

ORIGINAL RESEARCH

Factors associated with successful electrolarynx use after total laryngectomy, a multi-institutional study

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Abstract

Objective: To identify characteristics associated with successful electrolarynx (EL) use after total laryngectomy (TL).

Methods: Records of 196 adults who underwent TL from 03/15/2012 to 03/15/2022 at the University of Washington and Puget Sound Veterans Affairs were reviewed. Characteristics included age, Charlson Comorbidity Index, social support, pre-operative radiation (RT) and chemoradiation (CRT), and 6-month post-TL swallow status. EL success was evaluated using pre-defined criteria of intelligibility, reliability, and independence with use. Poisson regressions and robust standard error estimates were used to estimate unadjusted risk ratios for each characteristic. Statistically significant characteristics were included in multivariate analysis (MVA) to estimate adjusted risk ratios.

Results: Median age was 64, median Charlson Comorbidity Index was 5, 170 (87%) were male, 159 (81%) had high social support, and 159 (81%) attained post-TL full-oral diet. Pre-operatively, 110 (56%) had RT, including 55 (28%) with CRT. Ninety-three (47%) met our criteria for EL success. Characteristics significantly associated with EL success included social support ($p = .037$) and post-TL full-oral diet ($p = .037$); both approached significance on MVA. EL success varied by pre-operative treatment on univariate ($p = .005$) and MVA ($p = .014$). Compared to no prior RT or CRT, the probability of EL success was 29% higher with prior RT and 29% lower with prior CRT in MVA, although these associations did not reach significance.

Conclusions: In this retrospective review, EL success correlated with high social support, post-TL full-oral diet, and pre-operative treatment history. These results warrant validation in a larger prospective study to help guide the choice of voice rehabilitation modalities or intensified speech therapy.

Level of Evidence: 4.

KEYWORDS

laryngeal cancer/vocal fold dysplasia, post-laryngectomy speech and QOL, voice therapy

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1 | INTRODUCTION

Total laryngectomy (TL) can be a curative procedure for patients with advanced or recurrent laryngeal cancer not otherwise amenable to organ-preservation treatment. However, this surgery also results in major quality-of-life challenges as patients must adjust to the loss of natural voice. Voice rehabilitation can be approached through various methods, including an artificial larynx or “electrolarynx” (EL), tracheoesophageal puncture (TEP), or esophageal speech. Of the three voice rehabilitation methods, the majority of patients rely on EL or TEP for voicing, while only a small fraction can develop usable esophageal speech.¹ Compared to a TEP, the EL has the advantages of avoiding an additional invasive procedure, relative ease of use, and requiring minimal maintenance. The main disadvantages of EL voicing are the mechanical quality of the voice and decreased intelligibility with voiceless consonants, whereas TEP is superior in these dimensions.²

Developing functional use of the EL is facilitated through guidance by a speech-language pathologist (SLP), who can provide valuable coaching regarding optimal placement and on/off timing of the EL, tone and pitch control, over-articulation, as well as speech cadence and phrasing. In our experience, it is difficult to predict which patients will or will not be successful with the EL, be it due to problems with technique, motivation to practice, ability to manage mechanical device issues, or clinical factors (e.g., tissue fibrosis or edema). From our clinical experience, we have observed that social support, functional status, and neck tissue quality appear to play a role in the ability to use EL successfully. While factors associated with functional TEP outcomes have been studied, factors related to EL voice rehabilitation outcomes and success have yet to be explored.³ In this study, we investigated associations between clinicodemographic characteristics with successful use of the EL. We hypothesized that younger age, lower Charlson Comorbidity Index (CCI), higher social support, lesser extent of surgery, and full-oral post-operative diet at 6 months would be associated with a higher probability of successful EL use. Additionally, given the known effects of radiation therapy and chemoradiation on tissue fibrosis and thus vibratory capacity, we hypothesized that preoperative radiation and, to a greater extent, chemoradiation, would correlate with a lower chance of EL success and that the negative effect would increase over time.

2 | METHODS

2.1 | Patients

Medical records of adults who underwent TL between March 15, 2012, and March 15, 2022, at the University of Washington and Veterans Affairs (VA) Puget Sound were reviewed. Inclusion criteria included age ≥ 18 at the time of TL and at least two documented post-

laryngectomy visits in which the EL was offered and usage was assessed by an SLP. The latter inclusion criteria designated a minimum standard of available information to judge success or failure with EL, thus excluding those without enough documentation to make an accurate determination of EL use. Exclusion criteria included mental or physical limitations that made the patient an inappropriate candidate for EL usage preoperatively (e.g., hearing loss, dementia, amyotrophic lateral sclerosis, quadriplegia, total glossectomy, and nonfunctional premorbid speech). Patients fitting the above inclusion and exclusion criteria were included regardless of primary speech modality (e.g., TEP or esophageal speech), as we aimed to evaluate EL usage as an effective communication option regardless of its use as a primary or backup mode of communication. This study was reviewed and approved by the University of Washington Institutional Review Board and VA Puget Sound Institutional Review Board in accordance with the Declaration of Helsinki.

2.2 | Demographic and clinical characteristics

Patient demographics including age at TL, sex, race, and ethnicity were recorded. Clinical characteristics evaluated included the history of radiation or chemoradiation before laryngectomy, time between pre-operative radiation and TL, pre-laryngectomy opinion of the EL, extent of surgery, post-laryngectomy swallow status, social support, CCI, and history of TEP. The association between history of TEP and EL success was not evaluated due to the heterogeneous nature of the TEP variable (e.g., primary or secondary TEP, timing of TEP placement in relation to EL attempts, length of time TEP was maintained and/or used), which would preclude the ability to draw meaningful conclusions regarding this variable. Pre-laryngectomy opinion of the EL was documented as positive, negative, or neutral based on notes from patients' pre-TL SLP evaluations, in which patients are introduced to EL use and are given the opportunity to familiarize themselves with its use. Patients who did not undergo pre-TL SLP evaluations were categorized as “not evaluated” since their pre-TL EL opinions were not documented. Post-laryngectomy swallow status was assessed at 6 months post-operatively. Swallow status was dichotomized into a full oral diet, in which the patient did not rely at all on a feeding tube for nutrition, and feeding-tube dependent, in which the patient relied fully or partially on nutrition via a feeding tube. Social support was assessed at the time of TL and was classified as a binary characteristic, with low social support defined as living alone and without help from friends or relatives and high social support defined as living with a partner or having help from friends or relatives.

2.3 | Endpoints

The endpoint of this study was successful communication with the EL. This was defined as a binary outcome based on prespecified

FIGURE 1 Criteria used to define successful use of the electrolarynx.

Criteria to define successful use of electrolarynx	
<i>Intelligibility</i>	Can an average listener mostly understand the speech of the EL user? If an SLP note documented a percent intelligibility, $\geq 75\%$ was considered intelligible.
<i>Reliability</i>	Is the user able to access and operate the EL to communicate when needed? Intrinsic and extrinsic factors may make EL use an inconsistent mode of communication for certain patients. Examples of intrinsic factors included head and neck tissue factors (e.g., fluctuating pain, edema), upper extremity musculoskeletal factors (e.g., weakness, arthritic flares), efficiency of finding the “sweet spot” or proper placement of the EL. Examples of extrinsic factors included maintaining the equipment (e.g., losing the device or pieces like the intraoral adapter, replacing batteries) and consistently remembering how to operate the equipment.
<i>Independence</i>	Is the user cognitively and physically able to use the EL without assistance?

criteria regarding patients' *intelligibility*, *reliability*, and *independence* with the use of the EL using information gathered from the medical record (Figure 1).

Only patients who met all three criteria were categorized as successful users of the EL. The criteria were designed to determine which patients were able to communicate effectively and reliably with the EL when desired, regardless of whether the EL was the primary mode of communication or how frequently they used it.

2.4 | Statistical analysis

Summary statistics included median and interquartile range for continuous measures and frequency and percentage for categorical characteristics.

Poisson regressions and robust standard error estimates were fit to estimate unadjusted and adjusted risk ratios of successful EL use for each characteristic. In this study, risk ratios of successful use of the EL are termed “success ratios.” Two-sided Wald p -values $< .05$ were deemed statistically significant and 95% confidence intervals were reported. All analyses were evaluated at the University of Washington and VA populations together due to sample size constraints.

To estimate unadjusted success ratios, separate unadjusted Poisson regressions were fit for each characteristic. For the radiation-dependent characteristic “years between preoperative radiation and surgery,” a main effect for preoperative radiation and an additional main effect for the radiation-dependent characteristic were modeled. The exponentiated radiation-dependent characteristic coefficient corresponds to the EL success ratio for that characteristic, given preoperative radiation treatment.

Multivariate Poisson regression models were fit, including all characteristics that were statistically significant in the univariate analysis to identify factors associated with the successful use of EL in the presence of other relevant characteristics.

A secondary analysis was then conducted to evaluate for any confounding effects of the TEP variable on our initial results. Unadjusted success ratios were estimated as described above excluding patients with a history of TEP from the original cohort.

3 | RESULTS

Between March 15, 2012, and March 15, 2022, the medical records of 196 adult patients who underwent TL at the University of Washington ($n = 171$, 87%) and the VA Puget Sound ($n = 25$, 13%) were reviewed. Demographic and clinical characteristics are summarized in Table 1. Median age was 64 (interquartile range 57–70) and 170 (87%) were male. Most patients had high social support, in which they lived with a partner or had help from friends or relatives ($n = 159$, 81%). Pre-operatively, 110 (56%) had radiation, including 55 (28%) with concurrent chemotherapy. Most were able to attain a full-oral diet 6 months post-TL ($n = 159$, 81%). Ninety-three (47%) met our criteria for successful use of the EL.

In univariate analysis of demographic and clinical characteristics associated with successful use of the EL, we observed that social support ($p = .037$), preoperative treatment history ($p = .005$), and post-operative swallow status ($p = .037$) were significantly associated with EL success (Table 2). Among patients demonstrating successful EL use, those with high social support were 73% more likely to be successful EL users compared to those with low social support, with successful EL users comprising 82 (52%) patients with high social support and 11 (30%) patients with low social support. Successful EL users varied by preoperative treatment before laryngectomy ($p = .005$), with 40 (47%) patients having no prior treatment and 35 (64%) and 18 (33%) patients with prior RT and CRT, respectively. Compared to patients with no prior treatment, patients previously treated with RT alone were 37% more likely to be successful EL users, whereas those previously treated with CRT were 30% less likely to demonstrate EL success, although the association with CRT did not reach statistical significance. Additionally, 82 (52%) patients on a full-oral diet at 6 months post-operatively were successful EL users compared to 11 (30%) patients who were partially or fully feeding tube-dependent. On univariate analysis, patients who remained partially or fully dependent on a feeding tube at 6 months post-operatively were estimated to have a 42% decreased likelihood of EL success compared to patients who achieved a full oral diet. There was no evidence that age at surgery, CCI, years between preoperative radiation and surgery, or extent of surgery were associated with successful use of the EL.

TABLE 1 Demographic and clinical characteristics overall and by hospital.^a

Characteristic	Overall	Hospital	
	N = 196	University of Washington (N = 171)	Veterans Affairs (N = 25)
Age at surgery	64 (57, 70)	63 (56, 70)	64 (60, 70)
Male	170 (87)	145 (85)	25 (100)
Race			
White	165 (84)	147 (86)	18 (72)
Black	10 (5.1)	7 (4.1)	3 (12)
American Indian or Alaska Native	5 (2.6)	4 (2.3)	1 (4.0)
Asian	1 (0.5)	1 (0.6)	0 (0)
Unknown	15 (7.7)	12 (7.0)	3 (12)
Ethnicity			
Not Hispanic or Latino	139 (71)	118 (69)	21 (84)
Hispanic or Latino	7 (3.6)	6 (3.5)	1 (4.0)
Unknown	50 (26)	47 (27)	3 (12)
Charlson Comorbidity Index	5 (4, 6)	5 (4, 6)	5 (5, 6)
Social support			
Low (lives alone, without help from friends or relatives)	37 (19)	31 (18)	6 (24)
High (lives with partner or has help from friends or relatives)	159 (81)	140 (82)	19 (76)
Preoperative treatment			
No radiation or chemotherapy	86 (44%)	73 (43%)	13 (52%)
Radiation alone	55 (28%)	48 (28%)	7 (28%)
Chemoradiation	55 (28%)	50 (29%)	5 (20%)
Years between preoperative radiation and surgery ^b	1.6 (0.7, 5.3)	1.5 (0.7, 5.4)	2.8 (1.4, 4.1)
Preoperative opinion of electrolarynx			
Negative	19 (9.7)	19 (11)	0 (0)
Neutral	90 (46)	84 (49)	6 (24)
Positive	35 (18)	32 (19)	3 (12)
Not evaluated	52 (27)	36 (21)	16 (64)
Extent of surgery			
Total laryngectomy	149 (76)	130 (76)	19 (76)
Total laryngectomy and partial pharyngectomy	15 (7.7)	11 (6.4)	4 (16)
Total pharyngolaryngectomy	32 (16)	30 (18)	2 (8.0)
History of tracheoesophageal puncture	24 (12)	14 (8)	10 (40)
Swallow status 6 months post-operatively			
Full oral diet (feeding-tube independent)	159 (81)	134 (78)	25 (100)
Feeding-tube dependent (partially or fully)	37 (19)	37 (22)	0 (0)
Successful with electrolarynx	93 (47)	83 (49)	10 (40)

^aMedian (interquartile range) reported for quantitative characteristics and number (percentage) reported for categorical characteristics.

^bMedian and interquartile years between preoperative radiation and surgery are only calculated from the 110 patients who had preoperative radiation.

Characteristics significantly associated with EL success in the univariate analysis were included in the multivariate analysis (Table 2). In this model, preoperative treatment history was significantly associated with EL success while social support and post-operative feeding-tube dependence approached significance. In both the univariate and multivariate analysis, when compared to no prior treatment with RT or CRT, preoperative RT alone trended toward higher rates of EL

success while preoperative CRT trended toward lower rates of EL success, although neither pairwise comparison reached statistical significance.

In a secondary analysis excluding patients with a history of TEP (Table S1), the unadjusted success ratios were consistent in direction and magnitude to our findings in the original cohort that included patients with a history of TEP. Social support, preoperative treatment

TABLE 2 Unadjusted and adjusted electrolarynx success ratios.

Characteristic	Success with electrolarynx, N (%)	Univariate analyses		Multivariate analysis ^a	
		Success ratio (95% CI)	p-Value	Success ratio (95% CI)	p-Value
Age at surgery ^b		0.91 (0.79, 1.04)	.170		
Charlson Comorbidity Index		0.94 (0.86, 1.03)	.175		
Social support					
Low	11 (30)	Reference	.037	Reference	.061
High	82 (52)	1.73 (1.03, 2.91)		1.66 (0.98, 2.82)	
Preoperative treatment					
No radiation or chemotherapy	40 (47)	Reference	.005	Reference	.014
Radiation alone	35 (64)	1.37 (1.01, 1.85)		1.29 (0.96, 1.72)	
Chemoradiation	18 (33)	0.70 (0.45, 1.09)		0.71 (0.46, 1.11)	
Years between preoperative radiation and surgery ^c		1.00 (0.97, 1.03)	.896		
Preoperative opinion of electrolarynx					
Negative	7 (37)	Reference	.052		
Neutral	48 (53)	1.45 (0.78, 2.69)			
Positive	21 (60)	1.63 (0.85, 3.11)			
Not evaluated	17 (33)	0.89 (0.44, 1.8)			
Extent of surgery					
Total laryngectomy	73 (49)	Reference	.492		
Total laryngectomy and partial pharyngectomy	8 (53)	1.09 (0.66, 1.8)			
Total pharyngolaryngectomy	12 (38)	0.77 (0.48, 1.23)			
Swallow status 6 months post-operatively					
Full oral diet	82 (52)	Reference	.037	Reference	.077
Feeding-tube dependent	11 (30)	0.58 (0.34, 0.97)		0.62 (0.37, 1.05)	

Note: All univariate and multivariate analyses were fit using 196 patients. Bold values indicate *p* values that are significant or borderline significant, but these can be unbolded in the final manuscript.

^aMultivariate analysis included preoperative treatment, feeding-tube dependence, and social support main effects.

^bComparing patients who differ by 10 years.

^cAmong patients who received preoperative radiation.

history, and swallow status were still statistically significant in the secondary univariate analysis excluding patients with a history of TEP, though the success ratios for the different preoperative treatments were more similar ($p = .042$) than in the original cohort ($p = .005$).

4 | DISCUSSION

Despite the unique challenges with its use, the EL fills an important role in post-laryngectomy voice rehabilitation as a readily available, procedure-free option. However, there is a gap in knowledge regarding factors associated with functional outcomes and the success of EL use. The EL functions as a primary mode of communication for many but can also be a backup mode of communication for others who primarily rely on TEP.² EL users must overcome a multitude of voicing challenges with the device, including the mechanical sound quality, on/off timing, and pitch modulation. Despite being thought of as a relatively accessible mode of voice rehabilitation, the literature demonstrates that there is significant variability in the voice-related quality

of life in post-laryngectomy EL users, indicating a need to better identify patients at risk of being unsuccessful with the EL.⁴

Our study is the first to our knowledge to investigate factors specifically associated with successful EL use in TL patients. We found that patients with better social support and postoperative swallow function were more likely to be successful EL users. Additionally, we observed that the probability of successful EL use differed by preoperative treatment history of radiation or chemoradiation. There was no evidence that age at surgery, CCI, years between preoperative radiation and surgery, or extent of surgery were associated with the successful use of the EL. The extent of surgery was determined from billing codes, which place surgeries into broad predefined categories that could potentially mask heterogeneity and hide associations within this variable.

Overall, we found that less than half of patients trialed with an EL are able to successfully use it to verbally communicate after TL. This success rate is sobering, as the EL is typically presented as an accessible initial option for voice rehabilitation after TL. The first step to improving the EL success rate is understanding the disparity between

patients who have success with the EL and those who have not. Once patients less likely to be successful with the EL can be identified, the underlying reasons can be explored further and interventions developed to ultimately improve their voice rehabilitation outcomes. This may include increased pre- or post-TL education, more intensive SLP therapy, improved social support, or early adoption of alternate communication options.

Prior literature exploring factors related to post-laryngectomy voice rehabilitation has primarily focused on TEPs. Most results of studies on this topic have been inconsistent, likely due to literature comprising generally small retrospective studies without standardized outcome measures of successful voice rehabilitation.⁵ Factors consistently found to be associated with voice outcomes with TEP include general physical condition, medical comorbidities, communication demands, employment status, and extent of surgery.^{3,5,6} Additionally, multiple investigators have found that patient age and radiation therapy, both preoperative and postoperative, did not influence the success of TEP voice rehabilitation.⁷⁻¹⁰

While commonalities may exist across voice rehabilitation modalities, extrapolating TEP outcomes to the EL should be cautioned due to the different challenges and skill requirements of using each device. Furthermore, while the EL is typically offered as a post-TL voice rehabilitation modality for nearly all laryngectomy patients, a comparatively narrower population is offered TEP placement, with relative contraindications including poor vision or dexterity, inability to manage the care of the voice prosthesis and stoma, poor pulmonary function, esophageal stenosis, lack of support system, and lack of proximity to an SLP or otolaryngologist.¹¹ Our study included a relatively small percentage of TL patients who had a TEP placed ($n = 24$, 12%) at any time. This low percentage may reflect the wide five-state catchment area served by our tertiary academic centers, with some patients receiving care, including TEP, locally after their last known follow-up at our institutions. Despite the small number of patients with a history of TEP in our cohort, a secondary analysis excluding those with a history of TEP was conducted to evaluate for a potential confounding effect of the TEP variable on our original findings. In this secondary analysis, unadjusted success ratios were consistent in direction and magnitude with our findings in the original cohort that included patients with a history of TEP. Additionally, social support, preoperative treatment history, and swallow status remained statistically significant in the secondary analysis, indicating that the history of TEP does not appear to significantly affect our original findings. Our finding that greater social support is associated with an increased chance of EL success raises the possibility that higher communication demands, support from friends and family, as well as the ability to facilitate follow-up SLP visits may lead to increased practice and functional use of the EL. In TEPs, Saurajen et al. found that patients with more follow-up in voice restoration clinics had significantly better voices.⁹ While we did not specifically study the relationship between follow-up and EL success, we hypothesize that increased social support may facilitate follow-up or increase the need for follow-up secondary to communication demand.

Additionally, we found that intact post-operative swallow function correlated with successful EL use. In TEPs, there is a direct relationship between esophageal function and voice production. Studies have shown that abnormalities of the proximal esophagus are associated with worse TEP voice quality; likewise, placement of a TEP directly alters esophageal function through pressure changes in the esophagus during speech.^{12,13} A direct anatomical relationship between EL usage and swallow function does not exist, nor have correlations between EL usage and dysphagia been previously demonstrated. The association between EL usage and dysphagia warrants further investigation, particularly as they relate to treatment effects on tissue fibrosis and overall physical condition. Furthermore, in addition to reflecting physical tissue characteristics and function, swallow preservation following laryngectomy may be a result of continued SLP follow-up, which may impact EL success.¹⁴

We anticipated that prior RT would lead to increased tissue fibrosis with impaired vibratory function necessary for sound transmission with the EL and that these adverse effects would be further potentiated by concurrent chemotherapy, a known synergistic interaction.¹⁵ In the current study, we found that pre-operative treatment was significantly associated with EL success, although pairwise associations between EL success with RT and CRT, respectively, did not reach significance. It is reasonable to assume that patients who receive isolated radiation therapy typically represent those who present with early-stage disease, in contrast to those who present with advanced-stage disease requiring upfront laryngectomy or chemoradiation therapy. Thus, this intriguing finding may be reflective of the disease process or another variable captured within but not fully expounded by pre-operative treatment. Combined with evidence that swallow function may correlate with EL success, this suggests an interesting interplay between the effects of treatment on the functional and physical qualities of the neck/pharynx, social support, and communication demands that may influence EL compatibility. There are likely additional variables influencing the relationship between treatment history and EL success and warrant further investigation.

Despite the immense impact on quality of life, studying functional outcomes for voice rehabilitation after TL has long posed a challenge for researchers as no standard criteria exists to define success. While some authors have defined successful voice rehabilitation as the ability to speak *at all*, others have required that patients speak in a socially acceptable way.^{5,16} “Socially acceptable” speech, however, is subject to interpretation, with varying definitions from speaking full words to being able to carry out a phone conversation.^{5,17} In reality, a multitude of factors are important for successful verbal communication, including sound, pitch, speed and timing, overall intelligibility and comprehensibility, nonverbal expressions, and the patient's self-perceived quality and functionality of voice. Ideally, evaluating voice rehabilitation requires a multimodal approach, including acoustic analysis, listener perceptual evaluation, and patient-reported outcomes, which typically cannot be fully captured by a retrospective study design.¹⁸ We acknowledge these limitations in our study as well, as

we were unable to account for objective acoustic analysis or standardized patient-reported outcomes. However, in structuring our criteria for success to include a multifactorial evaluation of intelligibility, reliability, and independence of use, we have aimed to capture and combine elements of listener perceptual evaluation and functional measures that reflect the practical and patient-centered outcomes of successful EL use. As such, this work helps to define the criteria for post-laryngectomy voice success for future studies.

Along with the limitations of studying voice rehabilitation outcomes, our study was limited by the retrospective nature and the lack of standardized SLP postoperative assessments and interventions for EL voicing. We investigated a restricted number of demographic and clinical variables, selected based on our clinical experience and prior literature in TEP outcome studies, although multiple hypothesis testing remains a limitation in our exploratory study. Thus, while the variables we selected are by no means an exhaustive list, our findings represent a promising basis for further investigation in predictors of successful EL use. In this way, we hope to improve our understanding of successful voice rehabilitation methods to identify laryngectomy patients who may benefit from intensified SLP therapy, require alternate modes of communication, or may benefit from other peri-operative interventions to facilitate successful voice rehabilitation.

5 | CONCLUSIONS

In this study, we first proposed criteria to define successful voice rehabilitation with EL use. We then explored clinicodemographic characteristics associated with successful EL use in TL patients. We found that higher social support and a full-oral diet at 6 months post-laryngectomy were associated with a higher probability of successful EL use. Additionally, we observed that the probability of successful EL use significantly differed by preoperative treatment history of radiation or chemoradiation; with preoperative radiation trending toward a higher probability of EL success and chemoradiation trending toward lower EL success. These findings help define successful voice rehabilitation following TL and may help identify patients who require intensified voice rehabilitation therapy for successful EL use or alternate modes of communication and warrant validation in a larger, prospective cohort.

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CONFLICT OF INTEREST STATEMENT

The authors declare no potential conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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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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