GHM Open. 2026; 6(1):1-8.

ORIGINAL ARTICLE

DOI: 10.35772/ghmo.2025.01005

Retrospective evaluation of the effectiveness of flomoxef against infections with extended-spectrum β-lactamase-producing *Enterobacterales*

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Abstract: This retrospective, observational study evaluated the effectiveness and optimal dosage of flomoxef (FMOX) against infections with extended-spectrum β-lactamase (ESBL)-producing *Enterobacterales* (ESBLPE) by performing pharmacokinetic/pharmacodynamic analysis. Patients with ESBLPE infections treated using FMOX for ≥ 4 days were included. The time above the minimum inhibitory concentration (MIC) (TAM) was calculated using the FMOX MIC for ESBLPE and simulated FMOX concentration. Ten patients including six women (median age: 76 years, interquartile range: 61–91) were included. Most ESBLPE infections were urinary tract infections (UTIs, 60%). Among the ESBLPE isolates, eight were of *Escherichia coli*, one was of *Klebsiella pneumoniae*, and one was of *Proteus mirabilis*. Four patients had bacteremia secondary to ESBLPE infection. The most frequent MIC for FMOX was ≤ 0.12 mg/L (50%), followed by 0.25 mg/L and 0.5 mg/L. Clinical effectiveness was noted in 77.8% of cases. Regarding UTIs, effectiveness was noted in all five cases. Regarding non-UTIs, only 50% of cases showed clinical effectiveness. Regarding microbiological effectiveness, both cases in which evaluation was possible showed effectiveness. Despite the use of different doses, TAM was 100% in most cases. FMOX may be a potentially effective option for UTIs caused by ESBLPE, though larger studies are needed. FMOX effectiveness in non-UTI cases needs further evaluation.

***Keywords*:** ESBL, TAM, AMR, UTI

1. Introduction

Drug-resistant bacterial infections are a serious global threat. According to a recent report, the number of deaths related to bacterial drug resistance reached 4.71 million in 2021, of which 1.14 million are estimated to be due to antimicrobial resistance itself (*1*). In the context of antimicrobial resistance, third-generation cephalosporin-resistant *Enterobacterales* (3GCRE) are a growing problem worldwide and are ranked in the highest category on the World Health Organization's Bacterial Priority Pathogens List 2024 (*2*). The majority of 3GCRE are extended-spectrum β-lactamase (ESBL)-producing *Enterobacterales* (ESBLPE) (*3,4*). ESBL-producing bacteria contain enzymes that degrade antibacterial drugs with a β-lactam ring and are resistant to multiple antibacterial drugs. Carbapenems are considered the standard treatment for ESBLPE infections. However, there is a strong concern that their overuse will lead to an increase in carbapenem-resistant bacterial infections (*5*).

Flomoxef (FMOX), developed in Japan, is resistant to hydrolysis by ESBLs and is expected to be an alternative to carbapenems for the management of ESBLPE infections (*6*). It is not currently used in Europe or the United States, and data on its effectiveness and optimal dosage are limited (*7,8*). In addition, in Japan, cefmetazole, which is cheaper than FMOX, is also available as an alternative to carbapenems, which may be one of the reasons for the limited clinical data on FMOX in Japan.

Our group has previously reported that cefmetazole is effective against ESBLPE; however, owing to supply issues pertaining to cefmetazole, evaluating the effectiveness of FMOX in a similar analysis would further expand treatment options (*9*). Given the recent instability in the supply of antimicrobial agents, there are significant advantages of having multiple drugs available as carbapenem alternatives. At our facility, the National

Center for Global Health and Medicine, the supply of cefazolin decreased from 2019 to 2021 (*10*), and during this time, FMOX was used as an alternative when cefmetazole was less available following the decline in the supply of cefazolin. We conducted this study to evaluate the effectiveness and optimal dosage of FMOX by performing pharmacokinetic/pharmacodynamic (PK/PD) analysis in actual clinical practice in Japan by including cases from the aforementioned period when FMOX use was more frequent than usual. This study aimed to evaluate the clinical effectiveness and PK/PD-based appropriateness of flomoxef in treating ESBLPE infections in a real-world setting.

2. Materials and Methods

This retrospective observational study was conducted at the National Center for Global Health and Medicine, Japan.

2.1. Participants

Data of patients who met the inclusion criteria between January 2019 and December 2021 were extracted from the hospital's electronic medical records. The inclusion criteria were as follows: *i*) patients with ESBLPE infection for whom ESBLPE were detected in a clinical specimen, and *ii*) patients who received FMOX for at least four consecutive days. The exclusion criteria were as follows: *i*) patients under 18 years of age, *ii*) patients who received antimicrobial agents effective against ESBLPE before FMOX (*e.g*. meropenem or piperacillin/tazobactam, if the antimicrobial agent was ineffective owing to drug sensitivity, the patient was not excluded), *iii*) patients undergoing dialysis, *iv*) patients who wished to opt out from the study, and *v*) patients who were deemed unsuitable for inclusion in the study by the principal investigator (*e.g.*, patients for whom considerable clinical or laboratory data were missing).

2.2. Data collection

The following data was collected from the electronic medical records: age, sex, weight, serum creatinine level (at the start of treatment), main underlying disease, clinical syndrome of infection, treatment history (including history of antimicrobial drug administration and surgery), vital signs, laboratory test results, site of ESBLPE detection, name of bacteria detected at the same time (other than ESBLPE), presence or absence of ESBLPE in the blood, minimum inhibitory concentration (MIC) of FMOX against ESBLPE, number of days from symptom onset to FMOX administration, and FMOX dosage and administration, including infusion time.

2.3. Definitions

Each clinical infection was defined based on the judgement of infectious disease specialists. Microbiological effectiveness was defined as the disappearance of ESBLPE at the site from which the specimen whose culture initially tested positive was obtained. Clinical effectiveness was defined a priori as investigator-assessed improvement, with supportive objective measures including (when available) resolution of fever, improvement of white blood cell count and C-reactive protein, hemodynamic stability, and no required escalation to carbapenem due to non-response. These were judged by infectious disease specialists. Complicated urinary tract infections (UTIs) were defined as UTIs associated with factors that compromise the urinary tract or host defense, including urinary obstruction; urinary retention caused by neurological diseases; organ transplantation; and the presence of foreign bodies such as calculi, indwelling catheters, or other drainage devices (*11*). Creatinine clearance was calculated using the Cockcroft-Gault equation (*12*).

2.4. Microbiology

Species identification and MIC testing were performed using the MicroScan Walkaway 96 system (Siemens Healthcare Diagnostics, Tokyo, Japan) or MALDI Biotyper (Bruker, Bremen, Germany) based on the Clinical and Laboratory Standards Institute (CLSI) criteria (M100-S26) (*13*). The FMOX MIC was evaluated by broth microdilution using the Dry Plate Eiken (Eiken, Tokyo, Japan). The ESBL confirmation test was performed using cefotaxime-clavulanate and ceftazidime-clavulanate disks, according to the CLSI guideline (*14*).

2.5. Analysis of time above MIC

The time above MIC (TAM) for ESBLPE was calculated using the MIC of FMOX against ESBLPE and the concentration of FMOX based on a simulation (*15*). The simulation was performed using Phoenix software (Certara, Princeton, NJ, USA).

2.6. Ethics approval

The ethics committee of the National Center for Global Health and Medicine reviewed and approved this study and waived the need for informed patient consent (NCGM-S-004482-00 and NCGM-S-004889-00). This study was conducted in accordance with the tenets of the Declaration of Helsinki.

3. Results

3.1. Characteristics of the patients

Ten patients were included in the study. Patient

characteristics are summarized in Table 1. The median age of the patients was 76 years (interquartile range [IQR]: 61–91), and six (60%) were female. Underlying diseases included diabetes mellitus in two patients (20%), active malignancy in two patients (20%), and collagen vascular disease/autoimmune disease in one patient (10%). The median body weight was 47.1 kg (IQR: 37.3–59.2). The majority of clinical infections due to ESBLPE were UTIs (six cases [60%], including three cases of complicated UTIs), with one case each of intra-abdominal infection, skin and soft-tissue infections, pneumonia, and others (bacterial translocation due to colorectal cancer). Concurrent infections due to pathogens other than ESBLPE were seen in five patients (50%), with pneumonia seen in two patients (20%) and other infections seen in three patients (Table 1).

Table 1. Characteristics of patients who received FMOX against ESBLPE infection (*n* = 10)

Characteristics	Values
Clinical Characteristics	
Median age, years (IQR)	76 (61–91)
Female sex	6 (60%)
Diabetes mellitus	2 (20%)
Active malignancy	2 (20%)
Collagen disease/Autoimmune disease	1 (10%)
Median body weight, kg (IQR)	47.1 (37.3–59.2)
Median SCr (mg/dl) (IQR)	0.66 (0.55–0.87)
Median CrCl (mL/min) (IQR)	51.8 (27.2–83.7)
Clinical Infections due to ESBLPE	
UTI	6 (60%)
Complicated UTI	3 (30%)
Intraabdominal infection (cholangitis)	1 (10%)
Skin and soft-tissue infection (decubitus ulcer)	1 (10%)
Pneumonia	1 (10%)
Other[A]	1 (10%)
Concurrent infections due to pathogens other than ESBLPE	5 (50%)
Pneumonia	2 (20%)
Other[B]	3 (30%)
Pharmacotherapy	
Any antibiotic treatment prior to FMOX after obtaining culture[C]	5 (50%)
Median days from symptom onset to FMOX initiation (IQR)	3 (0–4)
Median duration of FMOX treatment, days (IQR)	9 (5–11)
Concurrent administration of other antibiotics[D]	5 (50%)
Antibiotics against ESBLPE infection after FMOX treatment[E]	4 (40%)

A. Bacterial translocation due to colon cancer. B. Pelvic inflammatory disease due to *Chlamydia trachomatis* (case 5); tuberculosis (pulmonary and urinary tract; case 3); bacteremia due to bacterial translocation from colon cancer (*Staphylococcus lugdunensis* that was not isolated concurrently with extended-spectrum beta-lactamase–producing *Escherichia coli*, case 6). C. Ampicillin/sulbactam and cefepime (case 1); cefepime and vancomycin (case 3); cefotaxime (case 5); cefazolin (case 6); ceftriaxone (case 7). D. Piperacillin (case 1); trimethoprim-sulfamethoxazole for the prevention of *Pneumocystis jirovecii* pneumonia (case 2); ampicillin (case 3); azithromycin (case 5); ceftriaxone (case 8). E. Fosfomycin (cases 2 and 7); meropenem (case 9); meropenem and levofloxacin (case 10). *Abbreviations*: CrCl, Creatinine clearance; ESBL, Extended-spectrum β-lactamase; ESBLPE, ESBL-producing *Enterobacterales*; FMOX, Flomoxef; IQR, Interquartile range; SCr, Serum creatinine; UTI, Urinary tract infection.

3.2. Pharmacotherapy

The pharmacotherapies used are summarized in Table 1. Antimicrobial treatment prior to FMOX was administered in five (50%) cases after obtaining the culture. The median number of days from symptom onset to FMOX initiation was 3 (IQR: 0–4). The median duration of FMOX treatment was 9 days (IQR: 5–11). Other antibiotics were concurrently administered to five (50%) patients, for all of whom polymicrobial isolation was achieved, or had a concurrent infection other than those due to ESBLPE. Antibiotics against ESBLPE infection were administered after FMOX in four (40%) cases. Treatment was judged clinically ineffective in two cases in which FMOX was escalated to meropenem.

3.3. Microbiology and MIC distribution

The microbiological and MIC distributions are shown in Table 2. Of the 10 ESBLPE infection cases, eight (80%) were attributable to *Escherichia coli*, one (10%) to *Klebsiella pneumoniae*, and another (10%) to *Proteus mirabilis*. Four patients (40%) developed bacteremia secondary to ESBLPE infection. In five cases (50%), other bacteria were detected at the site where ESBLPE was detected (polymicrobial isolation). The most frequent MIC for FMOX was ≤ 0.12 mg/L (*n* = 5 [50%]), followed by 0.25 mg/L (*n* = 4 [40%]), and 0.5 mg/L (*n* = 1 [10%]).

3.4. Clinical and microbiological effectiveness

Clinical effectiveness could be evaluated in nine cases and the treatment was found to be clinically effective in seven of these cases (77.8%, Table 3). In one UTI

Table 2. Microbiology and MIC distribution (*n* = 10)

Characteristics	Values
Species of ESBLPE	
ESBL-producing *Escherichia coli*	8 (80%)
ESBL-producing *Klebsiella pneumoniae*	1 (10%)
ESBL-producing *Proteus mirabilis*	1 (10%)
Bacteremia due to ESBLPE	4 (40%)
Polymicrobial isolation[A]	5 (50%)
MIC of FMOX	
< 0.12 mg/L	5 (50%)
0.25 mg/L	4 (40%)
0.5 mg/L	1 (10%)

A. Polymicrobial isolation was defined as the isolation of bacteria other than ESBLPE from the same culture specimen. *Enterococcus raffinosus*/Coagulase-negative *Staphylococcus* (case 2, urine); *Enterococcus faecalis* (case 3, urine & blood); *Klebsiella variicola* (case 4, urine); *Streptococcus anginosus* (case 9, wound); and *Klebsiella aerogenes* (case 11, sputum). *Abbreviations*: ESBL, Extended-spectrum β-lactamase; ESBLPE, ESBL-producing *Enterobacterales*; FMOX, Flomoxef; MIC, Minimum inhibitory concentration.

case, the evaluation of clinical effectiveness was impossible because of concurrent recurrent aspiration pneumonia. With regard to UTIs, effectiveness was noted in all five cases (100%) in which evaluation was possible. Regarding non-UTIs, clinical effectiveness was noted in only 50% of the cases (2/4). Microbiological effectiveness was evaluable in two cases — one UTI and one non-UTI — and was achieved in both (2/2, 100%).

3.5. Dosing and TAM in patients with ESBLPE infections who were successfully treated with FMOX

As summarized in Table 4, Time Above MIC (TAM) of 100% was achieved in all seven successfully treated patients at the tested MIC thresholds (≤ 0.25 mg/L). In the UTI subgroup (n = 5), this target was met across a wide range of dosing schedules (0.5–2 g every 6–24 hours) and at all levels of renal function (creatinine clearance [CrCl] range: < 19 to > 70 mL/min). The two patients in the non-UTI subgroup also achieved 100% TAM; one patient with a CrCl > 70 mL/min received 1g of FMOX every 6 hours, and the other patient with a CrCl of 40–69 mL/min received 2 g every 8 hours.

Table 3. Clinical and microbiological effectiveness

Effectiveness	Values
Clinically effective[A]	7/9 (77.8%)
Clinically effective against UTIs[A]	5/5 (100%)
Clinically effective against non-UTIs	2/4 (50%)
Microbiologically effective[B]	2/2 (100%)
Microbiologically effective against UTI	1/1 (100%)
Microbiologically effective against non-UTI	1/1 (100%)

A. In one case, evaluation was impossible owing to concurrent recurrent aspiration pneumonia. B. An evaluation of microbiological effectiveness was not possible in eight cases because a follow-up culture was not performed at the primary infection site. *Abbreviation*: UTI, Urinary tract infection.

3.6. Characteristics of patients having ESBLPE infections with unfavorable clinical responses to FMOX

The two cases of clinical ineffectiveness were both non-UTI cases (cholangitis and pneumonia, Table 5). The TAM was 88.9-100%, and the patients had multiple comorbidities.

4. Discussion

This study evaluated the effectiveness of a carbapenem-sparing therapy, FMOX, in the treatment of ESBLPE infections, which have become a global problem. Compared with existing studies on the effectiveness

Table 4. Summary of dosing and TAM in patients with infections due to ESBLPE who were successfully treated with FMOX (n = 7)

Dosing	Q (h)	Infusion time	FMOX MIC ≤ 0.12 mg/L	FMOX MIC = 0.25 mg/L	Range of TAM (%)
UTI cases					
CrCl ≥ 70 mL/min					
1 g	6	1 h	1		100
2 g[A]	8	1 h	1		100
CrCl = 40–69 mL/min					
2 g	12	30 min	1		100
CrCl = 20–39 mL/min					
1 g	12	NA	1		100
CrCl < 19 mL/min					
0.5 g	24	30 min		1	100
Non-UTI cases					
CrCl ≥ 70 mL/min					
1 g	6	1 h	1		100
CrCl = 40–69 mL/min					
2 g	8	1 h		1	100

A. After day 4, FMOX was administered as 2 g q12h. Abbreviations: CrCl, Creatinine clearance; ESBL, Extended-spectrum β-lactamase; ESBLPE, ESBL-producing *Enterobacterales*; FMOX, Flomoxef; h, hour (s); MIC, Minimum inhibitory concentration; NA, not available; Q, every; TAM, Time above MIC; UTI, Urinary tract infection.

Table 5. Characteristics of patients with infections caused by ESBLPE with an unfavorable clinical response to FMOX

Age /Sex	Major underlying diseases	Clinical infections/ Bacteremia due to ESBLPE	Species of ESBLPE	Polymicrobial isolation/ Concurrent infections due to pathogens other than ESBLPE	FMOX MIC for ESBLPE (mg/L)	Symptom onset to FMOX initiation (days)	Duration of FMOX treatment (days)	Dosing /Q/ Infusion time (hour)	CrCl (mL/min)	TAM (%)
94/M	Choledocholithiasis, Post-gastric surgery, Hypertension, Diabetes, Congestive heart failure	Cholangitis/Yes	ESBL-producing *Escherichia coli*	No/No	0.25	0	5	1 g/12 h/1	50.7	100
78/M	Rectal cancer (stage IV), Dysphagia, Glottis closure, ARDS, Delirium	Pneumonia/No	ESBL-producing *Proteus mirabilis*	Yes (*Klebsiella aerogenes*)/No	0.5	0	4	1 g/12 h/1	57.6	88.9

Abbreviations: ARDS, Acute respiratory distress syndrome; CrCl, Creatinine clearance; ESBL, Extended-spectrum β-lactamase; ESBLPE, ESBL-producing *Enterobacterales*; FMOX, Flomoxef; M, Male; MIC, Minimum inhibitory concentration; TAM, Time above MIC.

of FMOX, this study is novel in that it verified the effectiveness of FMOX in actual clinical cases by using PK/PD analysis. In addition, a strict judgment about the effectiveness of FMOX as a treatment was targeted by not including cases where the drug was administered for less than four days.

In this study, FMOX was effective in 77.8% (7/9) of cases where clinical effectiveness could be evaluated and in 100% (5/5) of UTI cases. Although different dosing regimens were used within the same renal function category, TAM was 100% in all cases in which treatment was effective. These results were consistent with simulations from previous PK/PD analyses (*15*); however, the current study also included dosage regimens that were not included in the simulation study. Despite the high TAM of 88.9-100%, FMOX was ineffective in two non-UTI cases, and the clinical effectiveness in non-UTI cases was 50% (2/4). Both cases of clinical ineffectiveness were in elderly patients with multiple underlying diseases: one patient had cholangitis and the other had pneumonia. In both cases, the MIC of FMOX was low (0.25 and 0.5 mg/L, respectively; attributable to ESBL-producing *E. coli* and ESBL-producing *P. mirabilis*, respectively). Nevertheless, FMOX was changed to meropenem owing to a lack of clinical response in both cases and was judged to be clinically ineffective.

Table 6 summarizes the studies which, to the best of our knowledge, compared the effectiveness of FMOX and carbapenems (*7,8,16,17*). All of these are observational studies, and although the types of bacteria differed, they all targeted ESBLPE. Two of the four reports showed that FMOX or FMOX/cefmetazole was not inferior to carbapenems (*8,16*), whereas in the other two reports, the use of FMOX was associated with poor prognosis (*7,17*). In a report by Matsumura *et al.* from Japan where the MIC_{90} of FMOX was ≤ 1 mg/L, FMOX was shown to be equivalent to carbapenems (*8*), whereas in another report by Lee *et al.* from Taiwan, FMOX MICs of ≥ 2 mg/L were associated with poor prognosis (*7*). In addition, Matsumura *et al.* reported that UTIs accounted for approximately 60% of infections in the cefmetazole or FMOX group (*8*), whereas according to Lee *et al.*, UTIs accounted for only approximately 20% of the infections in the FMOX group (*7*). Furthermore, Matsumura *et al.* limited their targets to ESBL-producing *E. coli* (*8*), whereas Lee *et al.* reported that ESBL-producing *Klebsiella pneumoniae* accounted for approximately 60% of infections (*7*). Most of the FMOX is excreted in the urine as an unchanged drug (*18*). Tashiro *et al.* (*19*) reported that free T > MIC is the most important PK/PD index for FMOX against ESBL-producing *E. coli*, with a target value exceeding 40%. FMOX protein binding was 36.2 ± 0.5% (*20*). Thus, for TAM with a total concentration assessed at 100%, the free concentration would be at least 60%, which also clinically supports their report on effectiveness (*19*).

Table 6. Previous studies that evaluated the effectiveness of FMOX against ESBLPE

Publication year, first author, country	Target	Patients number	MIC/susceptibility	Conclusion
2006, Lee *et al*., Taiwan (*16*)	ESBL-producing *Klebsiella pneumoniae* bacteremia	FMOX (*n* = 7), carbapenem (*n* = 20)	MICs of FMOX ranged from 0.032 to 2 mg/L (inoculum size 10^5 CFU/mL); from 1 to 8 mg/L (inoculum size 10^7 CFU/mL)	A high Pitt bacteremia score was an independent risk factor for mortality, while the use of FMOX or a carbapenem was not.
2012, Yang *et al*., Taiwan (*17*)	Nosocomial hemodialysis access-related bacteremia secondary to ESBL-producing Kp in patients on maintenance HD	FMOX (*n* = 29), imipenem (*n* = 16), meropenem (*n* = 12)	Only FMOX-susceptible ESBL-Kp were included (≤ 8 mg/L for FMOX were considered susceptible)	FMOX use, Pitt bacteremia score, and catheter-dependent HD for >30 days were independently associated with increased mortality.
2015, Mastumura *et al.*, Japan (*8*)	ESBL-EC bacteremia	Empirical cohort: CF (*n* = 26) *vs* carbapenem (*n* = 45); Definitive cohort: CF (*n* = 59) *vs* carbapenem (*n* = 54). CF (cefmetazole: FMOX = approximately 1:1)	98.3% of ESBL-EC isolates were susceptible (≤ 8 mg/L) to FMOX. The MIC_{50} and MIC_{90} were ≤ 1 and ≤ 1 mg/L, respectively	In patients without a hematological malignancy and neutropenia, CF treatment for patients with ESBL-EC infection was not associated with mortality compared with carbapenem treatment.
2015, Lee *et al.*, Taiwan (*7*)	Bacteremia due to ESBL-EC or ESBL-Kp	FMOX (*n* = 132), carbapenem (*n* = 257)	FMOX MICs of the isolates ranged between 0.25 mg/L and 8 mg/L, with 2 mg/L being the modal MIC (29.0%)	Multivariate regression analysis revealed that FMOX treatment for infection with isolates for which the FMOX MIC was 2–8 mg/L, concurrent pneumonia or urosepsis, and a Pitt bacteremia score of ≥ 4 were independently associated with 30-day mortality.

Abbreviations: CFU, colony-forming units; ESBL, Extended-spectrum β-lactamase; ESBL-EC, ESBL-producing *Escherichia coli*; ESBLPE, ESBL-producing *Enterobacterales*; ESBL-Kp; ESBL-producing *Klebsiella pneumoniae*; FMOX, Flomoxef; HD, Hemodialysis; MIC, Minimum inhibitory concentration.

Considering these and our results, caution is needed regarding the effectiveness of FMOX for non-UTIs and infection with ESBL-producing *K. pneumoniae* based on the current evidence.

At present, there is no mention of a breakpoint for FMOX in the CLSI guideline (*14*) or the European Committee on Antimicrobial Susceptibility Testing guidelines (*21*). In previous reports, MICs of ≤ 8 mg/L were judged to be sensitive (*22*), and this standard is also consistent with the CLSI susceptibility breakpoints for moxalactam (*14*), which is an oxacephem similar to FMOX (*23*). However, it is unclear whether an FMOX MIC as high as 8 mg/L is clinically effective under the standard dosing of FMOX, and as reported by Lee *et al.* (*7*), caution is required for higher MICs.

This study has significant limitations. The primary limitation is the small number of patients; therefore, the results must be interpreted with great caution. This is compounded by the fact that microbiological effectiveness could be examined in only two cases, further limiting the robustness of the findings. In the future, it would be desirable to conduct a randomized controlled trial to investigate the effectiveness of FMOX against ESBLPE infection.

In conclusion, FMOX may be a potentially effective option for UTIs caused by ESBLPE, though larger studies are needed.

Funding: This work was supported by Grants-in-Aid for Scientific Research (grant nos. 22K10598 and 22H03323).

Conflict of Interest: The authors have no conflicts of interest to disclose.

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Received April 7, 2025; Revised September 7, 2025; Accepted September 17, 2025.

Released online in J-STAGE as advance publication October 12, 2025.

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