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ORIGINAL RESEARCH

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Age-dependent treatment effect of vocal fold steroid injection for benign vocal fold lesions

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Abstract

Objective: Benign vocal fold lesions (BVFLs) cause voice disorders and impair social life. Recently, office-based vocal fold steroid injection (VFSI) has gained attention as a minimally invasive treatment for BVFLs. This study aimed to analyze the age-dependent treatment effect of VFSI and to clarify the indications for treatment.

Methods: In this retrospective cohort study, a total of 83 patients with BVFLs were treated with a similar regimen of VFSI. Three or four months after the injection, age-dependent phonological functions were evaluated. The differences between pre- and post-treatment findings were analyzed using the Wilcoxon matched-pair signed-rank test, and the correlation between patient age and improvement rates were determined by Pearson's correlation coefficient.

Results: Improvement in voice handicap index (VHI), which was the primary endpoint, was observed. Subjective and objective voice quality measurements also showed significant improvements. Subgroup analyses revealed that there was no age-related difference in the improvement of voice quality and that there was no improvement in aerodynamic effect in patients over 45 years of age.

Conclusion: This study clarified the age-dependent treatment effect of VFSI and provided the important suggestion of establishing indication criteria for BVFLs. The study results provided clarity on the indication criteria of VFSI and served as an important indicator for tailoring treatment to patients' needs.

Level of Evidence: 4

KEYWORDS
age-dependent treatment effect, benign vocal fold lesions, office surgery, steroid injection

1 | INTRODUCTION

Benign vocal fold lesions (BVFLs), such as chorditis, vocal nodules, vocal polyps, Reinke's edema (RE), and vocal scar, can cause various voice disorders, mainly breathy voice and hoarseness. The histological changes of BVFL include inflammation, increased vessel wall thickness, edema, and thickening of the basement membrane of RE. The irregular morphology of the mucosal-free margins of the vocal folds caused by these lesions results in an imbalance of bilateral vocal fold vibration and an enlarged glottal gap, which is the main cause of voice disorders.

Conservative treatments, such as medication, voice hygiene, and voice rehabilitation, are recommended as the primary therapy for BFVLs.[1] However, some cases are resistant to these conservative treatments, and cannot maintain voice rest due to social demands.[1–4] Conversely, laryngeal microsurgery performed under general anesthesia, although well proven to be effective,[5] is invasive and has the risk of vocal fold scarring and/or granulation.[4] Recently, vocal fold steroid injection (VFSI) has become more popular as an intermediate between conservative treatments and laryngeal microsurgery.[2,6,7] The advantages of VFSI include minimal invasiveness, can be performed under office-based local anesthesia, high treatment effect, repeatability, low risk of scarring, and cost-effectiveness.[2,6–9] Notably, VFSI has been used for more than 50 years, and several studies, including systemic reviews and meta-analyses,[10] have been published. In our previous study, VFSI was proved useful for BVFL, although the therapeutic effect varied depending on the type of lesion.[11]

However, no study has reported the differences in treatment effectiveness due to patient characteristics. Structural changes in the vocal folds are strongly associated with age and with gender.[12–15] The structure of the vocal folds differs between the elderly and the young. For example, in the elderly, atrophy of the vocal folds induces an increase in the glottal gap, and several studies have demonstrated the changes in vocal fold frequency with age. Therefore, differences in response to VFSI by age are observed. This clarification may be necessary to determine the indication for VFSI. Given that the effect of treatment varies with age, it is important to ascertain the age-dependent treatment effects to determine whether the efficacy of VFSI meets the needs of patients. Phonological function assessment can be subdivided into subjective evaluation, voice quality, aerodynamic analysis, and acoustic analysis. Depending on the patient's needs and available treatment options, a detailed analysis of phonological functions at different ages would reveal the indications and suitability of various treatment modalities for the patient's needs. The current study was conducted with the improved voice handicap index (VHI) as the primary endpoint and improvement in aerodynamic analysis; acoustic analysis; and total grade, roughness, breathiness, asthenia, and strain (tGRBAS) score as the secondary endpoints to verify the age-specific treatment effect of VFSI on BVFL and to establish the criteria for determining the indications.

2 | PATIENTS AND METHODS

2.1 | Study participants

This retrospective cohort study was approved by the Institutional Review Board of the International University of Health and Welfare (19-S-2). All participants provided written informed consent for VFSI to be performed and the possibility of future retrospective studies; the design of this study was not presented to them prior to treatment. Consent for the retrospective study was obtained by opt-out after the completion of treatment. A total of 83 patients (13 males and 70 females) who underwent VFSI for BVFL from 2014 to 2017 at the International University of Health and Welfare of Tokyo Voice Center were enrolled in the study. The participants overlapped with our previous study.[11] The participants' age ranged from 14 to 82 years (mean, 45.3 years): 44 and 39 patients were <45 and ≥45 years old, respectively. Among the 83 patients, 28 presented with vocal nodules; 15 with RE; 13 with chorditis; 11 with polyps; 8 with scars; and 8 with other lesions, including laryngeal granuloma and bamboo node of vocal folds. All participants had undergone multiple sessions of voice hygiene and voice therapy by skilled speech–language–hearing therapists for >3 months, but the results were unsatisfactory. The patients were offered both laryngeal microsurgery and office-based VFSI, and all patients chose VFSI. More than two to three phonosurgeons and speech–language–hearing therapists categorized the participants by referring to their clinical history and pre-treatment stroboscopic findings in the regular clinical conference. Participants were divided into two groups at age 45 years because they were almost equal in number, and power analysis showed a similar trend.

2.2 | VFSI procedure

VFSI was performed as previously reported.[11] Briefly, the pharynx and larynx were completely anesthetized with 4% lidocaine. Triamcinolone acetonide 3 mg was dissolved in a 0.3 ml depot solution (KENACORT-A; Bristol-Myers Squibb K. K., Tokyo, Japan) per side and then spread into the *superficial lamina propria* not into the muscle layer, by using a 23-gauge injection needle (Varixer; TOP Corp., Tokyo, Japan) under the transnasal fiberscopic monitoring of the larynx. Most of the patients had bilateral lesions and were injected bilaterally. Seven patients with unilateral lesions, mainly vocal polyps, were injected unilaterally. In all cases, only a single injection was performed. One to two hours after injection, the vital signs were checked, and laryngeal findings were observed for adverse events, such as allergy or abnormal hemorrhage. Patients were prescribed voice rest for 24 h.

2.3 | Voice laboratory measurements

Phonological evaluation by voice laboratory measurements was performed before the injection and 3–4 months after the injection. In this study, vowel utterances were used as stimuli to collect all outcome

data. The Japanese version of VHI,[16] which is a subjective voice assessment method, was used as the primary endpoint. Other secondary endpoints included the tGRBAS (the sum of the scores on the tGRBAS scale), maximum phonation time (MPT), mean airflow rate (MFR), pitch range (PR), jitter percentage (jitter%), shimmer percentage (shimmer%), speech fundamental frequency (SFF), noise-to-harmonic ratio (NHR), and sound pressure level (SPL). The MPT was measured using a stopwatch. MFR and SPL were measured using a PS-77E phonatory function analyzer (Nagashima Medical Instruments Co., Ltd., Tokyo, Japan). Jitter%, shimmer%, and NHR were assessed using a computerized speech lab (KayPENTAX, Montvale, NJ, USA). PR and SFF were semi-objectively measured using a keyboard and pitch meter. Treatment effect was assessed by comparing the pre- and post-treatment values of each voice laboratory measurement in all patients and subgroups. Patients were divided into two groups for analysis on the basis of their age into: patients below 45 years (<45) and patients ≥45 years. The improvement rates of VHI, tGRBAS, MPT, and MFR were calculated using the following formula: [(post-treatment value − pre-treatment value)/pre-treatment value]. The improvement rates were compared between the two groups. The lower values of VHI, tGRBAS, and MFR and the higher values of MPT indicates greater improvement and better treatment effectiveness. Furthermore, correlation with age was also performed.

2.4 | Statistical analysis

The differences between the means of pre- and post-treatment findings for the subgroups divided on the basis of age were analyzed using the Wilcoxon matched-pair signed-rank test. Significance was determined as $p < .01$ to avoid multiple comparison

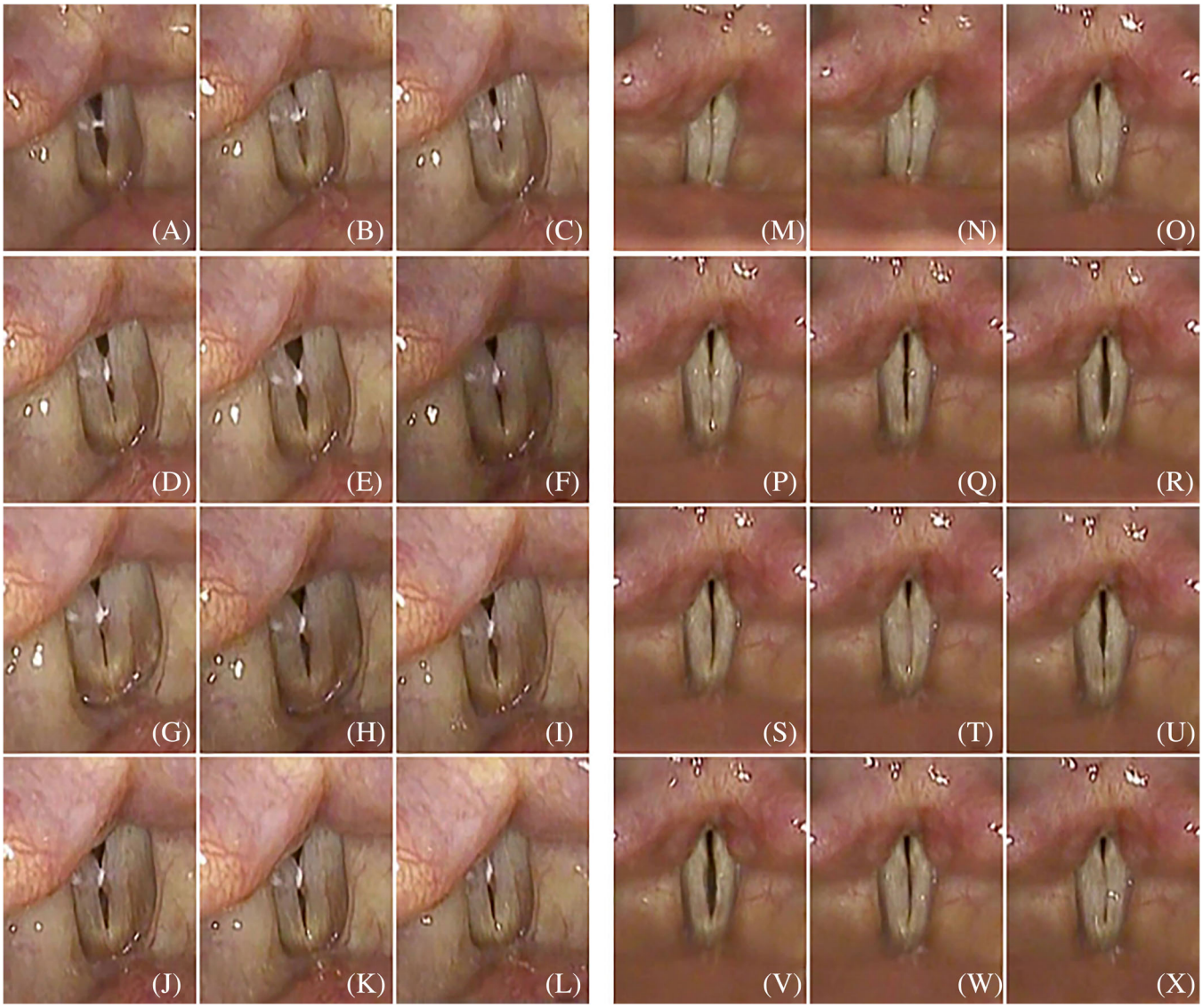

FIGURE 1 Stroboscopic vocal fold examination of a representative patient with vocal nodules. The patient was a 54-year-old woman and presented with severe dysphonia. Stroboscopy at the first visit showed vocal nodules (A–L); the free edges of the vocal folds were elevated, and there were glottic insufficiency and decreased vibration. VFSI was performed for the bilateral vocal folds. Three months after VFSI, her voice significantly improved. Stroboscopy showed reduced vocal fold elevation and glottic insufficiency and improved vocal fold vibration (1M–1X).

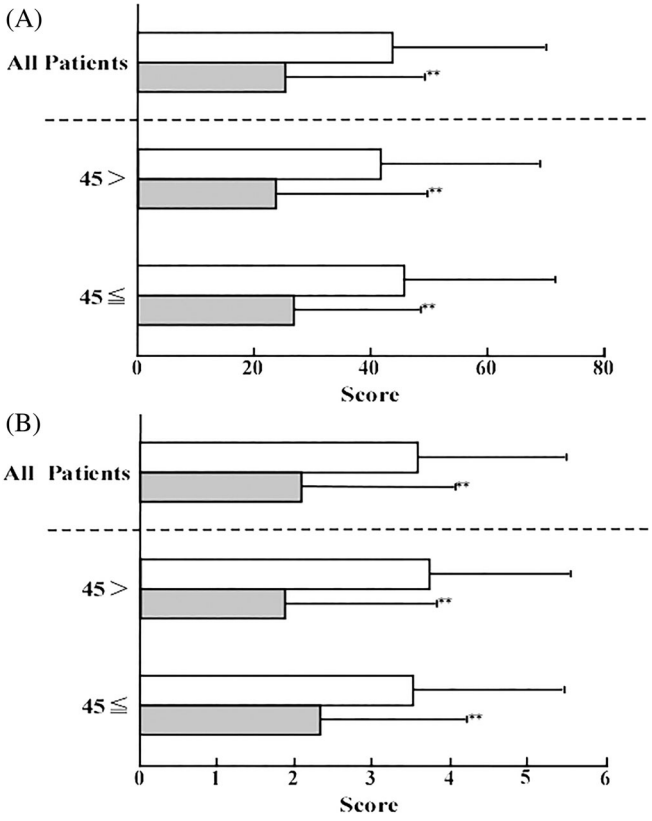

FIGURE 2 Pre- and post-treatment values of voice handicap index (VHI) scores and total grade, roughness, breathiness, asthenia, strain (tGRBAS) scale score. (A) Pre- and post-treatment values of total VHI scores. (B) Pre- and post-treatment values of tGRBAS scale scores. Open bars indicate pre-injection scores, and closed bars indicate post-injection scores. $^{**}p < .01$. "<45" means patients under 45 years of age, and "≤45" means patients who are 45 years of age or older

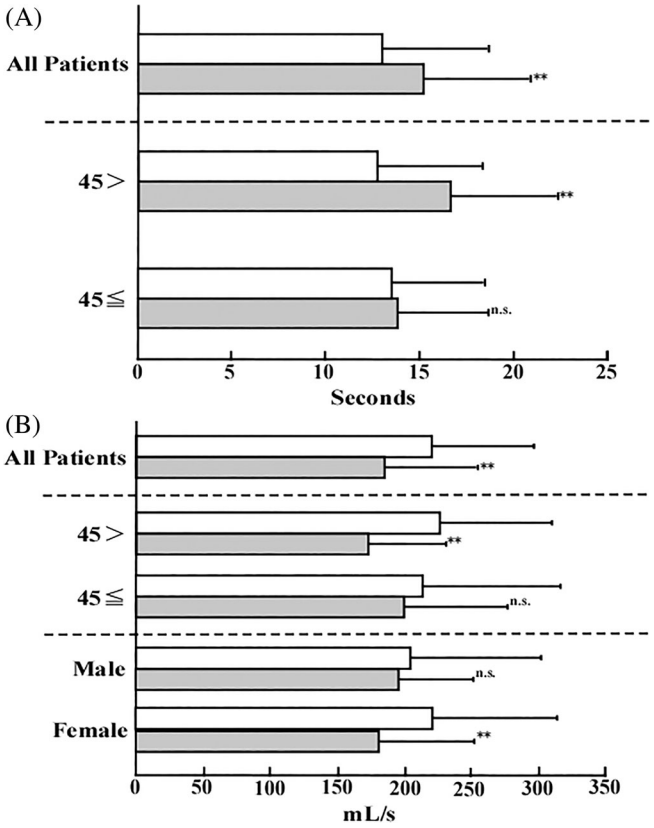

FIGURE 3 Pre- and post-treatment values of maximum phonation time (MPT) and mean airflow rate (MFR). (A) Pre- and post-injection values of MPT. (B) Pre- and post-injection values of MFR. Open bars indicate pre-injection scores, and closed bars indicate post-injection scores. $^{**}p < .01$. n.s. means no significant difference. "<45" means patients under 45 years of age, and "≤45" means patients who are 45 years of age or older

problems. The correlation between patient age and improvement rates of VHI, tGRBAS, MPT, and MFR was determined by Pearson's correlation coefficient. Significance was determined as $p < .01$ or $p < .05$. All statistical analyses were performed using SPSS statistical software (version 19.0, Armonk, NY, USA). To confirm the reliability of this study, we measured the effect size (η^2) of the primary outcome, VHI, and MPT. The values for all patients <45 and ≥45 years of age were greater than 0.8. These indicated that the study was sufficiently reliable.

3 | RESULTS

3.1 | Adverse events

A few days after VFSI, thickening and hematoma of the vocal folds and moderate to severe voice hoarseness were observed in some patients. However, all symptoms completely disappeared within 1 month. Diplophonia was observed in approximately 20 patients but resolved within 2–3 months in all patients.

3.2 | Representative cases

Figure 1 and Video S1 show the stroboscopic findings of a representative case. The patient was a 54-year-old woman who presented with severe dysphonia. Stroboscopy at the first visit revealed vocal nodules (Figure 1A–L); the free edges of the vocal folds were elevated, and glottic insufficiency and decreased vibration were observed. VFSI was performed for the bilateral vocal folds. Three months later, her voice significantly improved. Stroboscopy revealed reduced vocal fold elevation and glottic insufficiency and improved vocal fold vibration (1M–1X). The VHI score decreased from 60 to 33, and the MPT improved from 11.5 s to 13.0 s. The VHI scores and other voice laboratory measurements of most patients also improved.

3.3 | Changes in voice laboratory measurements after VFSI

The pre- and post-treatment VHI scores of all patients significantly improved from 44.8 ± 26.4 to 25.3 ± 23.9 (mean ± standard

TABLE 1 Pre- and post-treatment values of SFF, PR, shimmer%, and jitter% in all patients, patients <45 years old, and patients ≥45 years old (mean ± standard deviation)

	SFF (Hz)		PR (ST)		Shimmer%		Jitter%	
	Pre-	Post-	Pre-	Post-	Pre-	Post-	Pre-	Post-
All patients	175.3 ± 47.7	185.1 ± 48.2**	25.9 ± 7.9	29.1 ± 7.2**	4.6 ± 2.2	3.3 ± 1.9**	1.9 ± 1.4	1.6 ± 2.32
<45	181. 5 ± 42.1	192.8 ± 44.5**	27.1 ± 7.9	30.3 ± 6.5**	4.2 ± 2.1	3.2 ± 1.3**	1.8 ± 1.3	1.3 ± 0.6**
≥45	168.4 ± 49.1	183.6 ± 52.3**	24.5 ± 7.9	27.7 ± 7.7**	5.1 ± 2.2	3.9 ± 2.5**	1.9 ± 1.5	1.9 ± 3.3

Abbreviations: SFF, speech fundamental frequency; PR, pitch range; shimmer%, shimmer percentage; Jitter%, jitter percentage.
**$p < .05$.

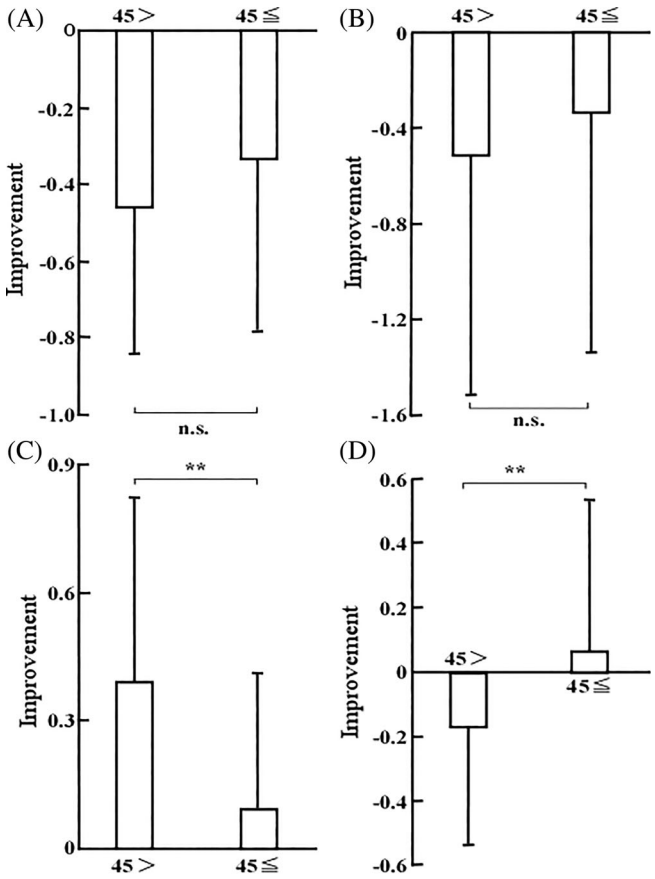

FIGURE 4 Comparison of the improvement rate between patients subgroups. (A) Voice handicap index; (B) total grade, roughness, breathiness, asthenia, strain; (C) maximum phonation time; and (D) mean airflow rate. **$p < .01$. n.s. means no significant difference. "<45" means patients under 45 years of age, and "≤45" means patients who are 45 years of age or older

deviation) ($p = 5.46E{-}11$). Subgroup analysis revealed that patients <45 and ≥45 years of age showed significant improvement from 41.9 ± 27.1 to 23.8 ± 25.9 ($p = 7.5E{-}08$) and 45.8 ± 25.9 to 26.9 ± 21.8 ($p = 6.07E{-}06$), respectively (Figure 2A). The pre- and post-treatment tGRBAS of all patients significantly decreased from 3.6 ± 2.1 to 1.9 ± 1.9 ($p = 4.3E{-}06$). Subgroup analysis revealed that the tGRBAS of patients <45 and ≥45 years of age significantly decreased from 3.7 ± 1.8 to 1.8 ± 1.9 ($p = 7.5E{-}10$) and 3.5 ± 1.9 to 2.3 ± 1.9 ($p = .00016$), respectively (Figure 2B).

The MPT and MFR are shown as the results of aerodynamic measurements in Figure 3. The MPT of all patients significantly improved from 13.1 ± 5.6 s to 15.4 ± 5.6 s ($p = 3.7E{-}05$). Subgroup analysis showed that the MPT of patients <45 years significantly improved from 12.7 ± 5.1 s to 16.7 ± 5.7 s ($p = 2.6E{-}05$). However, no such significance was observed in patients ≥45 years (Figure 3A) ($p = .69$). The MFR of all patients significantly decreased from 219.4 ± 92.8 ml/s to 185.3 ± 68.8 ml/s ($p = .00017$). Subgroup analysis revealed that the MFR of patients <45 years decreased from 225.2 ± 84.5 ml/s to 172.1 ± 58.3 ml/s ($p = 2.6E{-}05$), and no significant difference was observed in patients ≥45 years (Figure 3B) ($p = .31$). Given that MFR is gender specific, MFR was classified by gender. Female patients showed a significant decrease from 222 ± 92 ml/s to 182 ± 71 ml/s, whereas male patients showed no significant change with treatment. However, because of the large difference in the number of subjects, it is unclear whether these results indicate a difference in treatment effect by gender. The SFF, PR, shimmer%, and jitter % are shown as acoustic measurements in Table 1. The SFF of all patients significantly increased from 175.3 ± 47.7 Hz to 185.1 ± 48.2 Hz ($p = 8.3E{-}05$). Subgroup analysis revealed that the SFF of patients who are <45 and ≥45 years of age significantly increased from 181.5 ± 42.1 Hz to 192.8 ± 44.5 Hz ($p = .0099$) and 168.4 ± 49.1 Hz to 183.6 ± 52.3 Hz ($p = .0037$), respectively. The PR of all the patients significantly increased from 25.9 ± 7.9 ST to 29.1 ± 7.2 ST. Subgroup analysis revealed that the PR of patients who are <45 years and ≥45 years of age significantly increased from 27.1 ± 7.9 ST to 30.3 ± 6.5 ST ($p = .005$) and 24.5 ± 7.9 ST to 27.7 ± 7.7 ST ($p = .0042$), respectively. The shimmer% of all patients significantly decreased from 4.6 ± 2.2% and 3.3 ± 1.9% ($p = 1.7E{-}05$). Subgroup analysis revealed that the shimmer% of patients who are <45 and ≥45 years of age significantly decreased from 4.2 ± 2.1% to 3.2 ± 1.3% ($p = .0013$) and 5.1 ± 2.2% to 3.9 ± 2.5% ($p = .0043$), respectively. The jitter% of patients <45 years significantly decreased from 1.8 ± 1.3% to 1.3 ± 0.6% ($p = .003$). No such significance in jitter % were identified in all patients ($p = .15$) and patients ≥45 years ($p = .99$).

To clarify the therapeutic effect of age on VFSI, the difference in improvement rates between patients who are <45 and ≥45 years of age were compared. No significant differences were observed in VHI and tGRBAS scores between patients who are <45 and ≥45 years of age (Figure 4A,B) ($p = .17$ and $p = .17$, respectively). On the other

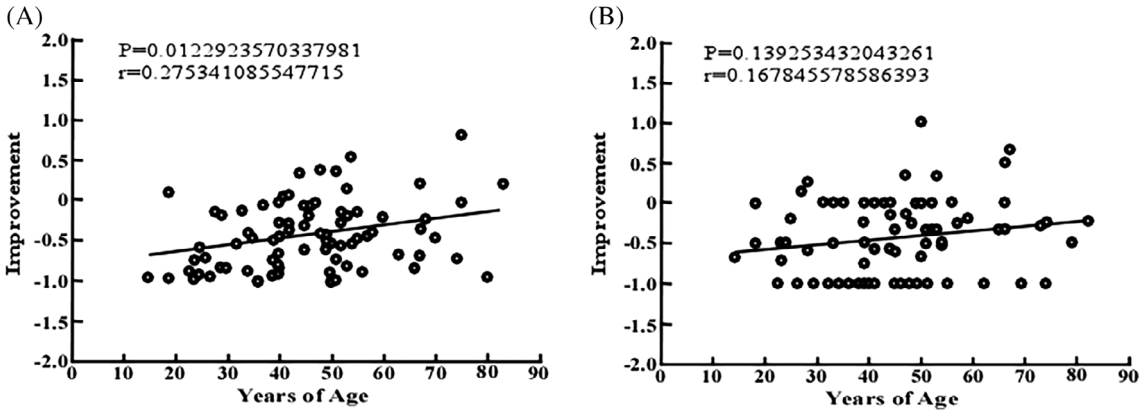

FIGURE 5 The correlation between improvement rate and age. (A) Voice handicap index improvement rate and age. (B) Total grade, roughness, breathiness, asthenia, strain improvement rate and age. (A) Showed significant correlation.

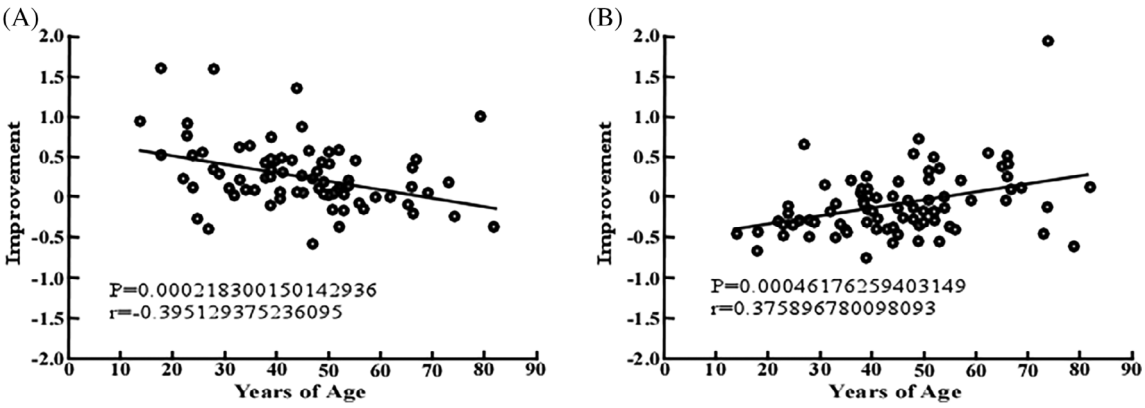

FIGURE 6 The correlation between improvement rate and age. (A) Maximum phonation time improvement rate and age. (B) Mean airflow rate improvement rate and age. Both showed significant.

hand, MPT scores showed mean improvements of 0.39 ± 0.43 and 0.09 ± 0.31 in patients who are <45 and ≥45 years of age, respectively. Significant differences were observed between these subgroups (Figure 4C) ($p = .00057$). Furthermore, significant improvements in MFR of −0.17 ± 0.27 and 0.08 ± 0.46 in patients who are <45 and ≥45 years of age (Figure 4D) were observed, respectively ($p = .00588$).

The improvement rate of VHI and patient age showed significant correlation with a correlation coefficient of 0.27 (Figure 5A) ($p = .012$), and tGRBAS showed no such correlation (Figure 5B) ($p = .13$). MPT and MFR, which indicate aerodynamic effect, significantly correlated with age with correlation coefficients of 0.39 (Figure 6A) ($p = .00021$) and 0.37 (Figure 6B) ($p = .00046$), respectively.

4 | DISCUSSION

The main advantage of VFSI is the ability to inject high concentrations of steroids locally with minimal systemic steroid effects.[2,6,10] Moreover, compared with other treatments, such as voice therapy and laryngeal microsurgery, VFSI requires less time for voice rest and makes it easier to schedule work after treatment.[2,11] Hence, VSFI could be a great "bridge" when conservative treatments (e.g., voice coverage and voice therapy) fail and when the patient has insufficient time to undergo laryngeal microsurgery.[2,3] The basis of our treatment for BVFL is conservative, such as medication and voice therapy. VFSI has been reported to be effective in the treatment of vocal nodules, chorditis, vocal polyps, RE, vocal scars, mucus retention cysts, and laryngeal granulomas.[1–3,6,10,11,17–19] However, no report has focused on the patient's characteristics. Although VFSI is an effective treatment for BVFL, it has some side effects, such as vocal fold muscle atrophy. Therefore, it should be strictly tailored to the patient's needs. For this purpose, we conducted voice laboratory measurements in detail regarding changes in treatment effect with age. As reported in many studies, VFSI significantly improved the VHI, tGRBAS, MPT, MFR, SFF, PR, and shimmer% scores in all patients. However, when patients were divided on the basis of age, there was significant improvement in tGRBAS, MPT, MFR, SFF, PR, shimmer%, and jitter% scores in patients <45 years, but no significant improvement was observed in MPT, MFR, SFF, and jitter% scores in patients ≥45 years.

The present study showed that there was no significant differences in VHI and tGRBAS of the improvement between <45 years and ≥45 years, but significant differences were present in the MPT and MFR scores. Furthermore, VHI showed a significant correlation with patient age. MPT and MFR, which are related to aerodynamic outcomes, showed a significant reduced effect with age. The study findings suggest that VFSI is an effective method, but the treatment effect in terms of aerodynamic outcomes may vary with age. This might be the reason for the decreased effectiveness of VHI with increasing age. Nevertheless, the study findings showed that VFSI is effective regardless of age; although age has little effect on the improvement of voice quality, it may have a greater effect on the improvement of the aerodynamic effect.

BVFL includes several types of lesions with different treatment efficiencies. Our previous study recruited eight patients for each lesion type who were matched for sex, age, and environment and also received similar regimens of VFSI. All voice laboratory measurement values significantly improved after VFSI in all the patients. Treatment effect varied with lesion type, and vocal nodules were the most amenable to VFSI, followed by chorditis, polyps, and scars.[11] It is still unclear how age affects the effect of VFSI. However, other studies also demonstrated that certain BVFLs are strongly associated with age.[12,15] In the present study, MPT and MFR did not improve in elderly patients. The reason for this may be related to the difference in glottal gap due to age-related vocal cord atrophy.[13–15] In our previous study that investigated basic fibroblast growth factor and steroid injection for vocal fold scarring, the glottal gap decreased, bFGF improved MPT and MFR, and steroid did not improve MPT or MFR. Thus, steroid infusion therapy may not have a medialization effect for reducing the glottis gap.[20] These changes result in an enlarged glottal gap, and VFSI may not be sufficient to correct the age-enhanced glottal gap.

Laryngeal microsurgery under general anesthesia is effective for BVFL, but it requires hospitalization for 2–3 days after surgery and prolonged voice rest. Conversely, VFSI is a simple and safe office-based treatment option for BVFL refractory to conservative voice therapy. An optimal regimen of VFSI has not been fully established. However, our regimen was uniform, and we believe that it guarantees a certain treatment effect on BVFL.

This study has a few limitations. First, this was a retrospective study, and the lesion size was not fully calculated because the recording conditions of laryngeal lesions differed between participants. Therefore, the size effect for voice improvement was not sufficiently elucidated. However, previous studies did not perform the uniform regimen, and the current study demonstrated that our regimen could guarantee a certain treatment effect on BVFL. Second, owing to the short follow-up period, the long-term outcomes of VFSI could not be determined. However, under the Japanese medical insurance system, the duration of hospital visits depends on the patient's willingness, and many patients drop out in long-term retrospective studies. Therefore, a prospective study should be planned to investigate the long-term results of this treatment. Third, to evaluate the accurate therapeutic effects of VFSI, the voice therapy only group should be examined. However, this study would provide sufficient evidence for the effect of VFSI because this study included participants who did not show improvements after voice therapy by a skilled speech–language pathologist. In fact, most participants who showed improvement with voice therapy and who sought further improvement were included. Fourth, although all participants received single injections, repeated injections or higher steroid concentrations may be required for intractable lesions. Notwithstanding the limitations, the present study reported valuable findings for standardizing the injection protocol and data collection schedule.

5 | CONCLUSION

We performed VFSI with a similar regimen in 83 patients. Improvement in VHI was observed, and other subjective and objective voice quality measurements also exhibited significant improvement. Furthermore, subgroup analysis showed that there was no age-related difference in the improvement of voice quality, and no improvement in aerodynamic effect was reported in the group with patients >45 years of age. The improvement rate of MPT and MFR significantly correlated with age, and the treatment effectiveness decreased with increasing age. These results clarified the indication criteria of VFSI and served as an important indicator for tailoring treatment to patients' needs.

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CONFLICT OF INTEREST

None.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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