastomosis was superior to all other techniques with the greatest increases of MPT (mean increase 5.2 seconds; 95% CI, 4.1 to 6.3 seconds) and reduction of VHI (mean reduction, 31.5 points; 95% CI, 26.8 to 36.2 points) at 12 months postoperatively ($P < 0.04$). Age was another relevant variable, although children improved significantly more than those older in MPT improvement (5.8 vs 4.3 seconds; $P = 0.02$) and VHI score reduction (35.8 vs 25.4; $P = 0.01$). The time of surgery was also significant in both MPT (5.7 vs 4.1 seconds; $P = 0.01$) and VHI results (33.9 vs 24.1; $P = 0.007$), with early reinnervation significantly superior to delayed one. Interestingly, the etiology of the UVFP—(iatrogenic or non-iatrogenic) had no impact on treatment success ($P = 0.38$). The better result in children is almost certainly due to more rapid regrowth in the more plastic nervous tissue of children, and the value of direct re-innervation emphasizes the importance of nerve repair at primary surgery wherever possible. Such data provide crucial information for clinical decision-making in the context of the limitations of the retrospective subgroup analysis requested.

Future research priorities

Future studies should focus on:

1. Conducting large-scale, multi-center RCTs to compare reinnervation techniques with alternative surgical interventions for UVFP, helping to establish clear superiority or complementary roles of each approach.
2. Standardizing reporting guidelines and outcome measures to facilitate meta-analyses and improve inter-study comparisons, ensuring more reliable synthesis of results.
3. Investigating the impact of factors such as time since nerve injury and preoperative laryngeal EMG findings on patient selection and outcome prediction, to better tailor treatment strategies.
4. Exploring combination therapies, such as integrating temporary injection augmentation with reinnervation, to optimize both immediate and long-term outcomes for patients.[52]
5. Advancing selective reinnervation techniques to minimize the risk of synkinesis and enhance functional outcomes, thus refining the precision and effectiveness of these procedures.

CONCLUSION

Laryngeal reinnervation procedures show promising outcomes in enhancing vocal function and quality of life for UVFP patients. Among these techniques, AC-RLN anastomosis is the most frequently utilized and has demonstrated generally favorable results. Alternative methods, including nerve-muscle pedicle transfer and selective reinnervation, also exhibit potential, though comparative data remain limited. Despite variability in surgical approaches, outcome measures, and study designs, laryngeal reinnervation offers distinct advantages over static medialization procedures, particularly in terms of achieving a more natural voice quality and facilitating ongoing neuronal remodeling. Future research should focus on standardizing outcome measures, refining patient selection criteria, and exploring combination therapies to optimize both short- and long-term results. Large-scale, multi-center RCTs and further advancements in selective reinnervation techniques are crucial to definitively establish the efficacy and long-term benefits of these procedures.

Research Ethics

The authors further confirm that any aspect of the work covered in this manuscript that has involved human patients has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

Intellectual Property

The authors confirm that they have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing the authors confirm that they have followed the regulations of our institutions concerning intellectual property.

Authorship

All listed authors meet the ICMJE criteria. The authors attest that all authors contributed significantly to the creation of this manuscript, each having fulfilled criteria as established by the ICMJE.

Conflict of Interest

The authors declare no conflict of interest. There has been no significant financial support for this work that could have influenced its outcome.

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