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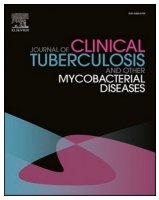

Antimicrobial susceptibility analysis of isepamicin combination treatments in *Mycobacterium abscessus* species

Yukari Kato [a], Hiroaki Ihara [a,f,*], Satomi Takei [b], Ayako Nakamura [g], Yuichi Fujimoto [a], Tetsuya Handoh [b], Kana Kurokawa [a], Yuta Arai [a], Kohei Shibayama [a], Issei Sumiyoshi [a], Yusuke Ochi [a], Junko Watanabe [a], Kazuaki Hoshi [a,d], Shigeki Misawa [h], Shinsaku Togo [a,c], Toshio Naito [e], Yoko Tabe [b], Takashi Miida [b], Kazuhisa Takahashi [a]

[a] *Department of Respiratory Medicine, Graduate School of Medicine, Juntendo University, Faculty of Medicine, Tokyo, Japan*
[b] *Department of Clinical Laboratory Medicine, Graduate School of Medicine, Juntendo University, Faculty of Medicine, Tokyo, Japan*
[c] *Research Institute for Diseases of Old Ages, Graduate School of Medicine, Juntendo University, Faculty of Medicine, Tokyo, Japan*
[d] *Leading Center for the Development and Research of Cancer Medicine, Graduate School of Medicine, Juntendo University, Faculty of Medicine, Tokyo, Japan*
[e] *Department of General Medicine, Graduate School of Medicine, Juntendo University, Faculty of Medicine, Tokyo, Japan*
[f] *Koto Hospital, Tokyo, Japan*
[g] *Juntendo Tokyo Koto Geriatric Medical Center, Tokyo, Japan*
[h] *Department of Clinical Laboratory Technology, Juntendo University, Faculty of Medical Science, Tokyo, Japan*

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ABSTRACT

This study evaluated the antimicrobial potency of the combination of isepamicin (ISP) for *Mycobacterium abscessus* species (MABS). 34 clinical MABS strains were isolated from clinical samples. Of them, 11 (32.4 %) were *M. abscessus* subsp. *abscessus* (Mab), 22 (64.7 %) were *M. abscessus* subsp. *massiliense* (Mma), and one (2.9 %) was *M. abscessus* subsp. *bolletii* (Mbo). We compared susceptibility to sitafloxacin (STFX)-ISP and clarithromycin (CLR)-ISP combinations with those of the antimicrobial agents alone, and synergistic effects were observed in 41.2 % and 17.6 % when treated with STFX-ISP and CLR-ISP. By hierarchical cluster analysis, the isolates divided into treatment-sensitive and treatment-resistant groups. Non-Mma or rough colony isolates were significantly likely to belong to the treatment-sensitive group ($p = 0.024$, $p < 0.001$, respectively). These results suggest that the ISP-containing combination could be a new therapeutic strategy for MABS, especially in cases of non-Mma: treatment-refractory subspecies, and rough morphotypes: high-virulence morphotypes.

1. Introduction

Mycobacterium abscessus species (MABS) is a rapidly growing mycobacteria (RGM) that grows within 7 days on agar media. MABS is resistant to various antibiotics, including antitubercular drugs [1,2]; therefore, it is considered one of the most treatment-refractory nontuberculous mycobacteria (NTM). Some RGMs, such as *M. abscessus*, *M. chelonae,* and *M. smegmatis,* have rough and smooth colony phenotypes depending on glycopeptidolipids (GPLs) expression levels [3]. Notably, smooth morphotypes form biofilms that protect from the surrounding factors, including antibiotics. However, rough morphotypes are generally more virulent than smooth morphotypes. In 2020, new NTM treatment guidelines were developed, and the strategies for MABS treatment have dramatically advanced by increasing the number of novel treatment options, such as clofazimine, linezolid, tigecycline, and inhaled amikacin (AMK) [4]. However, treatment benefits are limited to negative culture conversion, and a complete cure by antimicrobial treatment remains extremely rare. Therefore, it is necessary to develop more effective treatments. Several studies have revealed that high susceptibility to macrolides is associated with good treatment outcomes; therefore, macrolides play a critical role in treating MABS [4,5]. Aminoglycosides, especially AMK, have been proposed as second-choice agents for MABS because of the diversity of administration routes (parenteral or inhaled) and low MIC levels. Moreover, Sitafloxacin (STFX) is an oral fluoroquinolone with higher antimicrobial potency than previous quinolones, such as levofloxacin and ciprofloxacin [6].

* Corresponding author at: Department of Respiratory Medicine, Juntendo University, Faculty of Medicine & Graduate School of Medicine, 2-1-1 Hongo, Bunkyo-Ku, Tokyo 113-8421, Japan.
E-mail address: h-ihara@juntendo.ac.jp (H. Ihara).

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Table 1
MICs of each antimicrobial, subspecies, colony morphotypes, and the characteristics of patients isolated from each strain.

		The characteristics of patients				Alone			Combination		Combination	
Mab	Colony	Age (year)	Sex	Smoking	Comorbidity	ISP	STFX	CLR	STFX	ISP	CLR	ISP
Strain 1	Smooth	79	Male	No	BE, IS	4	4	4	0.5	2	8	0.5
Strain 2	Rough	54	Female	Yes	BE	4	4	4	0.5	2	2	0.5
Strain 3	Smooth	83	Male	No	BE	8	2	128	1	2	128	8
Strain 4	Smooth	67	Male	No	DM, IS	4	1	1	0.25	2	1	0.5
Strain 5	Rough	65	Male	No	BE, DM, IS	2	2	1	0.12	2	1	0.5
Strain 6	Rough	38	Female	Yes	–	2	0.5	0.12	0.12	2	0.12	0.5
Strain 7	Rough	56	Female	No	IS	1	1	4	0.12	1	4	0.5
Strain 8	Smooth	65	Male	No	IS	4	2	128	0.5	2	4	0.5
Strain 9	Rough	53	Male	No	–	2	0.5	8	0.12	2	8	4
Strain 10	Smooth	75	Female	No	DM, IS	8	2	0.5	1	2	0.5	0.5
Strain 11	Smooth	79	Male	Yes	DM, IS	4	2	0.25	4	4	0.25	0.5
Mma												
Strain 12	Rough	79	Male	Yes	BE	8	2	128	0.5	2	128	8
Strain 13	Rough	74	Female	No	–	4	1	0.12	0.25	2	16	2
Strain 14	Smooth	67	Female	No	IS	8	8	1	8	8	1	0.5
Strain 15	Rough	66	Male	Yes	–	4	2	0.06	0.5	2	0.06	0.5
Strain 16	Smooth	44	Female	No	BE, IS	4	2	0.12	1	2	0.25	0.5
Strain 17	Smooth	62	Female	No	BE	8	8	0.25	8	8	0.5	0.5
Strain 18	Smooth	65	Female	No	BE, IS	8	4	128	4	8	128	8
Strain 19	Smooth	41	Female	No	IS	8	8	0.5	8	8	0.5	0.5
Strain 20	Smooth	53	Female	No	–	4	8	0.5	8	4	0.5	0.5
Strain 21	Rough	59	Female	No	IS	2	1	0.06	0.12	2	0.06	0.5
Strain 22	Smooth	50	Male	No	–	4	1	0.12	0.25	2	0.12	0.5
Strain 23	Smooth	69	Male	Yes	IS	8	4	0.5	4	8	0.5	0.5
Strain 24	Rough	78	Male	Yes	–	4	1	0.06	0.25	2	0.06	0.5
Strain 25	Smooth	40	Female	No	IS	8	4	0.25	4	8	0.5	0.5
Strain 26	Smooth	52	Female	No	BE, IS	4	2	0.25	4	4	0.25	0.5
Strain 27	Rough	72	Female	Yes	BE	4	1	0.06	0.12	2	0.06	0.5
Strain 28	Smooth	72	Female	Yes	BE	8	4	0.25	4	8	0.5	0.5
Strain 29	Smooth	58	Male	Yes	–	8	2	0.25	4	8	0.25	0.5
Strain 30	Smooth	73	Male	Yes	–	8	2	0.25	4	8	0.5	0.5
Strain 31	Rough	78	Female	No	BE	2	2	0.25	0.12	2	0.12	0.5
Strain 32	Rough	30	Female	No	BE, IS	8	1	0.25	1	0.5	0.06	0.5
Strain 33	Rough	83	Male	Yes	BE	8	2	0.25	1	2	0.06	0.5
Mbo												
Strain 34	Rough	78	Male	Yes	–	2	1	64	0.12	2	64	4

Abbreviations: Mab, *Mycobacterium abscessus* subsp. *abscessus*; Mma, *Mycobacterium abscessus* subsp. *massiliense*; Mbo, *Mycobacterium abscessus* subsp. *bolletii*; BE, bronchiectasis; DM; diabetes mellitus, IS; immunosuppression

Importantly, several previous studies have suggested that STFX may be effective in MABS treatment [7,8]. Isepamicin (ISP), a derivative of gentamicin B, is one of the latest aminoglycosides introduced into clinical practice (in 1988 in Japan) [9,10] and is less affected by aminoglycoside-inactivating enzymes than AMK [11]. In *in vitro* susceptibility testing of 117 MABS, ISP showed lower MIC levels than did AMK [12]. Therefore, ISP combination therapy is a promising therapeutic option. We previously demonstrated the synergistic antimicrobial effect of the STFX-arbekacin combination on rough morphotypes [13]. Here, we investigated the synergistic antimicrobial effect of ISP, STFX, and clarithromycin (CLR) on the same isolates used in our previous study.

2. Methods

2.1. Isolated strains used in the study

In the present study, 34 identical isolates of MABS strains from our previous studies [13,14] at Juntendo University Hospital from 2011 to 2020 were analyzed for susceptibility to various antimicrobials. Among these 34 strains, 11 (32.4 %), 22 (64.7 %), and one (2.9 %) were identified as *M. abscessus* subsp. *abscessus* (Mab), *M. abscessus* subsp. *massiliense* (Mma), and *M. abscessus* subsp. *bolletii* (Mbo), respectively. The details of the characteristics of the patients from whom MABS was isolated have been described in our previous paper [13].

2.2. Determination of MABS

We identified three subspecies of MABS by analyzing the combination of 16S rRNA, *rpoB*, *hsp65*, and *erm* gene sequence data as in previously described methods [15,16].

Additional methodological information is provided in Supplementary Methods.

2.3. Antimicrobial susceptibility testing

Susceptibility testing was performed following the Clinical and Laboratory Standard Institute (CLSI) guideline M24-A2 [17]. The bacterial suspension was diluted to a concentration of 1–5 $\times$ 10^5 colony-forming units (CFU)/mL in cation-adjusted Mueller-Hinton broth (CAMHB). The final suspension was inoculated onto a customized breakpoint checkerboard plate (Eiken Chemical Co., Ltd., Japan). Subsequently, the concentrations of the antibiotics tested ranged as follows: CLR from 0.06 to 64 μg/mL, ISP from 0.25 to 64 μg/mL, and STFX from 0.12 to 32 μg/mL. MICs for each antimicrobial agent were determined using the CLSI-recommended broth microdilution method. The panels were set up with a 96-channel dispenser, and each well was introduced at a concentration of 1 $\times$ 10^5 CFU/mL. After 7 d of incubation at 35 °C, the MICs were determined. The effect of each combination was assessed using fractional inhibitory concentration index (FICI) analysis [18]. FICI was calculated as follows: Σ (FIC A+FIC B), where FIC A is the MIC of compound A in combination / MIC of compound A alone, and FIC B is the MIC of compound B in combination / MIC of compound B alone. The combination is considered synergistic when the Σ FIC is $\leq$ 0.5, additive

	No.	Subspecies	FICI of STFX+ISP	FICI of CLR+ISP
A	1	Mab	0.625	2.125
	12	Mma	0.5	2
	3	Mab	0.75	2
	13	Mma	0.75	2
	9	Mab	1.24	2
	34	Mbo	1.12	2
	16	Mma	1	2.208
B	2	Mab	0.625	0.625
	15	Mma	0.75	0.625
	31	Mma	1.06	0.605
	8	Mab	0.75	0.156
	33	Mma	0.75	0.303
	32	Mma	1.0625	0.303
	4	Mab	0.75	1.25
	10	Mab	0.75	1.063
	22	Mma	0.75	1.125
	24	Mma	0.75	1.125
	27	Mma	0.62	1.125
	5	Mab	1.06	1.25
	7	Mab	1.12	1.25
	21	Mma	1.12	1.25
	6	Mab	1.24	1.25
C	11	Mab	3	1.125
	26	Mma	3	1.125
	29	Mma	3	1.063
	14	Mma	2	1.063
	19	Mma	2	1.063
	23	Mma	2	1.063
	20	Mma	2	1.125
D	17	Mma	2	2.063
	25	Mma	2	2.063
	28	Mma	2	2.063
	18	Mma	2	2
	30	Mma	3	2.063

FICI ≦0.5	Synergy
0.5 < FICI≦1	Additive
1 < FICI≦2	Indifference
2 < FICI	Antagonism

Fig. 1. Hierarchical cluster analysis of the FICI of sitafloxacin-isepamicin and clarithromycin-isepamicin. The strains were categorized into four groups (clusters A, B, C, and D). Light green, green, yellow, and red signify synergy, additivity, indifference, and antagonism, respectively. Abbreviations: FICI, fractional inhibitory concentration index; STFX, sitafloxacin; ISP, isepamicin; CLR, clarithromycin.

when the Σ FIC is > 0.5 to ≤ 1, indifferent when the Σ FIC is > 1 to ≤ 2, and antagonistic when the Σ FIC is > 2. Inducible CLR resistance is defined as having a MIC of ≤ 2 μg/mL on day 3 and a MIC of ≥ 8 μg/mL on day 14 (Table S2).

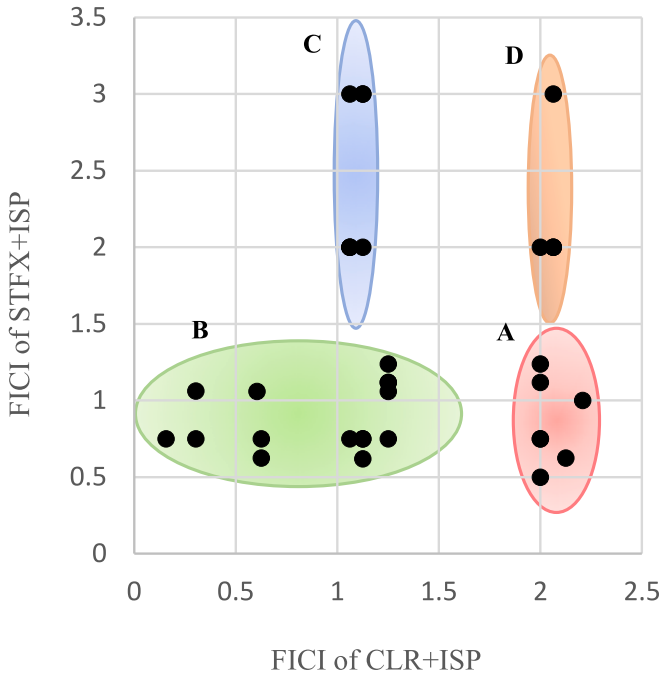

Fig. 2. Distribution map of the FICI of STFX-ISP and CLR-ISP. Each colored circle indicates four clusters identified by hierarchical cluster analysis (red, cluster A; green, cluster B; Blue, cluster C; orange, cluster D). Abbreviations: FICI, fractional inhibitory concentration index; STFX, sitafloxacin; ISP, isepamicin; CLR, clarithromycin.

2.4. Statistical analysis

We performed hierarchical cluster analysis using Ward's method on the FICI of the two antimicrobial combinations. The results are presented visually using a dendrogram. Categorical variables were compared using the chi-square test or Fisher's exact test. Differences were considered statistically significant at $p < 0.05$. All statistical analyses were performed using the JMP software, version 14.2.0 (SAS Institute Japan, Japan).

3. Results

3.1. Cluster analysis of the FIC index of STFX-ISP and CLR-ISP in MABS isolates

The MIC values of the combinations of STFX-ISP and CLR-ISP were compared with those of the antimicrobial agents alone. The subspecies, colony morphotypes, and characteristics of the patients isolated from each strain are described in Table 1. Out of the 34 strains, 27 were detected from sputum or bronchial lavage, 2 from gastric juice, 3 from subcutaneous abscesses, 1 from blood, and 1 from stool. No case was found where multiple species were detected from a single patient. The FICI is divided into the following four categories: synergy, additive, indifference, and antagonism. Moreover, four clusters were identified using a hierarchical cluster analysis of the FICI of STFX-ISP and CLR-ISP (Fig. 1). Of the 34 strains, 14 (41.2 %) treated with STFX-ISP and 6 (17.6 %) treated with CLR-ISP showed synergistic and addictive effects. Synergy and additive effects showed a trend of including clusters A and B and indifference and antagonism effects in clusters C and D. The distribution map between the FICI of STFX-ISP and CLR-ISP revealed that clusters A+B had low levels of the STFX-ISP FICI, while clusters C+D had relatively high levels of the CLR-ISP FICI (Fig. 2).

Table 2
The number of cluster A+B and cluster C+D in each clinical status.

		Cluster		
		A+B N=22 (%)	C+D N=12 (%)	*p* value
Subspecies	Mma	11 (32.4)	11 (32.4)	0.024*
	Non-Mma	11 (32.4)	1 (2.9)	
Age	<65 years	8 (23.5)	6 (17.6)	0.340
	≥65 years	14 (41.2)	6 (17.6)	
Sex	Male	12 (35.3)	4 (11.8)	0.236
	Female	10 (29.4)	8 (23.5)	
Smoking history	Yes	8 (23.5)	5 (14.7)	0.522
	No	14 (41.2)	7 (20.6)	
With bronchiectasis	Yes	10 (29.4)	4 (11.8)	0.377
	No	12 (35.3)	8 (23.5)	
Lesion area	Pulmonary	19 (55.9)	10 (29.4)	0.590
	Extrapulmonary	3 (8.8)	2 (5.9)	
With immunosuppression	Yes	9 (26.5)	7 (20.6)	0.331
	No	13 (38.2)	5 (14.7)	
With diabetes	Yes	3 (8.8)	1 (2.9)	0.556
	No	19 (55.9)	11 (32.4)	
Pretreatment of antibiotics	Yes	9 (26.5)	6 (17.6)	0.610
	No	13 (38.2)	6 (17.6)	
Colony morphotypes	Smooth	7 (20.6)	12 (35.3)	<0.001**
	Rough	15 (44.1)	0 (0)	
Inducible CLR resistance	Yes	5 14.7)	0 (0)	0.137
	No	17 (50.0)	12 (35.3)	

Antibiotics including clarithromycin (n = 3).
* *p* value < 0.05, ** *p* value < 0.01.
Abbreviations: Mma, *Mycobacterium abscessus* subsp. *massiliense;* CLR, clarithromycin

3.2. Relationship between treatment response group and clinical patient characteristics

We investigated the factors involved in the treatment response groups and classified the four clusters into two groups: a treatment-sensitive group (clusters A+B) and a treatment-resistant group (clusters C+D). The Mma strains were likely to belong to the treatment-resistant group ($p = 0.024$), and rough colony morphotypes were included in the treatment-responsive group ($p < 0.001$) (Table 2). Finally, differences in other clinical parameters such as age, sex, smoking history, lesion area, treatment history of antibiotics, complications of bronchiectasis, immunosuppression, inducible CLR resistance, and diabetes were not observed between the two groups.

4. Discussion

The present study investigated the potential efficacy of ISP combination treatment. Interestingly, isolates where both of STFX-ISP and CLR-ISP are effective included Mab and Mbo, which are treatment-refractor subspecies, and rough morphotypes, which are high-virulence morphotypes. To our knowledge, this is the first study to investigate the antimicrobial synergy of ISP combination regimens against MABS.

MABS is one of the most treatment-refractory mycobacteria, and a standard treatment for the complete cure has not yet been reported. The 2020 NTM treatment guidelines recommend new approaches for MABS treatment, which depend on macrolide susceptibility and multidrug therapy with at least two to three active antimicrobials [4]). In addition to antimicrobial susceptibility analysis, we speculated that modification of the colony morphotype is a more appropriate process. Importantly, MABS presents two colony morphotypes: smooth and rough. The smooth morphotype has large amounts of surface GPLs, contributing to forming biofilms, whereas the rough morphotype has fewer GPLs and is associated with cording, which may be responsible for the enhancement of virulence [19]. In general, it has been thought that MABS first colonizes the patient's airway as a smooth morphotype because of the protective efficacy of GPLs in the surrounding environment; then, the rough morphotype alternation enhances its virulence. The study targeting 182 MABS patients reported the rough morphotype presented with longer disease duration, more severe symptoms, higher levels of inflammatory factors such as C-reactive protein, tumor necrosis factor-α (TNF-α), and interferon-γ (IFN-γ), and greater decline in pulmonary function [20]. Similarly, in a study of 71 MABS isolates, a rough morphotype was significantly associated with worse clinical outcomes and various findings, including complications from immunosuppression or pulmonary diseases [21]. Together, these results suggest that an effective treatment for rough-morphotype MABS may be directly associated with good clinical outcomes.

Furthermore, aminoglycosides are important agents in treating MABS next to macrolides. Notably, AMK has shown excellent activity against RGMs in several studies and is currently the most widely used aminoglycoside for treating MABS. However, AMK resistance in MABS has been consistently observed, and the AMK resistance gene in MABS was recently detected. MABS contain various aminoglycoside-modifying enzymes, *aac*(2′), *eis1,* and *eis2*, which are involved in specific aminoglycoside resistance [22]. So, there is increasing attention on the alternative drugs of AMK.

ISP is an aminoglycoside mainly used in Asia that has shown excellent activity against a wide range of bacteria, including MABS. An *in vitro* study in 117 MABS isolates revealed that ISP had a lower level of MIC50 and MIC90 than did AMK (MIC50: 8 μg/mL vs. 16 μg/mL and MIC90: 16 μg/mL vs. 32 μg/mL, respectively) [12]. ISP is a relatively less toxic aminoglycosides [23]. Finally, the ototoxicity of ISP has been reported to be less than that of AMK [24]. In our study, the MICs of ISP were significantly higher than that of AMK ($p < 0.001$, Table S3). But, the differences of detailed molecular mechanisms between AMK and ISP was not analyzed. It is uncertain which are optimal aminoglycosides for the first-line treatment of MABS.

The number of isolates treated in our study was limited, and the clinical data of ISP has been still insufficient. This study was performed *in vitro*, and clinical responses to therapy were not demonstrated. Further studies are required to confirm these findings. In conclusion, we speculated that the STFX-ISP and CLR-ISP combinations presented a synergistic effect in the Mab and Mbo subspecies and rough morphotypes in MABS. Thus, the ISP-containing combination therapy could provide a new therapeutic option in patients with MABS infection.

Ethical approval

The study was approved by the Independent Ethics Committee at Juntendo University Hospital (approval no. 18-010 and 19-038) and adhered to the tenets of the Declaration of Helsinki.

CRediT authorship contribution statement

Yukari Kato: Writing – original draft, Methodology, Formal analysis, Conceptualization. **Hiroaki Ihara:** Writing – review & editing, Writing – original draft, Methodology, Funding acquisition, Formal

analysis, Conceptualization. **Satomi Takei:** Investigation, Data curation. **Ayako Nakamura:** Investigation, Data curation. **Yuichi Fujimoto:** Methodology, Conceptualization. **Tetsuya Handoh:** Investigation, Data curation. **Kana Kurokawa:** Methodology, Conceptualization. **Yuta Arai:** Methodology, Conceptualization. **Kohei Shibayama:** Methodology, Conceptualization. **Issei Sumiyoshi:** Methodology, Conceptualization. **Yusuke Ochi:** Methodology, Conceptualization. **Junko Watanabe:** Methodology, Conceptualization. **Kazuaki Hoshi:** Methodology, Conceptualization. **Shigeki Misawa:** Investigation, Data curation. **Shinsaku Togo:** Writing – review & editing, Supervision, Methodology, Funding acquisition, Conceptualization. **Toshio Naito:** Methodology, Conceptualization. **Yoko Tabe:** Investigation, Data curation. **Takashi Miida:** Investigation, Data curation. **Kazuhisa Takahashi:** Writing – review & editing, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jctube.2024.100464.

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