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ORIGINAL ARTICLE

Effect of Perioperative Inhaled Tiotropium for patients with chronic Obstructive Pulmonary disease in Esophageal cancer surgery (EPITOPE): an open-label, randomized, parallel-group pilot study

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Abstract

Objective Chronic obstructive pulmonary disease (COPD) is a risk factor for pneumonia following esophagectomy. This study aimed to investigate the efficacy of perioperative inhaled tiotropium in patients with COPD undergoing esophagectomy.

Methods This open-label, randomized controlled trial randomly assigned 32 patients with COPD undergoing esophagectomy to conventional management or addition of tiotropium inhalation. The intervention group received tiotropium from two weeks before esophagectomy until the final evaluation one month after esophagectomy. The primary outcome was the incidence of pneumonia within 30 postoperative days. We also assessed the changes and the percentages from baseline in pulmonary function and walking distance of the incremental shuttle walking test to just before esophagectomy and final evaluation.

Results Enrolled patients were randomly assigned to the control group ($n = 18$) and the intervention group ($n = 14$). Pneumonia was recorded in 4 (28.6%) and 5 (27.8%) patients in the intervention and control groups, respectively (risk difference: 0.8%, 95% confidence interval: − 30.6 to 32.2). The intervention group demonstrated a significant improvement in pulmonary function and walking distance preoperatively. Further, the pulmonary function test was significantly better preoperatively in the intervention group than in the control group. Postoperatively, pulmonary function deterioration was more significant in the control group than in the intervention group.

Conclusions Preoperative tiotropium inhalation significantly improved pulmonary function and exercise tolerance in patients with COPD undergoing esophagectomy. The perioperative tiotropium did not reduce pneumonia after esophagectomy, but it may contribute to patient recovery by reducing postoperative pulmonary function deterioration.

Keywords Esophagectomy · Chronic obstructive pulmonary disease · Tiotropium · Pneumonia · Pulmonary function

Introduction

Esophagectomy for esophageal cancer is related to a high postoperative complication incidence. Postoperative pneumonia is one of the most prevalent complications, which is significantly associated with increased operative mortality [1–3] and may worsen long-term outcomes [4–8].

Chronic obstructive pulmonary disease (COPD) shares a common risk factor—cigarette smoking, with squamous cell carcinomas of the upper aerodigestive tract, which is the predominant histological subtype of esophageal cancer in Japan [9]. COPD or impaired pulmonary function is one of the independent risk factors for pulmonary complications after esophagectomy [1–3, 10, 11], but the optimal preventive measures against postoperative pneumonia in patients undergoing esophagectomy remain unclear. The number of

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patients with esophageal cancer with COPD or impaired pulmonary function may further increase, as the population ages, and countermeasures against postoperative pneumonia need to be considered.

A previous retrospective study revealed that two-week preoperative treatment with tiotropium, which is a long-acting, antimuscarinic antagonist (LAMA) bronchodilator used in treating patients with COPD, improved symptoms, and pulmonary function in COPD patients who undergo lung cancer surgery [12]. Therefore, we hypothesized that perioperative inhaled tiotropium improved patients' pulmonary function and exercise tolerance, which decreased the incidence of pneumonia after esophagectomy for patients with COPD. However, no study investigated the preventive use of tiotropium in patients with COPD undergoing esophageal cancer surgery. This open-label, randomized, parallel-group pilot study aimed to investigate the efficacy of perioperative inhaled tiotropium in patients with COPD undergoing esophageal cancer surgery (EPITOPE study).

Methods

Design and participants

EPITOPE is a prospective, single-center, open-label, randomized controlled study that investigates the effect of perioperative inhaled tiotropium on the incidence of postoperative pneumonia, pulmonary function, and exercise tolerance of patients with COPD in esophageal cancer surgery. The study design has been previously published in detail [13]. Inclusion criteria were patients undergoing transthoracic subtotal esophagectomy for esophageal cancer, aged ≥ 20 years, who had a history of smoking but quit smoking, were having airflow limitation with forced expiratory volume in one second % (FEV1%) of < 70% assessed by spirometry, and who signed written informed consent. Patients with other diseases causing airflow limitation including bronchial asthma-COPD overlap syndrome were excluded. Other exclusion criteria were allergy to atropine or drugs similar to atropine, undergoing pharyngolaryngoesophagectomy, two-staged esophagectomy, or reconstruction without gastric conduit, having a history of thoracic surgery, glaucoma, prostatic hypertrophy, heart failure, atrial fibrillation, inhalation for COPD, psychiatric disease, and active infection, and unsuitable conditions for safe conduct of this study as evaluated by investigators. All participants signed written informed consent before registration.

The institutional review board of the Japanese Foundation for Cancer Research approved this study (No. 2019-1069), which was conducted under the principles of the Declaration of Helsinki and Ethical Guidelines for Medical and Health Research Involving Human Subjects. This study was registered at the University Hospital Medical Information Network Clinical Trials Registry (UMIN000037922), one of the network members of the Japan Primary Registries Network, and meets the World Health Organization registry criteria. The 2nd Japanese Association for Thoracic Surgery award for young investigators in 2019 supported this trial.

Randomization

Non-masked investigators conducted participant enrollment. All eligible patients were randomly assigned in a 1:1 ratio using an electronic data capture system (Viedoc; Pharma Consulting Group, Uppsala, Sweden) into conventional management without (control group) or with tiotropium inhalation (intervention group). Further, it was stratified by baseline FEV1% (< 60% or 60% to < 70%). Randomization was performed at least two weeks before surgery, and study treatment was initiated afterward.

Study treatment

Multidisciplinary perioperative management was provided for patients who were scheduled for esophagectomy [14]. Preoperatively, oral cleaning, and breathing exercises using a training device were routinely initiated. Patients trained at home for at least two weeks and continued training until esophagectomy. Oral cleaning, breathing exercises, and gait training were routinely performed in the intensive care unit from the first day after esophagectomy. An advanced physical training program using devices, such as a bike, was provided after discharge from the intensive care unit.

Patients assigned to the intervention group received tiotropium of 5 μg once daily via Respimat inhaler after randomization for at least two weeks until esophagectomy. Tiotropium was re-delivered from the first day after esophagectomy and was continued until the day of the final evaluation scheduled after one month (30–44 days). Inhalation or administration of the expectorants and temporary inhalation of a short-acting bronchodilator were permitted during this study period. However, the continuous inhalation of any long-acting bronchodilators and inhaled corticosteroids was not permitted.

The prescribed surgical procedure in this study includes subtotal esophagectomy with gastric conduit reconstruction. Thoracic and abdominal procedures in either an open or a minimally invasive approach were acceptable. Additionally, patients undergoing robot-assisted surgery were included. Thoracoscopic and robot-assisted thoracoscopic procedures were performed on a patient in a prone position with carbon dioxide artificial pneumothorax without one-lung ventilation. Methylprednisolone was intravenously administered at 250 mg immediately before the first skin incision for all cases.

Data collection

All data were collected via an electronic case report form, and personal identifying information was deleted from the data, whereas a linkable anonymized number was set.

Registered physical therapists measured walking distance in the incremental shuttle walking test (ISWT) as the baseline assessment after registration. The ISWT, which assesses maximal exercise capacity based on the distance walked around a 10 m course following different speeds dictated by an audio signal, is a widely used, simple, and inexpensive test to evaluate exercise tolerance in patients with COPD [15]. Walking distance in the ISWT and pulmonary function (vital capacity [VC], forced vital capacity [FVC], and FEV1) were re-evaluated just before and one month after esophagectomy (30–44 days). Details of surgical procedures and postoperative complications were collected. Medication adherence was assessed by checking the scale of inhalers, and all adverse events were recorded during this study.

Outcomes

The primary outcome was the incidence of pneumonia within 30 days after esophagectomy. Pneumonia was defined according to new infiltrates on chest X-ray or computed tomography, combined with high temperature, elevated serum C-reactive protein level, increased leukocyte count, or purulent sputum. The secondary outcomes evaluated for efficacy analysis include the incidence of cardiovascular complications within 30 days after esophagectomy, the incidence of any postoperative complications within 30 days after esophagectomy, pulmonary function (baseline, preoperative, and postoperative one month), walking distance in the ISWT (baseline, preoperative, and postoperative one month), and mortality within 30 days after esophagectomy. All postoperative complications were classified under the Clavien–Dindo grading system [16]. The investigators captured all adverse events throughout the study, and those with a reasonable causal association with the study treatment were considered treatment-related adverse events.

Statistical analysis

The estimated incidence of patients with COPD who undergo esophagectomy was approximately 10% in previous Japanese nationwide studies [17, 18]. The target sample size was identified based on the annual number of esophagectomy cases at our institution, considering the exploratory aspects of the study and completing it in two years. We assumed that 16 eligible patients could be enrolled annually, and trial recruitment continued after enrolling at least 32 patients.

The efficacy analysis set included all randomly assigned patients who underwent esophagectomy and completed the final evaluation one month postoperatively. The safety analysis set included all patients who were randomly assigned and who received at least one dose of tiotropium during the study period. Data analyses were conducted with the intention-to-treat principle. All statistical analyses were descriptive and presented 95% confidence intervals (CIs) rather than a *p*-value of testing. No missing data were imputed. We estimated the risk difference of the incidence of pneumonia between the groups and its 95% CI using Wald's method for the primary analysis. The secondary categorical outcomes were evaluated by the risk difference and their 95% CIs. The secondary continuous outcomes were summarized by the change and percent change from baseline and their 95% CIs. The SAS software (version 9.4; SAS Institute Inc., Cary, NC, USA) was used for all statistical analyses.

Results

Trial recruitment started in October 2019. However, the coronavirus disease 2019 (COVID-19) pandemic in Japan began in March 2020, and thus, the national government declared the first state of emergency, urging people to avoid unnecessary physical contact and keep a social distance. Afterward, we experienced several waves of the COVID-19 pandemic, and the progress in this study was remarkably behind the plan. The registration was extended and completed in April 2024.

Supplemental Figure 1 shows the CONSORT diagram. Of the 34 patients enrolled, 33 patients, excluding one patient who met an exclusion criterion after registration, were randomly assigned to each group. The analysis set excluded one patient who withdrew consent after randomization. Finally, the analysis set included 18 patients with conventional management and 14 with additional inhaled tiotropium. The efficacy and safety analysis sets included the same population.

Table 1 lists the baseline characteristics of patients. The intervention and control groups consisted of 13 (92.9%) men and 1 (7.1%) women, and 17 (94.4%) men and 1 (5.6%) women, respectively. The median age was 67.1 years and 69.9 years in the intervention and control groups, respectively. The baseline demographics, including patient physique, smoking index (= daily number of cigarettes × smoking years), pulmonary function, walking distance in the ISWT, clinical tumor stage, and preoperative treatment, demonstrated no significant differences. Regarding stratified assignment, 3 (21.4%) and 3 (16.7%) patients exhibited a baseline FEV1% of < 60% in the intervention and control groups, respectively.

Table 1 Baseline characteristics of participants

		Intervention group	Control group
Sex	Women	1 (7.1)	1 (5.6)
	Men	13 (92.9)	17 (94.4)
Age, years		67.1 (7.7)	69.9 (4.6)
Height, cm		170.8 (5.9)	169.9 (8.0)
Weight, kg		65.4 (8.3)	65.6 (10.1)
Performance status	0	2 (14.3)	3 (16.7)
	1	12 (85.7)	15 (83.3)
Smoking index		734.3 (487.9)	796.7 (533.7)
Pulmonary function	VC, L	3.84 (0.61)	3.87 (0.58)
	FVC, L	3.85 (0.69)	3.89 (0.56)
	FEV1, L	2.48 (0.51)	2.55 (0.42)
	FEV1%	64.1 (5.1)	65.3 (4.5)
Walking distance in the ISWT, m		462.1 (149.9)	473.5 (116.3)
Clinical tumor stage	I	6 (42.9)	6 (35.3)
	II	3 (21.4)	3 (17.6)
	III	5 (35.7)	8 (47.1)
Preoperative treatment	None / Endoscopic	6 (42.9)	5 (27.8)
	Chemotherapy	8 (57.1)	11 (61.1)
	Chemoradiotherapy	0 (0.0)	2 (11.1)
Robot-assisted surgery		2 (14.3)	4 (22.2)
Field of lymph node dissection	Two-field	10 (71.4)	12 (66.7)
	Three-field	4 (28.6)	6 (33.3)
Bleeding, mL		94.6 (55.4)	115.3 (101.6)
Time, min		443.3 (64.4)	482.4 (73.6)

Data are presented as number (%) or mean (standard deviation)

ISWT incremental shuttle walking test

Table 1 also shows details of the surgical procedures. All patients underwent subtotal esophagectomy with gastric conduit reconstruction in thoracoscopic and laparoscopic approaches. Robot-assisted surgery was performed in 2 (14.3%) and 4 (22.2%), and three-field lymph node dissection was conducted in 4 (28.6%) and 6 (33.3%) patients in the intervention and control groups, respectively.

No treatment-related adverse events due to perioperative inhaled tiotropium were identified during the study period, and all patients in the intervention group completed perioperative inhalation until the final evaluation. The mean treatment durations were 24.0 and 35.1 days, and inhalation treatment adherences were 90.5% and 93.4% pre- and postoperatively, respectively.

Table 2 shows the primary outcome of pneumonia within 30 postoperative days in 4 (28.6%, 95% CI: 8.4%–58.1%) and 5 (27.8%, 95% CI: 9.7%–53.5%) patients in the intervention and control groups, respectively. No significant risk difference was found in the incidence (0.8%, 95% CI: − 30.6% to 32.2%), and also there were no significant differences in severity of pneumonia and in pneumonia incidence before the resumption of oral intake. Regarding secondary categorical outcomes evaluated, no significant differences were found in the 30-day incidences of cardiovascular complications and any postoperative complications, including recurrent laryngeal nerve palsy, anastomotic leakage, and surgical site infection. Both groups demonstrated no 30-day mortality.

Figure 1 and Supplemental Table 1 show the changes and percent changes from the baseline of pulmonary function tests and the ISWT walking distance. Preoperatively, a significant improvement of percent changes from the baseline in pulmonary function tests was found in the intervention group, as evidenced by the increase in VC (7.4%, 95% CI: 2.5%–12.3%), FVC (5.9%, 95% CI: 1.0%–10.9%), and FEV1 (7.8%, 95% CI: 2.5%–13.0%). Additionally, a significant increase in VC (7.6%, 95% CI: 2.2%–12.9%), FVC (6.9%, 95% CI: 1.5%–12.3%), and FEV1 (10.4%, 95% CI: 4.3%–16.5%) was found in the intervention group when compared with the control group. A significant increase in preoperative walking distance from the baseline was observed in the intervention group (18.7%, 95% CI: 5.1%–32.3%). Furthermore, the increase in walking distance was more significant in the intervention group than in the control group, although without statistical significance. Postoperatively, pulmonary function significantly deteriorated

Table 2 Primary and secondary categorical outcomes

	Intervention group		Control group		
	Number	Incidence, %	Number	Incidence, %	Risk difference, %
Primary outcome					
Pneumonia	4	28.6 (8.4 to 58.1)	5	27.8 (9.7 to 53.5)	0.8 (−30.6 to 32.2)
Secondary outcomes					
Any postoperative complications	8	42.9 (17.7 to 71.1)	9	50.0 (26.0 to 74.0)	−7.1 (−41.9 to 27.6)
Cardiovascular complications	1	7.1 (0.2 to 33.9)	0	0.0 (0.0 to 18.5)	7.1 (−6.3 to 20.6)
30-day mortality	0	0.0 (0.0 to 23.2)	0	0.0 (0.0 to 18.5)	-
Detail of other complications					
Recurrent laryngeal nerve palsy	1	7.1 (0.2 to 33.9)	5	27.8 (9.7 to 53.5)	−20.6 (−45.3 to 4.1)
Anastomotic leakage	2	14.3 (1.8 to 42.8)	2	11.1 (1.4 to 34.7)	3.2 (−20.2 to 26.6)
Surgical site infection	0	0.0 (0.0 to 23.2)	1	5.6 (0.1 to 27.3)	−5.6 (−16.1 to 5.0)
Miscellaneous	2	14.3 (1.8 to 42.8)	3	16.7 (3.6 to 41.4)	−2.4 (−27.5 to 22.8)

Incidences and risk differences are presented as % (95% confidence interval [CI])

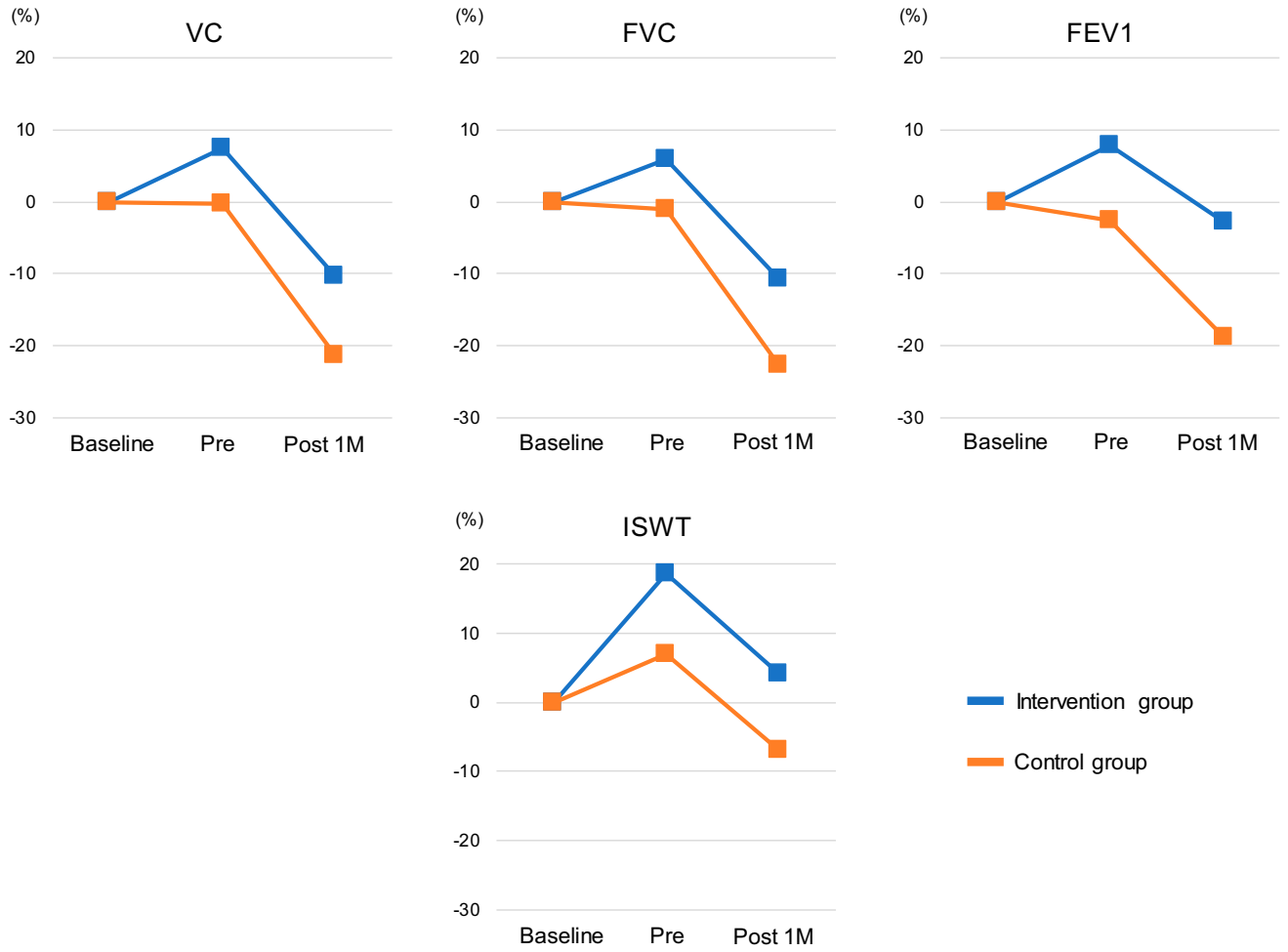

Fig. 1 Percent changes of pulmonary function and walking distance of the ISWT from the baseline

from the baseline in both groups. However, the deterioration was more significant in the control group than in the intervention group. Significant differences were observed in VC (11.0%, 95% CI: 5.6%–16.4%), FVC (11.9%, 95% CI: 4.9%–18.9%), and FEV1 (16.1%, 95% CI: 8.1%–24%). The ISWT walking distance was declined after esophagectomy in both groups, but with no significant changes from the baseline. The distance was maintained in the intervention group when compared with the control group.

Discussion

This randomized, parallel-group, pilot study investigated the efficacy of perioperative inhaled tiotropium in patients with COPD undergoing esophageal cancer surgery. The results revealed that preoperative pulmonary function and exercise tolerance were significantly improved after preoperative treatment with inhaled tiotropium, although it did not reduce the incidence of postoperative pneumonia after esophagectomy. Meanwhile, pulmonary function significantly deteriorated after esophagectomy; however, the deterioration could be mitigated with the intervention. Further, the intervention group possibly maintained postoperative exercise tolerance. To the best of our knowledge, this is the first prospective study to demonstrate the efficacy of tiotropium for patients with COPD undergoing esophagectomy.

Postoperative pneumonia is one of the most predominant complications after esophagectomy for esophageal cancer [1–3]. Moreover, it is related to increased operative mortality, prolonged hospital stays, increased healthcare costs, and impaired long-term survival [4–8, 19, 20]. Reportedly, COPD is one of the independent risk factors for postoperative pneumonia after esophagectomy [1–3, 10, 11], and thus, preventive measures against postoperative pneumonia after esophagectomy should be clarified. Significant evidence has not been established, but various pharmacological treatments, such as corticosteroids, neutrophil elastase inhibitors, and vitamins, may be efficacious in reducing pulmonary complications [3].

Tiotropium inhalation for patients with COPD is known to improve patient's quality of life, exercise tolerance, and pulmonary function, thereby reducing the risk of COPD exacerbations [21–23]. However, this pilot study revealed no advantage of inhalation for reducing postoperative pneumonia. Multiple factors could affect postoperative pneumonia development, and pulmonary function improvement alone may not have enough power to reduce the incidence. Otherwise, the inadequate efficacy of a single bronchodilator may have caused this result. Generally, combining two bronchodilators with different mechanisms of action, LAMA and long-acting β2 agonist (LABA), can improve efficacy compared with a single bronchodilator without increasing adverse effects [24]. Indeed, combination therapy was more effective than single agents in improving pulmonary function and reducing the risk of COPD exacerbations [25–28], indicating that combination therapy of LAMA/LABA may contribute to reducing postoperative pneumonia after esophagectomy.

Meanwhile, we verified the advantages of perioperative tiotropium inhalation for improving or maintaining pulmonary function and exercise tolerance before and after esophagectomy. It may facilitate surgical treatment for patients with COPD, whose pulmonary function is at the borderline for transthoracic surgery. Moreover, mitigation of the deterioration with inhalation could improve postoperative patient quality of life, considering that obstructive and restrictive ventilatory impairment after esophagectomy would progress even after a minimally invasive approach.

Several limitations should be addressed in this study. First, this is a pilot study consisting of a small sample size in a single institute. We just aimed to estimate outcomes, not to truly investigate significant differences, because no studies examined the effect of tiotropium in patients undergoing esophageal cancer surgery. Second, we experienced the COVID-19 pandemic during this study, which could affect the results, although a recent nationwide study concluded that the morbidity rate during the pandemic did not worsen in patients undergoing esophageal cancer surgery [29]. Third, we did not assess patient-reported and long-term outcomes in this study. Therefore, we could not conclude the association of improving or maintaining pulmonary function and exercise tolerance with improved postoperative patient quality of life and prognosis. Further, we should validate our results and investigate the above issues by conducting a multicenter randomized controlled study in the future.

Conclusions

This study demonstrated the efficacy of perioperative tiotropium inhalation on preoperative pulmonary function and exercise tolerance improvement for patients with COPD undergoing esophagectomy. Perioperative tiotropium did not reduce the incidence of postoperative pneumonia after esophagectomy, but postoperative pulmonary function deterioration could be mitigated with the intervention. Our results may help expand surgical indications for patients with COPD and improve postoperative patient quality of life.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11748-024-02083-1.

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Data availability The datasets generated and analyzed in this study are not publicly available but are available from the corresponding author upon reasonable request.

Declarations

Conflict of interest The authors have no conflicts of interest to declare.

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