



# Short-term effects of low-dose tolvaptan in acute decompensated heart failure patients with severe aortic stenosis: The LOHAS registry<sup>☆</sup>

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## ABSTRACT

**Background:** Tolvaptan exerts potent diuretic effects in heart failure patients without hemodynamic instability. Nonetheless, its clinical efficacy for acute decompensated heart failure (ADHF) due to severe aortic stenosis (AS) remains unclear. This study aimed to evaluate the short-term effects of tolvaptan in ADHF patients with severe AS.

**Methods:** The LOW-Dose Tolvaptan (7.5 mg) in Decompensated Heart Failure Patients with Severe Aortic Stenosis (LOHAS) registry is a multicenter (7 centers) prospective registry that assessed the short-term effects of tolvaptan in subjects hospitalized for ADHF with severe AS. A total of 59 subjects were enrolled between September 2014 and December 2017. The primary endpoints were changes in body weight and fluid balance measured daily from baseline up to 4 days.

**Results:** The median [interquartile range] patient age and aortic valve area were 85.0 [81.0–89.0] years and 0.58 [0.42–0.74] cm<sup>2</sup>, respectively. Body weight continuously decreased, and fluid balance was maintained from baseline to day 4 ( $p < 0.001$ ,  $p = 0.194$ , respectively). Median serum B-type natriuretic peptide concentration significantly decreased from 910.5 to 740.0 pg/mL by day 4 ( $p = 0.002$ ). However, systolic blood pressure and heart rate were non-significantly changed ( $p = 0.250$ ,  $p = 0.656$ , respectively). Hyponatremia ( $<130$  mEq/L) and worsening renal function occurred in 2 (3.4%) and 4 (6.8%) patients, respectively.

**Conclusions:** Short-term treatment with low-dose tolvaptan is safe and effective, providing stable hemodynamic parameters in patients with ADHF and severe AS.

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## 1. Introduction

The development of congestive heart failure (HF) in patients with severe aortic stenosis (AS) is associated with a high mortality rate, unless aortic valve replacement (AVR) is performed [1–5]. However, in

some patients with decompensated HF, multiple coexisting disorders make them unable to receive surgical intervention for AS [6,7].

The treatment goal in HF patients with severe AS is to decrease preload and afterload. However, in some cases, diuretic responses to existing natriuretics are severely limited due to a relatively fixed outflow obstruction and delayed recovery from hypotension. Administration of loop diuretics remains the first-line therapy for improving fluid retention in HF patients. Nevertheless, loop diuretics frequently develop electrolyte abnormalities and inhibit the macula densa of the nephron, results in further release of renin and stimulation of neurohormones and acute vasoconstriction response [8]. In the setting of severe AS,

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the intravascular volume depletion alone may be dangerous leading to systematic hypotension, even if transient.

Tolvaptan is an oral selective V2 receptor antagonist that increases net volume loss and improves symptomatic congestion by excretion of free water into urine, maintaining hemodynamics and renal function even in patients with HF [9–13]. However, its clinical efficacy in patients with acute decompensated HF due to severe AS is yet to be clarified. This study aimed to evaluate the short-term effects of tolvaptan in acute decompensated HF patients with severe AS.

## 2. Methods

### 2.1. Study population and design

The LOHAS registry (Low-Dose Tolvaptan in Decompensated Heart Failure Patients with Severe Aortic Stenosis) is a multicenter prospective registry that assessed the short-term effects of tolvaptan in subjects hospitalized for acute decompensated HF and severe AS. Between September 2014 and December 2017, a total of 59 eligible patients were prospectively enrolled in the LOHAS registry. The patients were treated at the Teikyo University School of Medicine (Tokyo, Japan;  $n = 30$ ), St. Marianna University School of Medicine (Kanagawa, Japan;  $n = 9$ ), Tokai University School of Medicine (Kanagawa, Japan;  $n = 6$ ), Nishiarai Heart Center Hospital (Tokyo, Japan;  $n = 5$ ), Osaka City University School of Medicine (Osaka, Japan;  $n = 5$ ), Tokyo Metropolitan Geriatric Medical Center (Tokyo, Japan;  $n = 3$ ), and Nagoya Heart Center (Aichi, Japan;  $n = 1$ ). The inclusion criterion was acute decompensated HF patients with severe AS (aortic valve area  $<1.0 \text{ cm}^2$ ). Patients were diagnosed with HF using the Framingham diagnostic criteria for HF [14]. The primary exclusion criteria were patients with (1) shock (systolic blood pressure [sBP]  $<90 \text{ mmHg}$ ) on admission, (2) acute coronary syndrome within 30 days prior to admission, (3) active systemic infection, (4) hypernatremia ( $\geq 145 \text{ mEq/mL}$ ), and (5) dialysis dependence.

### 2.2. Procedures

Registration was performed immediately after acquisition of informed consent (within 24 h after admission) by an on-site physician. After registration, eligible patients started taking a dose of 7.5 mg of tolvaptan on day 1. Patients concomitantly received all clinically indicated HF therapies including diuretics. The dosing and variety of diuretics therapies were decided by the physician in each hospital. All eligible patients could take medication by mouth or via a gastric tube, even those requiring ventilation assistance. Some patients received mechanical intervention for AS including balloon aortic valvuloplasty (BAV), transcatheter aortic valve implantation (TAVI), or AVR during the treatment period; however, none of the patients underwent mechanical intervention before day 4. A data and safety committee monitored the data to ensure patient safety. All sites received investigational review board approval, and all subjects provided written informed consent. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by each institution's human research committee. This registry was registered with the University Hospital Medical Information Network (Reg No: UMIN000020423).

### 2.3. Endpoints

The primary endpoints were change in body weight between admission and day 4 and change in fluid balance measured daily from baseline up to day 4. Secondary endpoints included change in urine volume, sBP, diastolic blood pressure (dBP), heart rate (HR), and fluid retention presenting as cardiothoracic ratio on chest radiography, which was performed daily from baseline up to day 4. Renal function (serum creatinine, estimated glomerular filtration rate [eGFR], and cystatin C), urine tests (osmolality), neurohumoral factors (serum B-type

natriuretic peptide [BNP]), duration of ventilation assistance, appearance of arrhythmia, in-hospital prognoses (length of intensive care unit [ICU] stay, total hospitalization period, in-hospital mortality), duration between administration and mechanical intervention (TAVI, BAV, AVR), rate of discontinuation of tolvaptan up to day 4, and incidence of hypernatremia ( $>150 \text{ mEq/L}$ ) up to day 4 were also evaluated. Worsening renal function (WRF) was defined as an increase in serum creatinine level  $>0.3 \text{ mg/dL}$  from baseline during hospitalization.

### 2.4. Statistical analysis

Continuous variables were assessed for a normal distribution using the Shapiro–Wilk test and are expressed as mean  $\pm$  standard deviation or as median [interquartile range], as appropriate. Categorical variables are expressed as numeric values and percentages. Changes in continuous variables were analyzed using paired *t*-test or one-way ANOVA. Data were analyzed using PASW version 24 (SPSS Inc., Chicago, Illinois, USA).

## 3. Results

### 3.1. Patient characteristics

The baseline characteristics of the study subjects are presented in Table 1. The median age was 85.0 [81.0–89.0] years and 71.0% of the patients were female. Atrial fibrillation was prevalent in 20 (33.9%) patients and the median creatinine level was 1.07 [1.03–1.11] mg/dL. The median serum cystatin C level was 1.35 [1.02–1.68] mg/L. The median serum sodium level was 140 [138–142] mEq/L and the median BNP level was 910.5 [429.5–1391.0] pg/mL.

### 3.2. Echocardiographic data of the study population

Echocardiographic findings at baseline in the study population are presented in Table 1. The median left ventricular ejection fraction (LVEF) was 51.0% [34.5–57.5%] and the prevalence of patients with LVEF  $<40\%$  was 26.4%. The median aortic valve area was 0.58 [0.42–0.74]  $\text{cm}^2$  and the mean pressure gradient was  $46.9 \pm 30.4 \text{ mmHg}$ . The prevalence of moderate or severe mitral regurgitation (MR) was 13.2%.

### 3.3. Clinical outcomes and events

Clinical outcomes are shown in Table 2, excluding the outcomes of 2 patients who died during the study period. Comparing baseline and day 4, the prevalence of orthopnea, peripheral edema, jugular venous distension, pleural effusion, and lung edema significantly decreased. The cardiothoracic ratio on chest radiography and median serum BNP concentration significantly decreased from 61.7% to 59.4% ( $p < 0.001$ ) and from 910.5 to 740.0 pg/mL ( $p = 0.002$ ), respectively. The prevalence of proteinuria significantly decreased, but the median serum creatinine level and eGFR showed no significant change. However, the median serum sodium concentration significantly increased from 140 to 143 mEq/L ( $p < 0.001$ ).

Clinical events during hospitalization are shown in Table 3. Discontinuation of tolvaptan within 4 days occurred in 7 patients (11.9%). The reasons for discontinuation included hypernatremia, dehydration, decision by the attending physician, and patient refusal. Hypernatremia ( $>150 \text{ mEq/L}$ ) within 4 days after admission occurred in 2 patients (3.4%) and appeared on day 2 in both patients. WRF occurred in 4 patients (6.8%) and the in-hospital mortality rate was 5.1%. Mechanical intervention (surgical or transcatheter aortic valve replacement) was performed for 29 patients (49.2%) within a mean duration of  $5.6 \pm 8.2$  days after admission.

**Table 1**  
Baseline characteristics of the study population.

Variables	
Patient number, n	59
Age, years	85.0 [81.0–89.0]
Male sex	23 (39.0%)
Height, cm	148.1 [141.5–154.7]
Weight, kg	49.8 [40.8–58.8]
BSA, m <sup>2</sup>	1.41 [1.28–1.54]
BMI, kg/m <sup>2</sup>	22.2 [19.5–24.9]
Orthopnea	54 (91.5%)
Peripheral edema	47 (79.7%)
Jugular venous distension	45 (76.3%)
Pleural effusion	47 (79.7%)
Lung edema	53 (89.8%)
Cardiothoracic ratio (chest radiograph), %	61.7 [58.1–65.3]
NYHA functional class	
I	0 (0%)
II	7 (11.9%)
III	26 (44.1%)
IV	26 (44.1%)
Atrial fibrillation	20 (33.9%)
ST change	38 (64.4%)
CRBBB	6 (10.2%)
CLBBB	5 (8.5%)
Heart rate, beats/min	78 [65–91]
Systolic BP, mmHg	125 [109–141]
>140	19 (32.2%)
100–140	38 (64.4%)
<100	2 (3.4%)
Diastolic BP, mmHg	68 [57–79]
Proteinuria	
1+	9 (15.3%)
2+	6 (10.2%)
3+	2 (3.4%)
Urine specific gravity	1.011 [1.008–1.014]
Urine osmolality, mOsm/kg H <sub>2</sub> O	393 [323–463]
Serum creatinine, mg/dL	1.07 [1.03–1.11]
Cystatin C, mg/L	1.35 [1.02–1.68]
Serum sodium, mEq/L	140 [138–142]
Serum osmolality, mOsm/kg H <sub>2</sub> O	292.0 [285.5–298.5]
BNP, pg/mL	910.5 [429.5–1391.0]
Echocardiographic data	
LVDd, mm	46.7 ± 7.8
LVDs, mm	35.5 ± 8.4
IVS, mm	12.0 [10.3–13.7]
PW, mm	11.0 [9.2–12.8]
LVEF, %	51.0 [34.5–57.5]
LVEF <40%	14 (26.4%)
LVEDV, mL	87.9 [67.5–108.3]
LVESV, mL	40.7 [30.0–65.3]
SV (by PW), mL	56.6 ± 17.7
SVI, mL/m <sup>2</sup>	38.2 ± 12.0
SVI <35 mL/m <sup>2</sup>	21 (39.6%)
Aortic valve area, cm <sup>2</sup>	0.58 [0.42–0.74]
Aortic valve area index, cm <sup>2</sup> /m <sup>2</sup>	0.38 [0.28–0.48]
Mean pressure gradient, mmHg	46.9 ± 30.4
DCT, ms	220.0 [158.2–282.0]
E/e' ratio	21.6 [15.0–28.2]
LA volume, mL	94.8 [73.4–116.2]
IVC diameter (expiration), mm	10.0 [5.3–14.8]
IVC diameter (inspiration), mm	5.0 [–0.8–10.8]
AR moderate/severe, %	4 (7.5%)
MR moderate/severe, %	7 (12.2%)
TR moderate/severe, %	5 (9.4%)

Values are expressed as n (%) or mean ± SD or as median [IQR]. AR, aortic valve regurgitation; BMI, body mass index; BNP, B-type natriuretic peptide; BP, blood pressure; BSA, body surface area; CLBBB, complete left bundle branch block; CRBBB, complete right bundle branch block; DCT, deceleration time; IVC, inferior vena cava; IVS, interventricular septum; LA, left atrium; LVDd, left ventricular end-diastolic diameter; LVDs, left ventricular end-systolic diameter; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; MR, mitral valve regurgitation; NYHA, New York Heart Association; PW, posterior wall; SV, systolic volume; SVI, systolic volume index; TR, tricuspid valve regurgitation.

**Table 2**  
Clinical outcomes.

Variable	Baseline	Day 4	p-Value
Patient number, n	59	57	
Orthopnea	54 (91.5%)	9 (15.3%)	<0.001
Peripheral edema	47 (79.7%)	21 (35.6)	<0.001
Jugular venous distension	45 (76.3%)	18 (30.5%)	<0.001
Pleural effusion	47 (79.7%)	36 (61.0%)	0.049
Lung edema	53 (89.8%)	24 (40.7%)	<0.001
Cardiothoracic ratio (chest radiograph), %	61.7 [58.1–65.3]	59.4 [55.2–63.6]	<0.001
Atrial fibrillation	20 (33.9%)	18 (30.5%)	0.790
Proteinuria			0.011
1+	9 (15.3%)	6 (10.2%)	
2+	6 (10.2%)	4 (6.8%)	
3+	2 (3.4%)	1 (1.7%)	
Serum creatinine, mg/dL	1.07 [1.03–1.11]	1.07 [0.71–1.41]	0.321
Cystatin C, mg/L	1.35 [1.02–1.68]	1.49 [1.09–1.89]	0.014
eGFR (mL/min/1.73 m <sup>2</sup> )	36.5 [21.6–51.4]	36.0 [24.7–47.3]	0.066
Serum sodium, mEq/L	140 [138–142]	143 [141–145]	<0.001
BNP, pg/mL	910.5	740.0	0.002
	[429.5–1391.0]	[200.0–1280.0]	

Values are expressed as n (%) or as median [IQR]. BNP, B-type natriuretic peptide; eGFR, estimated glomerular filtration rate.

### 3.4. Endpoints within 4 days after admission

Fig. 1 shows the time courses of changes in body weight, urine volume, and fluid balance. Daily body weight continuously decreased from baseline up to day 4 ( $p < 0.001$ ). Both daily urine volume and fluid balance were continuously maintained up to day 4 ( $p = 0.576$ ,  $p = 0.194$ , respectively).

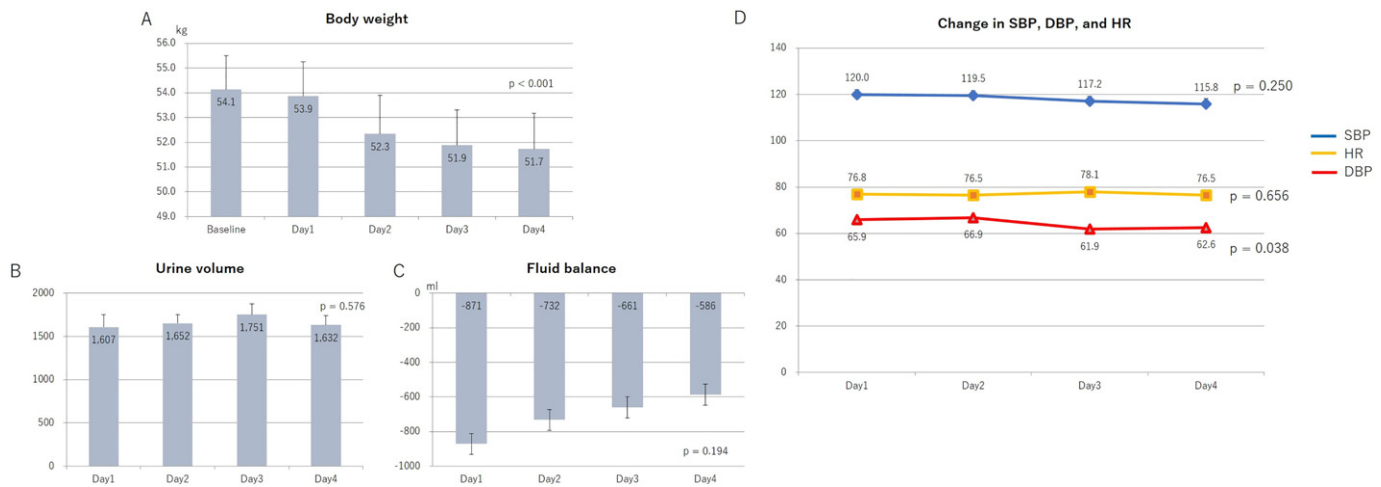
### 3.5. Changes in other parameters within 4 days after admission

Fig. 1D shows the changes in sBP, dBP, and HR. sBP and HR did not significantly change ( $p = 0.250$ ,  $p = 0.656$ , respectively). However, dBP significantly decreased from baseline to day 4 ( $p = 0.038$ ).

**Table 3**  
Clinical events.

Variable	
Patient number, n	59
Discontinuation of tolvaptan up to day 4	7 (11.9%)
2nd day	2
3rd day	3
4th day	2
Reason for discontinuation of tolvaptan	7 (11.9%)
Hyponatremia (>150 mEq)	2
Dehydration	2
Physician judgment	2
Patient refusal	1
Hyponatremia (>150 mEq) up to day 4	2 (3.4%)
4 h	0
2nd day	2
3rd day	0
4th day	0
WRF	4 (6.8%)
Stroke	1 (1.7%)
In-hospital mortality	3 (5.1%)
Ventilation assistance	27
Duration of ventilation assistance (days)	2.9 ± 7.3
ICU stay (days)	2.0 [1.0–3.0]
Total hospital stay (days)	20.0
	[11.5–28.5]
Mechanical intervention for AS	29 (49.2%)
Duration between administration and mechanical intervention for AS	12.0 ± 6.0

Values are expressed as n (%), median [IQR], or mean ± SD. AS, aortic stenosis; ICU, intensive care unit; WRF, worsening renal function.



**Fig. 1.** Changes in body weight, urine volume, fluid balance, systolic or diastolic blood pressure, and heart rate. Daily body weight continuously decreased from baseline up to day 4 ( $p < 0.001$ , A). Both daily urine volume and fluid balance were continuously maintained up to day 4 ( $p = 0.576$ ,  $p = 0.194$ , respectively, B and C). While dBP significantly decreased from baseline to day 4 ( $p = 0.038$ ), sBP and HR did not significantly change ( $p = 0.250$ ,  $p = 0.656$ , respectively, D).

#### 4. Discussion

The present study showed the short-term clinical effects of tolvaptan in acute decompensated HF patients with severe AS from a prospective multicenter registry. Short-term treatment with 7.5 mg of tolvaptan was a safe and effective treatment, showing decreased body weight and improved signs of fluid overload accompanied with stability in hemodynamic parameters in patients with HF and severe AS, who are a high-risk and refractory population.

The treatment for HF with severe AS mainly focuses on relieving stenosis by mechanical intervention, because the medical treatment for HF with severe AS has been unsatisfactory. Administration of loop diuretics remains the first-line therapy for improving fluid retention in HF patients. However, loop diuretics frequently develop electrolyte abnormalities, mainly hyponatremia, hypokalemia and hypomagnesemia. The loop diuretics inhibit the macula densa of the nephron. This results in further release of renin and stimulation of neurohormones and acute vasoconstriction response [8]. In the setting of severe AS, such an acute vasoconstriction response of loop diuretics may be dangerous leading to systematic hypotension, even if transient. Tolvaptan is an oral selective V2 receptor antagonist that increases net volume loss in patients with HF without adversely affecting hemodynamics [9,12,15,16]. Previous pilot studies demonstrated the safety and efficacy of tolvaptan treatment in patients with HF and severe AS [17,18]; however, these studies did not fully clarify its safety and efficacy based on a prospective multicenter design. The present LOHAS registry showed comparative results with these previous reports, demonstrating increased urine output, reduced body weight, and improved symptoms and serum BNP levels without affecting blood pressure, heart rate, and renal function even in elderly patients with severe AS.

Tolvaptan significantly increases water excretion into the urine and occasionally results in hyponatremia. The incidence of hyponatremia was 1.7% in the EVEREST study in which patients were treated with 30 mg of tolvaptan [19]. In the SMILE trial, the incidence of hyponatremia, defined as serum sodium  $\geq 150$  mEq/L, was 3.65% [20]. In the present LOHAS registry, the incidence of hyponatremia, which was also defined as serum sodium  $\geq 150$  mEq/L, was 3.4%. The incidence was comparative with those in previous studies even in patients with HF and severe AS. Previous studies showed an increased mortality rate in patients with hyponatremia acquired in the ICU [21,22]; therefore, the prevention of hyponatremia is important in the use of tolvaptan. A previous study showed that risk factors for hyponatremia after the initiation of tolvaptan included baseline serum sodium concentrations, serum potassium concentrations, ratio of creatinine to blood urea

nitrogen, initial tolvaptan dose, and age [20]. Moreover, to prevent hyponatremia, a lower dose ( $\leq 7.5$  mg) of tolvaptan was recommended for older ( $>80$  years) patients [23]. In the present LOHAS registry, the median age of the study population was 85 years. Even with such a notably elderly population, a dose of 7.5 mg of tolvaptan effectively decreased body weight and improved HF symptoms with a low incidence of hyponatremia. Likewise, in previous studies, the effectiveness of very-low-dose (3.75 mg) tolvaptan for elderly patients with severe AS was reported [17,18]. Our study did not compare the effect of tolvaptan dose; however, it suggested that a dose of 7.5 mg of tolvaptan is also effective and safe for very elderly patients with severe AS.

Patients with HF and severe AS usually have a low cardiac output and decreased renal blood flow. Several studies demonstrated that tolvaptan was less likely to cause WRF than other diuretics by preserving plasma volume through increasing serum osmolality [24,25]. The present LOHAS registry showed a low incidence of WRF, although eGFR significantly decreased during the follow-up. This phenomenon may be due to the very advanced patient age, severe AS with low cardiac output, or dose-dependent effect. With respect to renal function, a lower dose of 3.75 mg of tolvaptan may be better for very elderly patients and for severe AS, as previous reports have shown [17,18].

In recent years, TAVI has evolved as a mainstream therapy for treating patients with severe symptomatic AS, instead of surgical AVR [26,27]. As a result, the number of patients undergoing TAVI worldwide has markedly increased. In patients with HF and worsening hemodynamics undergoing TAVI, medical HF treatment and stabilization of the hemodynamic state are the first-line therapies. As this study showed, tolvaptan is a safe and effective therapy for HF with severe AS, without adversely affecting the hemodynamics. With regard to safety, tolvaptan is useful as a bridge therapy with mechanical interventions for severe AS such as TAVI without decompensation.

##### 4.1. Limitations

This was a prospective single-arm observational study with a relatively small sample size. Therefore, we could not evaluate the direct effects of tolvaptan treatment on HF after the exclusion of the effects of standard therapy. A randomized controlled study comparing tolvaptan with standard therapy and standard therapy alone is necessary to clarify the direct effects of tolvaptan for the treatment of HF. Moreover, this study did not study the dose-dependent effects of tolvaptan. Further studies will be needed to investigate the safety and efficacy of very-low-dose (e.g. 3.75 mg) tolvaptan in patients with HF and severe AS. In addition, the lack of data on diuretics concomitantly used with



tolvaptan and previous heart failure hospitalization are limitations of this study.

## 5. Conclusions

The present LOHAS registry demonstrated the short-term effects of tolvaptan in HF patients with severe AS. Short-term treatment with low-dose tolvaptan was safe and effective for acute decompensated HF, showing increased urine volume, decreased body weight, and improved signs of fluid overload accompanied with stability in hemodynamic parameters in patients with HF and severe AS.

## CRediT authorship contribution statement

**Yusuke Watanabe:** Conceptualization, Formal analysis, Funding acquisition, Investigation, Methodology, Writing - original draft, Writing - review & editing. **Yugo Nara:** Data curation. **Hirofumi Hioki:** Data curation. **Hideyuki Kawashima:** Data curation. **Akihisa Kataoka:** Writing - review & editing. **Makoto Nakashima:** Data curation. **Yosuke Nishihata:** Writing - review & editing. **Kentaro Hayashida:** Writing - review & editing. **Masanori Yamamoto:** Writing - review & editing. **Jun Tanaka:** Writing - review & editing. **Kazuki Mizutani:** Writing - review & editing. **Kentaro Jujo:** Conceptualization, Formal analysis, Investigation, Methodology, Writing - review & editing. **Gaku Nakazawa:** Writing - review & editing. **Masaki Izumo:** Writing - review & editing. **Ken Kozuma:** Visualization, Supervision.

## Declaration of competing interest

The authors declare that there is no conflict of interest.

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