Article

Liuzijue Qigong: A Voice Training Method For Unilateral Vocal Fold Paralysis Patients

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Abstract

Objectives: Liuzijue Qigong (LQG), a kind of traditional Chinese health exercise (TCHE), is not only widely used to strengthen physical fitness and maintain psychological well-being in the elderly but has also been utilized to help improve respiratory function. As respiratory support is an important driving force for speech production, it is logical to postulate that the LQG training method with 6 monosyllabic speech sounds, *xū, hē, hū, sī, chuī*, and *xī*, can help individuals (1) experience a relaxing and natural state of speech production, (2) eliminate voice symptoms, and (3) improve their overall body function and mood. In the current study, we hypothesized that the LQG method with these 6 sounds can be effective in improving vocal function in subjects with unilateral vocal fold paralysis (UVFP) in comparison with a conventional voice therapy method.

Methods: A total of 48 patients with UVFP who met the inclusion criteria were randomly divided into 2 groups. Twenty-four subjects in the experimental group were trained with LQG, and those in the control group received conventional voice training (abdominal breathing and yawn-sign exercises) for a total of 4 sessions, twice a week. Patients in both groups were assessed with acoustic tests, the GRBAS scale, the Voice Handicap Index (VHI-10), and the Hospital Anxiety and Depression Scale (HADS) pre- and posttreatment. Statistical analysis was conducted using nonparametric tests and *t* tests.

Results: There existed significant changes in maximum phonation time (MPT), jitter, shimmer, normalized noise energy (NNE), GRBAS scores, VHI-10 scores, and grade of A in HADS scores pre- and posttreatment in both the experimental group and the control group ($P < .004$). However, no significant changes were seen posttreatment between the 2 groups ($P > .05$).

Conclusions: LQG could help improve vocal function in UVFP patients as our preliminary data showed no significant differences between LQG and conventional voice therapy methods.

Keywords

Liuzijue Qigong (LQG), unilateral vocal fold paralysis (UVFP), hoarseness, miscellaneous, GRBAS, VHI-10, HADS

Introduction

Unilateral vocal fold paralysis (UVFP) is characterized by immobility of 1 vocal fold (VF), which may cause failure of adduction or abduction and affect respiration and voice production.[1] Insufficient respiratory support can be seen in many UVFP patients in the form of incomplete closure of laryngeal valving due to VF paralysis and poor control of respiration during speech production. The vocal symptoms of UVFP include roughness, breathiness, and hoarseness, which reflect aperiodicity of the amplitude and frequency of VC vibration.[2,3] Breathiness refers to frictional noise as the air flow moves across the glottis. The glottal leakage in cases of paramedian and lateral UVFP is much greater than that observed in cases of median UVFP.

The key period for UVFP management is within 1 year, and timely and effective treatment could help patients restore voice function.[4,5] Patients are instructed in the yawn-sigh technique, semioccluded vocal tract exercises (SOVT), and Smith's accent technique (SAT) to produce words as softly and easily as possible and maintain a relaxed, open vocal tract without excessive compensatory movements of the unaffected VF.[6] Lip trill, also viewed as a sort of SOVT, is introduced to improve glottal closure.[6]

In ancient Chinese literature, Liuzijue Qigong (LQG) has been one of the most popular traditional Chinese health exercises (TCHE) to improve human health. LQG is somewhat equivalent to conventional voice therapy methods because both contain components that regulate respiratory functions.[7,8] Ancient Chinese people produced different sounds in the practice of LQG because the pronunciation of LQG varied among dialects, words, accents, and across time, although the different pronunciations shared the same written characters.[9] China's General Administration of Sport then issued an accurate, government-standardized pronunciation for LQG with 6 monosyllables corresponding to 6 real words, *xū, hē, hū, sī, chuī, xī*, in 2010, based on respiratory exercises using a medium vocal intensity.

When these words are split into syllable-initial and syllable-final portions, the production is quite similar to conventional voice therapy methods.[10] For example, 2 of the words begin with /h/ and are produced in a very relaxed way, similar to the yawn-sigh.[11,12] Four words begin with /s/, /x/, or /ch/ so that the tongue tip is elevated to the alveolar ridge or the hard palate with a small vocal tract constriction, forming a semiobstruction with elevated air resistance; this is somewhat similar to SOVT exercises that can make phonation easier and more economical. The final sounds of the 6 words are all high vowels. When producing high vowels, the increased acoustic impedance in the vocal tract can potentially decrease the impact force (collision or impact stress) during vocal fold oscillation, minimizing damage to the VF.[10] The method is also similar to the SAT, which selects /i/, /u/, and /ü/ as the speech materials (voice samples).[5] LQG consists of various combinations of syllable-initial and syllable-final sounds as a TCHE to regulate negative emotions.[13]

The potential psychological stress in UVFP patients is a key factor affecting the results of voice therapy. Individuals with UVFP often lack self-confidence and may avoid participation in social communication. Zheng et al[14] group suggested that LQG training could reduce panic and anxiety, while Sun et al[15] group reported that LQG training could improve life quality among the elderly. Both psychological and physiological changes are relevant to the "gentle" voice production encouraged through LQG training. Those who persevere in LQG training are more likely to be in a peaceful mood with positive emotions. Furthermore, TCHE could increase the frequency of social communication and promote positive psychological and physiological states.

Therefore, our study hypothesized that LQG could effectively improve and regulate respiratory and vocal function, as measured by acoustic analysis, auditory-perceptual evaluation, and a quality of life questionnaire, and could eliminate negative emotions, as measured by self-assessment of anxiety and depression.

Materials and methods

Participants

A total of 52 UVFP patients with various etiologies were recruited from the outpatient Department of Otolaryngology in the Seventh People's Hospital, Yueyang Hospital, and Changhai Hospital from June 2016 to July 2017.

Inclusion criteria

Inclusion criteria included: post-onset time of within 0 to 6 months, UVFP caused by central or peripheral nerve injury, post-onset time of more than 6 months, able to undergo acoustic data measurement, not impaired in cognition, able to cooperate with the speech therapist, signed an informed consent form.

Exclusion criteria

Exclusion criteria included patients with laryngeal cancer, hysterical aphasia, laryngeal nuclei, laryngeal syphilis, laryngeal diphtheria, and bilateral vocal fold paralysis and currently undergoing voice therapy. The following situations also disqualified the subjects from inclusion in the study: patients and family members who did not cooperate with the therapist, the onset of other serious diseases during treatment, no data collection posttreatment.

Spontaneous recovery of recurrent laryngeal nerve (RLN) injuries typically occurs within 6 months post onset.[4] Electromyography (EMG) examinations can be used to qualitatively analyze intrinsic laryngeal muscle activities and provide a prognosis for UVFP. Among those with a post-onset time within 0 to 6 months and UVFP caused by central or peripheral nerve injury who withdrew post-voice

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Table 1. Basic Characteristics of All Subjects Pretreatment.

Characteristic	LQG Group, n = 26	Control Group, n = 26	*P* Value
Age, mean ± SD	47.28 ± 14.69	45.72 ± 14.12	.697[a]
Male, %	38.5	34.6	.500[b]
Left paralysis, %	69.2	65.4	.500[b]
Acoustic parameters, mean ± SD			
MPT	4.43 ± 4.71	6.85 ± 7.33	.113[a]
Jitter	1.54 ± 1.12	1.85 ± 1.39	.647[a]
Shimmer	6.83 ± 3.51	7.41 ± 3.94	.580[a]
NNE	−3.10 ± 2.67	−2.48 ± 2.19	.487[a]
GRBAS scores, mean ± SD			
Grade	2.54 ± 0.71	2.62 ± 0.64	.723[a]
Roughness	2.38 ± 0.85	2.58 ± 0.70	.392[a]
Breathiness	2.42 ± 0.76	2.58 ± 0.70	.410[a]
Asthenia	2.35 ± 0.94	2.46 ± 0.95	.423[a]
Strain	2.19 ± 1.06	2.38 ± 0.98	.437[a]
VHI-10 score, mean ± SD	24.19 ± 10.80	27.31 ± 8.61	.314[a]
HADS scores, mean ± SD			
Anxiety	13.67 ± 1.61	17.17 ± 1.22	.0957[a]
Depression	11.08 ± 1.70	13.04 ± 1.35	.3577[a]

Abbreviations: HADS, Hospital Anxiety and Depression Scale; LQG, Liuzijue Qigong; MPT, maximum phonation time; NNE, normalized noise energy; VHI-10, Voice Handicap Index.
[a]Independent sample *t* test.
[b]Fisher's exact test.

training and those who did not undergo EMG examination or withdrew post-voice training, EMG examination showed that the RLN had recovered spontaneously and the movement ability of the affected VF was restored.

In our study, 1 subject in the LQG group failed to actively cooperate with the therapist and was excluded. In another case, the patient underwent RLN transplantation after the first session of voice treatment and was also excluded. Two patients in the control group who did not return for the EMG examination after 6 months were excluded. In summary, 4 cases were excluded from the study. Table 1 shows the basic information for all the subjects.

All the subjects were assigned to either the experimental group or the control group according to the random number generators in SPSS 21.0. The time post-onset and type of UVFP play an extremely important role in evaluating the voice quality of UVFP patients and were taken into consideration for the stratified randomization: post-onset time within 0 to 12 months with median paralysis, post-onset time within 0 to approximately12 months with paramedian paralysis, post-onset time over 12 months with median paralysis, and post-onset is over 12 months with paramedian paralysis. Median means that the affected VF is fixed at midline; patients with median UVFP lose mobility of each VF, and speech is arduous, resulting in voice fatigue and hoarseness. Paramedian means that the affected VF cannot autonomously move to the midline during speech, so the voice quality becomes weak and breathy during the closed phase. Lateral paralysis was excluded because of poor glottal closure, which prevented acoustic data from being measured.

Informed consent was obtained from all subjects, and the experimental protocol was approved by the local institutional review board.

Treatment program

The subjects in the experimental group were trained in LQG exercises, while those in the control group received conventional voice therapy. The patients in the experimental group warmed up with abdominal breathing, then tightened their lips and started LQG training, producing *xū, hē, hū, sī, chuī*, and *xī*. Voice therapy in the control group consisted of learning and practice of abdominal breathing, yawning during inspiration, and sighing (phonation) as long and as naturally as possible to produce *hā, hāi, hōu, hēi, huī*, and *huā* during expiration.

The patients underwent training for 30 minutes each time twice a week, for a total of 4 times in 2 weeks, in a voice training room; daily home practice lasted 30 minutes for a total of 2 weeks. The training was subject specific. Evidence showed that closely distributed (intensive) practice had positive effects on motor learning skills during voice treatment.[16] In our pre-experiment, a therapy duration of 2 weeks was shown to have positive effects[10] and was appropriate to provide patients the general idea of LQG and minimize the possibility of spontaneous recovery of the RLN interfering with the effect of LQG.

The social media app WeChat was used to monitor the progress of the home practice every Saturday and Sunday during the therapy sessions.

Voice analysis

The patients in both groups were examined with acoustic analysis, auditory perceptual evaluations of voice quality with the GRBAS scale, self-assessed quality of life using the VHI-10 scale, and self-assessed emotion using the HADS both before and after voice training.

Jitter, shimmer, and normalized noise energy (NNE) variables were measured in the acoustic signals of sustained phonation of /æ/ as acoustic correlates of the aperiodicity of vocal fold vibration, which are related to the perceptual signs of roughness and hoarseness. Dr. Voice (Tiger Electronics, Seattle, Washington, USA) was used in a quiet therapy room for the acoustic analysis.

GRBAS, a commonly used rating scale for the auditory-perceptual assessment of voice quality, represents grade, roughness, breathiness, asthenia, and strain. One speech pathologist (J.T.) specializing in voice disorders judged the perceptual voice quality of all voice samples using the scale, while the other 2 speech pathologists (T.W.W. and Q.L.) judged the perceptual voice quality of 14 voice samples that were randomly selected (approximately 30% of the total voice samples) to reduce subjective factors. A total of 210 data points (14 voice samples × 5 variables × 3 SLPs) were collected. Intraclass correlation (ICC) variables were all higher than .7 and varied from .798 to 1 with a mean value of .964, indicating that the perceptual evaluation results were highly consistent.

The VHI-10 is a self-assessment scale with a total of 10 questions that address functional, physical, and emotional aspects of the self-perceived handicap associated with voice problems. The Chinese version of the VHI-10 was based on the study of Li et al.[17]

The HADS can be used to assess anxiety and depression in patients. It consists of 14 items: 7 items for depression and 7 items for anxiety. The higher the score, the more likely the patient has anxiety and depression.

Statistical analysis

Statistical analysis was conducted with SPSS 21.0 software. A series of nonparametric tests and *t* tests were conducted to compare the differences in acoustic parameters pre– and post–voice training. For the GRBAS and VHI-10 scale ratings, Wilcoxon signed-rank and *t* tests were adopted. A 2 × 2 × 2 factorial design was used to compare the curative effects between the experimental and control groups at different points post-onset and with different types of UVFP.

Table 2. Comparison of Mean Changes Pre– and Post–Voice Training Within Each Group.

	LQG Group	Control Group
Outcome Measure (d)	Mean ± SD	
Acoustic parameters		
MPT	4.64 ± 3.33	2.71 ± 1.83
P value	<.001	<.001
Jitter	1.09 ± 0.84	1.35 ± 1.36
P value	<.001	<.001
Shimmer	4.33 ± 2.63	4.19 ± 4.12
P value	<.001	<.001
NNE	8.74 ± 4.28	7.78 ± 6.01
P value	<.001	<.001
GRBAS subscale		
Grade	1.58 ± 0.78	1.46 ± 0.83
P value	<.001	<.001
Roughness	1.83 ± 0.87	1.58 ± 0.93
P value	<.001	<.001
Breathiness	1.88 ± 0.80	1.54 ± 0.98
P value	<.001	<.001
Asthenia	1.96 ± 0.95	1.67 ± 1.09
P value	<.001	<.001
Strain	1.67 ± 1.13	1.42 ± 1.10
P value	<.001	<.001
VHI-10 scale	3.92 ± 4.02	3.88 ± 5.25
P value	<.001	<.001
HADS subscale		
Anxiety	2.58 ± 0.78	4.13 ± 0.99
P value	.006	.002
Depression	1.96 ± 0.87	2.21 ± 1.05
P value	.032	.043

Abbreviations: d, differences pre– and post–voice training; HADS, Hospital Anxiety and Depression Scale; LQG, Liuzijue Qigong; MPT, maximum phonation time; NNE, normalized noise energy; VHI-10, Voice Handicap Index.

A total of 12 outcome variables were evaluated in the study. To minimize Type I errors, the *P* value for the level of significance (alpha) was .004, according to calculation of the Bonferroni correction.

Results and analysis

Analysis of the effect of voice training

Maximum phonation time (MPT) increased significantly, while jitter, shimmer, and NNE decreased significantly post-treatment for both the experimental group and the control group, reaching statistical significance ($P < .001$). The GRBAS rating and the VHI-10 scale score also decreased significantly for both groups posttreatment ($P < .001$) (compare Table 1 and Table 3). The results showed that both the experimental treatment and the control treatment had a good effect on the improvement of voice problems (see Table 2).

Table 3. Comparison of Mean Changes Between Both Groups Post–Voice Training.

Outcome Measure	LQG Group	Control Group	P Value
	Mean ± SD		
Acoustic parameters			
MPT	9.44 ± 5.17	10.02 ± 6.56	.404
Jitter	0.35 ± 0.46	0.44 ± 0.52	.234
Shimmer	2.16 ± 1.24	2.91 ± 2.03	.046
NNE	−12.07 ± 4.77	−10.38 ± 5.93	.043
GRBAS subscale			
Grade	0.92 ± 0.93	1.13 ± 0.95	.441
Roughness	0.50 ± 0.66	0.96 ± 0.96	.084
Breathiness	0.50 ± 0.66	1.00 ± 0.98	.067
Asthenia	0.33 ± 0.57	0.75 ± 0.90	.088
Strain	0.46 ± 0.78	0.92 ± 0.88	.039
VHI-10 scale	19.38 ± 11.70	22.71 ± 10.44	.369
HADS subscale			
Anxiety	11.08 ± 1.70	13.04 ± 1.35	.417
Depression	10.83 ± 1.67	12.13 ± 1.41	.584

Abbreviations: HADS, Hospital Anxiety and Depression Scale; LQG, Liuzijue Qigong; MPT, maximum phonation time; NNE, normalized noise energy; VHI-10, Voice Handicap Index.

Comparison of the effect of voice training between the 2 groups

The differences in MPT, jitter, shimmer, and NNE posttreatment between the 2 groups were not statistically significant ($P > .004$), suggesting that the 2 treatment groups experienced similar effects for improving insufficient respiratory support and aperiodicity of vocal fold vibration (see Table 3). Similarly, improvements in the GRBAS scores, the VHI-10 scores, and the HADS scores were not significantly different between the 2 groups ($P > .004$; see Table 3).

Changes in the acoustic parameters of the 2 groups posttreatment were not affected by the UVFP post-onset time ($P > .004$). The changes in jitter, shimmer, and NNE posttreatment were affected by the type of UVFP ($P \leq .004$), while the changes in MPT were not affected ($P > .004$; see Table 4).

Discussion

Hoarseness is the key symptom of UVFP that sometimes accompanies depression and anxiety. The etiologies of UVFP vary from person to person and include brain diseases, iatrogenic trauma (surgery of the thyroid, carotid artery, cervical spine, etc), malignant tumors, viral infections (eg, herpes zoster, herpes simplex virus, and cytomegalovirus), and metabolic and idiopathic diseases.[18] To enlarge the sample size, all sorts of UVFP were included in this study. Our study eventually verified that LQG could effectively improve hoarseness and address negative emotions among patients with various etiologies of UVFP.

Table 4. The Effect of the Correlation of UVFP Post-Onset Duration and Type With Acoustic Parameters on Treatment.

Outcome Measure	P-Value	
	Time Post-Onset	Type
Acoustic parameters		
MPT	.173	.106
Jitter	.797	.004
Shimmer	.157	.001
NNE	.057	.002

Abbreviations: MPT, maximum phonation time; NNE, normalized noise energy; UVFP, unilateral vocal fold paralysis.

LQG improved respiratory function

UVFP patients often suffer from elevated glottal flow but excessive lung pressure due to incomplete glottal closure during phonation. The average airflow rate and the subglottal pressure/lung pressure are higher than normal. Dastolfo et al[19] suggested that voice training could reduce those 2 parameters in UVFP patients.

In our study, the changes in MPT were not significantly different between the 2 groups ($P > .004$). When patients use thoracic breathing, the contraction of sternocleidomastoid and scalene muscles increases neck tension and general vocal fatigue. However, better coordinated activities of the intercostal muscles and abdominal muscles occurred during abdominal breathing in the control group, which could help patients increase inspiratory capacity in a relaxed state, potentially reducing glottal impact stress during phonation and extending the maximum phonation time. Breathing with retracted lips and abdominal breathing, as recommended in LQG, are used to control the airflow speed, which could reduce the average airflow rate and improve respiratory and vocal function. Therefore, it was considered that the 2 treatments had a similar effect on breath support (see Table 3).

LQG improved vocal function

Some studies have shown that glottal width could be related to the type or mode of phonation: When an individual speaks with "glottal attack," the glottal width can be less than 0; when SOVT or SAT is used, the glottal width is approximately 0 mm to 0.5 mm; when yawn-sigh is used, the glottal width is 1 mm to 2 mm; and the glottal width is more than 3 mm in cases of breathy voice.[20]

There were no significant differences in the changes of jitter, shimmer, and NNE between the 2 groups posttreatment ($P > .004$). UVFP patients with poor glottal closure often overcompensate, resulting in a lower output-cost ratio (OCR) for phonation[21] and hoarseness.

To minimize the glottal attack mode of phonation, LQG was used in the experimental group. The patients were taught to produce *hē* and *hū* to achieve a relatively relaxed and natural state of phonation (similar to the yawn-sigh) and *xū, sī, chuī*, and *xī* (similar to SOVT) and /i/, /u/, and /ü/ (similar to SAT) to decrease laryngeal tension and achieve a more complete glottal closure. At that time, the glottal width was approximately 0.5 mm, which indicates high vocal economy as the OCR was found to reach its maximum value, a glottal width of 0.5 mm.[21] The 6 monosyllabic real words used in the control group all started with the consonant /h/, which could be regarded as a soft-onset type of phonation to reduce laryngeal muscle tension (see Table 3).

Generally, both groups of patients benefited from both the LQG and the conventional voice training, as reflected by the SLP-rated voice quality, measured with the GRBAS scale, and the self-assessed handicap, measured with the VHI-10 scale (see Table 3).

LQG led to positive emotion

In our study, one factor that we focused on was emotion. Li et al[13] suggested that LQG could regulate mood in individuals. We hoped that those who persevered with the treatment program could be equipped with better emotion compared to patients who anxiously gave up voice training halfway through. However, there were no significant differences in the anxiety and depression domains of the HADS score between the groups posttreatment ($P > .004$). That is, the improvement in the anxiety and depression scores in the daily lives of UVFP patients was similar in both groups (see Table 3). Further research is required to better show whether patients' emotions could truly improve after practicing LQG with 6 body movements corresponding to the 6 words.

The relationship between the UVFP post-onset time and voice training

Chen et al[4] suggested that the critical period for voice training was within 1 year; however, our study showed that there were no significant differences related to the time post-onset of paralysis in acoustic parameters between the 2 groups post–voice training ($P > .004$; see Table 4). A possible reason is that those with a post-onset duration of more than 12 months often speak with a high degree of glottal attack to overcompensate for any long-term hoarseness and breathiness. The regularity of VF vibration is negatively impacted by vocal misuse. Although surgical intervention can move the affected VFs to the midline to reduce glottal width and breathiness, bad compensatory habits such as hyperadduction are not changed, resulting in persistent voice problems such as hoarseness and breathiness. Voice therapy can help correct compensatory vocalization habits and restore the regularity of vocal fold vibration. LQG can take advantage of SOVT-like and SAT-like strategies to maintain the optimal glottal width of approximately 0.5 mm associated with a barely abducted glottis, thus reducing breathiness and improving hoarseness.

The relationship between the type of UVFP and voice training

There were statistically significant differences across the types of paralysis in the acoustic parameters between the two groups posttreatment ($P \leq .004$, as shown in Table 4), indicating that the VF paralysis type had a significant influence on the therapeutic effect.

Mattioli et al[22] summarized 2 stages of voice treatment: promotion of glottal closure and improvement of voice quality. The glottal width in cases of paramedian UVFP was larger than that in cases of median UVFP because it was much more difficult for subjects with paramedian UVFP to cross midline for compensation. Our subjects needed to spend more time practicing the correct way to promote glottal closure and reduce breathiness. Therefore, the use of the same 4 voice training times might lead to a diminished curative effect; that is, the effect of voice training for subjects with median UVFP may have been better.[4]

There were no significant differences associated with the type of paralysis in MPT changes between the 2 groups posttreatment ($P > .004$). It has been suggested that the OCR is positively correlated with intraglottal impact stress.[21] Although the average airflow produced by subjects with paramedian UVFP was higher than produced by patients with median UVFP, OCR could actually be lower because of the lower acoustic pressure resulting from the incomplete glottal closure. Hence, through practicing abdominal support, subjects with paramedian UVFP might have been more capable of developing relaxed phonation and thus prolonging the maximum phonation time. Hence, changes in MPT may not be directly linked to the type of UVFP.

Limitations and outlooks

First, in our study, voice therapy lasted for only 2 weeks because the treatment plan aimed to regulate respiratory and vocal functions. If the training frequency and duration were increased and body movements to correspond to the production of the 6 real words were added, the LQG method might become even more effective.

Second, aerodynamic analysis has often been used to measure subglottal pressure and average airflow in clinical practice. In future studies, differences in air flow and pressure when producing *xū, hē, hū, sī, chuī*, and *xī* should be evaluated to determine how they might be affected.

Finally, we will continue our research with a considerably enlarged sample size.

Conclusions

LQG could improve hoarseness in UVFP patients, and it showed a therapeutic effect similar to that of the conventional voice therapy approaches of abdominal breathing and yawn-sign exercises. LQG offers a convenient voice training method without limitations of treatment site.

The time since the onset of UVFP did not seem to affect jitter, shimmer, and NNE measures posttreatment, while the type of UVFP seemed to affect these measures. The treatment effect seemed to be better for the median type of vocal fold paralysis than for the paramedian type of paralysis. The post-onset time and type of UVFP did not seem to significantly affect MPT.

Authors' Note

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Ethics approval and consent to participate

The study was approved by the ethics committee of Yueyang Hospital. Patients voluntarily joined the trial and provided informed consent, and we ensured that their legitimate rights and interests would not be violated.

Consent for publication

The results of the study were published on the premise of patient agreement to publication for scientific purposes, and the manuscript was approved by all authors for publication.

Availability of data and material

All of the data and materials are available.

Declaration of Conflicting Interests

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

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