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BRIEF REPORT

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Association of estimated plasma volume and weight loss after long-term administration and subsequent discontinuation of the sodium-glucose cotransporter-2 inhibitor tofogliflozin

Yasuhiro Matsubayashi MD[1] | Akihiro Yoshida PhD[1,2] | Hideki Suganami PhD[3] | Momoko Oe MS[1,2] | Takaaki Sato MD[1] | Yuta Yaguchi MD[1] | Kazuya Fujihara MD[1] | Takaho Yamada MD[1] | Shiro Tanaka PhD[4] | Kohei Kaku MD[5] | Hirohito Sone MD[1]

[1]Department of Haematology, Endocrinology and Metabolism, Faculty of Medicine, Niigata University, Niigata, Japan

[2]Kowa Company, Ltd, Tokyo, Japan

[3]Clinical Data Science Department, Kowa Company, Ltd, Tokyo, Japan

[4]Department of Clinical Biostatistics, Graduate School of Medicine, Kyoto University, Kyoto, Japan

[5]Kawasaki Medical School, Okayama, Japan

Correspondence
Hirohito Sone, MD, Department of Hematology, Endocrinology and Metabolism, Faculty of Medicine, Niigata University, Niigata, Japan.
Email: sone@med.niigata-u.ac.jp

Abstract

Sodium-glucose cotransporter-2 inhibitors (SGLT2) are drugs that have been reported to have several effects through the regulation of plasma volume, for example, antihypertensive effects. This study aimed to clarify the impact of long-term administration and subsequent discontinuation of the SGLT2 inhibitor tofogliflozin on estimated plasma volume (ePV), brain natriuretic peptide (BNP) and the relationship between changes in ePV, BNP and body weight (BW). Data from 157 participants with type 2 diabetes receiving tofogliflozin monotherapy in a phase 3 study were analysed. Changes in variables or correlations among them during a 52-week administration and a 2-week post-treatment period were investigated. Percent change in ePV was calculated using the Strauss formula. Significant decreases in BW, ePV and ln-transformed BNP (ln-BNP) were noted by week 52. %ΔBW was not significantly correlated with %ΔePV and Δln-BNP, while %ΔePV was significantly correlated with Δln-BNP. Two weeks after discontinuation of tofogliflozin, BW, ePV and ln-BNP were significantly increased. %ΔBW was significantly correlated with %ΔePV and Δln-BNP. Furthermore, ePV and BNP were significantly higher than baseline levels.

KEYWORDS
antidiabetic drug, heart failure, SGLT2 inhibitor, type 2 diabetes

1 | INTRODUCTION

Sodium-glucose cotransporter-2 (SGLT2) inhibitors promote diuresis through urinary sodium and glucose excretion, which influence plasma and interstitial volume.[1] The regulation of plasma volume (PV) by SGLT2 inhibitors may be partially associated with its cardioprotective effects.[2] In daily clinical settings, understanding changes in PV associated with SGLT2 inhibitor administration is important. Standard techniques for measuring PV require dilution methods with radioisotopes and so on,[3] making these methods difficult to perform in routine clinical situations. Recently, comparison of actual PV, using a ^{125}I-human serum albumin technique, with estimated PV (ePV) using the Strauss formula after administration of an SGLT2 inhibitor suggested that the degrees of reductions in both using these techniques were similar and that reductions in ePV might be similar to those in the actual PV regardless of participants'

TABLE 1 Values for study participants at baseline, at weeks 52 and 54, and changes from baseline to week 52 and from week 52 to 2 weeks after discontinuation of tofogliflozin therapy

All (n = 157)	Baseline	At week 52	Change from baseline to week 52	At week 54	Change from week 52 to 54
Age, years	57.9 (10.7)	-	-	-	-
Men/women, n (%)	105 (66.9)/52 (33.1)	-	-	-	-
TOFO (20 mg/4 0 mg), n (%)	49 (31.2)/108 (68.8)	-	-	-	-
Concomitant antihypertensive drugs, n (%)	57 (36.3)	-	-	-	-
ARBs/ACE inhibitors/CCBs/beta-blockers, n (%)	40 (25.5)/3 (1.9)/31 (19.7)/5 (3.2)	-	-	-	-
Duration of diabetes, years	5.7 (5.1)	-	-	-	-
HOMA-IR	3.5 (2.8)	-	-	-	-
HOMA-β	40.7 (37.1)	-	-	-	-
Systolic blood pressure, mmHg	129.5 (14.7)	125.2 (15.4)	−4.3 (15.2)*	127.7 (15.7)	2.5 (13.8)**
Diastolic blood pressure, mm Hg	77.5 (10.6)	75.7 (9.2)	−1.8 (9.6)**	77.1 (9.5)	1.4 (8.4)**
Pulse rate	72.8 (11.5)	72.8 (11.1)	0.0 (9.8)	72.4 (10.8)	−0.4 (8.1)
BMI, kg/m^2	25.5 (4.3)	24.3 (4.1)	−1.2 (0.9)*	24.6 (4.2)	0.3 (0.3)*
Body weight, kg	69.0 (15.0)	65.7 (14.6)	−3.3 (2.5)*	66.6 (14.8)	0.9 (0.8)*
Waist circumference, cm	89.5 (10.4)	86.2 (9.7)	−3.3 (3.9)*	-	-
eGFR, mL/min/1.73m^2	83.2 (17.5)	86.0 (19.3)	2.9 (8.5)*	87.7 (19.6)	1.7 (8.4)**
HbA1c, % (mmol/mol)	7.8 (0.8) 61.7 (9.2)	7.2 (0.7) 54.6 (7.6)	−0.7 (0.7)* −7.1 (7.7)*	7.3 (0.8) 55.9 (8.9)	0.1 (0.2)* 1.2 (2.4)*
Fasting plasma glucose, mg/dL (mmol/L)	152.9 (29.7) 8.5 (1.6)	128.0 (20.7) 7.1 (1.1)	−24.9 (25.9)* −1.4 (1.4)*	141.1 (32.5) 7.8 (1.8)	13.1 (21.7)* 0.7 (1.2)*
Fasting insulin, pmol/L	55.8 (45.2)	39.4 (31.2)	−16.4 (24.5)*	48.1 (40.4)	8.7 (22.4)*
Fasting C-peptide, pmol/L	473.5 (229.6)	412.8 (185.0)	−60.7 (125.3)*	457.7 (217.4)	44.9 (128.9)*
FFA, mmol/L	0.58 (0.22)	0.62 (0.21)	0.03 (0.23)	0.48 (0.19)	−0.14 (0.23)*
HDL cholesterol, mg/dL (mmol/L)	61.2 (17.5) 1.6 (0.5)	67.3 (20.8) 1.7 (0.5)	6.1 (10.4)* 0.2 (0.3)*	66.6 (19.1) 1.7 (0.5)	−0.7 (8.6) 0.0 (0.2)
LDL cholesterol, mg/dL (mmol/L)	122.4 (31.2) 3.2 (0.8)	121.9 (30.1) 3.2 (0.8)	−0.5 (22.8) 0.0 (0.6)	122.1 (27.6) 3.2 (0.7)	0.2 (17.8) 0.0 (0.5)
Ln-TG, mg/dL (mmol/L)	4.8 (0.6) 0.3 (0.6)	4.6 (0.6) 0.2 (0.6)	−0.2 (0.5)* −0.2 (0.5)*	4.8 (0.5) 0.3 (0.5)	0.1 (0.4)* 0.1 (0.4)*
Adiponectin, μg/mL	7.2 (3.4)	8.4 (4.0)	1.3 (1.8)*	9.0 (4.3)	0.6 (1.3)*
BNP, pg/mL	8.9 (5.5-14.7)	7.0 (4.3-14.0)	−0.2 (−4.0-2.4)	9.5 (5.9-18.5)	2.0 (0.0-7.3)*
Ln-BNP, ln(pg/mL)	2.2 (0.7)	2.1 (0.7)	−0.1 (0.6)**	2.4 (0.8)	0.3 (0.6)*
Haematocrit, %	43.3 (4.0)	44.2 (4.4)	0.9 (2.7)*	42.8 (4.6)	−1.4 (2.0)*
Haemoglobin, g/dL	14.7 (1.4)	14.9 (1.6)	0.2 (0.9)***	14.5 (1.6)	−0.5 (0.6)*
Uric acid, mg/dL	5.1 (1.3)	4.6 (1.2)	−0.5 (0.8)*	4.9 (1.3)	0.3 (0.7)*
BUN, mg/dL	14.9 (3.4)	16.8 (4.1)	1.9 (3.4)*	14.6 (3.7)	−2.2 (3.3)*
Ln-β-hydroxybutyrate, ln(μmol/L)	3.9 (0.8)	4.5 (0.9)	0.7 (1.0)*	3.7 (0.8)	−0.9 (0.9)*
Estimated PV, mL	2421.3 (378.5)	-		-	
Percent change in estimated PV, %			−2.4 (10.4)***		6.4 (8.1)*

Note: Data are expressed as mean (SD), unless otherwise stated. Data are expressed as median (interquartile range) for BNP values. Paired *t*-test, baseline vs. week 52 and week 52 vs. week 54. Wilcoxon signed-rank test for BNP values, baseline vs. week 52 and week 52 vs. week 54. Baseline estimated PV was calculated by the Kaplan-Hakim formula: (1 − Ht) × (a + [b × weight in kg]) where adjustment factors were a = 1530 in males and 864 in females, and b = 41 in males and 47.9 in females. Percentage change in ePV (%ΔePV) was calculated by the Strauss formula[1]: 100 × (pre Hb/post Hb) × ([100 − post-Ht]/[100 − pre-Ht]) −100.
Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; BMI, body mass index; BNP, brain natriuretic peptide; BUN, blood urea nitrogen; CCB, calcium channel blocker; eGFR, estimated glomerular filtration rate; ePV, estimated plasma volume; FFA, free fatty acids; Hb, haemoglobin; HOMA-IR, homeostatic model assessment of insulin resistance; HOMA-β, homeostatic model assessment of β-cell function; HDL, high-density lipoprotein; Ht, haematocrit; LDL, low-density lipoprotein; ln-BNP, ln-transformed BNP; PV, plasma volume; TG, triglycerides; TOFO, tofogliflozin.
*P < 0.001. **P < 0.05. ***P < 0.01.

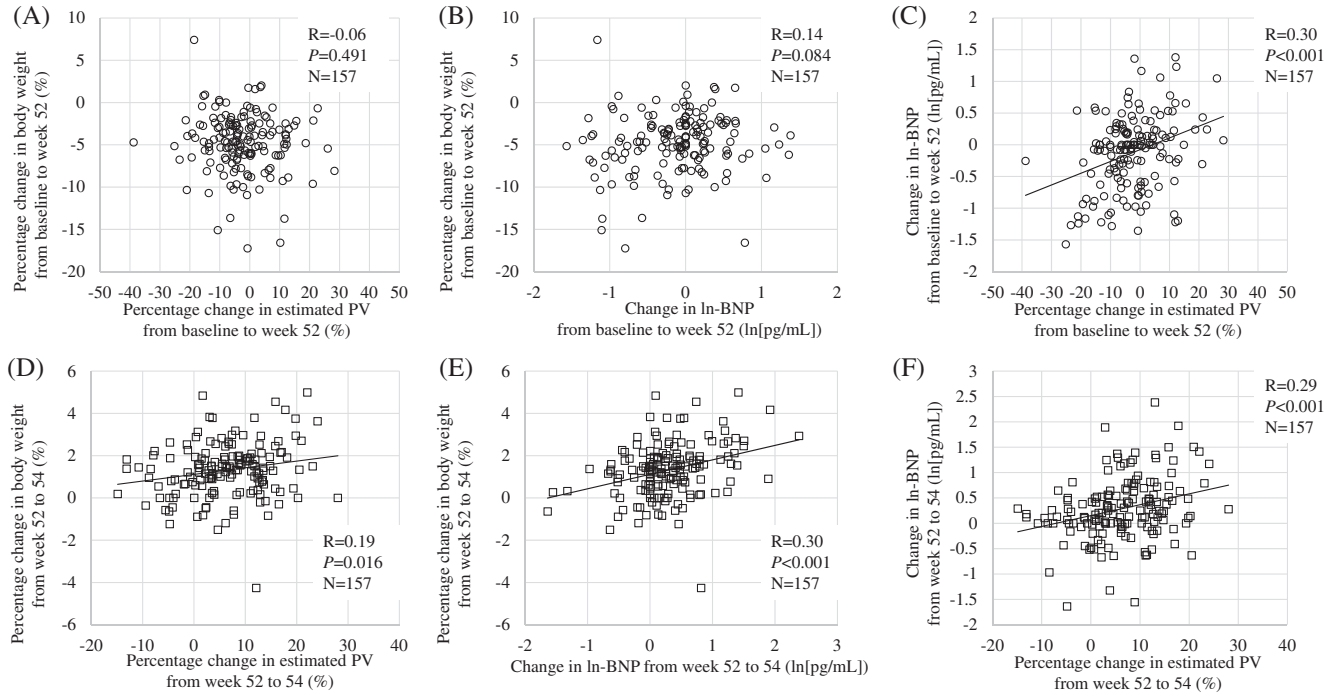

FIGURE 1 Correlations for each combination among changes in body weight, brain natriuretic peptide (BNP) and estimated plasma volume (PV) from baseline to week 52 and from week 52 to 2 weeks after discontinuation of tofogliflozin therapy. (A) Correlation between percentage change in body weight and percentage change in estimated PV (ePV) from baseline to week 52. (B) Correlation between percentage change in body weight and change in ln-transformed BNP (ln-BNP) from baseline to week 52. (C) Correlation between percentage change in ePV and change in ln-BNP from baseline to week 52. (D) Correlation between percentage change in body weight and ePV from week 52 to 2 weeks after discontinuation of tofogliflozin therapy. (E) Correlation between percentage change in body weight and change in ln-BNP from week 52 to 2 weeks after discontinuation of tofogliflozin therapy. (F) Correlation between percentage change in ePV and change in ln-BNP from week 52 to 2 weeks after discontinuation of tofogliflozin therapy. Correlation analysis was performed using Spearman's correlation coefficient

background.[4] However, the validity of using ePV as an index of PV changes due to SGLT2 inhibitors (especially short-term changes) was not fully established,[4] but there is no other PV index that can be easily calculated in routine clinical practice. Since previous studies related to SGLT2 inhibitors used ePV,[5,6] we used ePV in the present study.

Reduced body weight (BW) by SGLT2 inhibitors might be attributable not only to loss of PV but also to fat mass and lean muscle loss via increased calorie loss through urinary glucose excretion.[7] However, little is known about PV after long-term administration of an SGLT2 inhibitor or its association with BW and PV-related variables. How these variables and their relations change when discontinuing this drug in clinical settings is of interest. The present study aimed to clarify these clinical issues.

2 | MATERIALS AND METHODS

A post hoc analysis of a tofogliflozin phase 3 study in individuals with type 2 diabetes (T2D) during 52 weeks of administration of tofogliflozin (half-life 5–6 hours[8]) and 2 weeks after its discontinuation (non-placebo-controlled trial)[9] was conducted. Doses of tofogliflozin monotherapy (20 mg and 40 mg) were compared. The design and results of that study were previously reported (Table S1).[9] Individual-level data from the core 52-week tofogliflozin treatment period and the 2 weeks subsequent to discontinuation were analysed. Because we aimed to investigate PV and its association with BW during both periods, 24 participants who did not complete the entire 54-week study period and whose PV could not be estimated due to missing data were excluded from these analyses. To assess the effects of tofogliflozin on PV correctly, nine participants receiving diuretics as concomitant antihypertensive drugs were also excluded from analysis.

Table 1 shows the baseline values of the 157 study participants. Baseline ePV was calculated using the Kaplan-Hakim formula: (1 − Hematocrit (Ht)) × (a + [b × weight in kg]), where adjustment factors were a = 1530 in males and 864 in females, and b = 41 in males and 47.9 in females.[10] Percentage change in ePV (%ΔePV) was calculated using the Strauss formula[4]: 100 × (pre Hemoglobin (Hb)/post Hb) × ([100 − post Ht]/[100 − pre Ht]) −100. Demographics were summarized with appropriate descriptive statistics (means and standard deviation [SD] or medians and interquartile ranges for continuous variables and numerals and percentages for categorical variables).

Changes in variables from baseline to week 4, baseline to week 52 and from week 52 to week 54, that is, 2 weeks after discontinuation of tofogliflozin, were analysed using a paired *t*-test or Wilcoxon signed-rank test.

Analyses of correlations of combinations among %ΔBW, change in ln-transformed brain natriuretic peptide (Δln-BNP) and %ΔePV

from baseline to week 52 were performed using Spearman's rank-order correlation coefficients. Also investigated were correlations among combinations of %ΔBW, Δln-BNP and %ΔePV from baseline to week 52 and from week 52 to week 54. Finally, correlations between %ΔBW and changes in other clinical variables shown in Tables S2 and S3 were examined. To investigate the correlation between the early effect of tofogliflozin on %ΔePV and the impact of discontinuation on %ΔePV, correlations among combinations of %ΔePV from baseline to week 4 and from week 52 to week 54 were examined. Figure S3 shows line graphs of %ePV and %BW over time.

To identify clinical factors that might affect the %ΔePV from baseline to week 52 (Table S4) or the %ΔBW from week 52 to week 54 (Table S5), clinically significant baseline variables were included as potential factors in a generalized linear model. These models were followed by stepwise model selection for factors with P values <0.15.

All data were analysed using the SAS System, release 9.3 (SAS Institute, Cary, North Carolina). The (two-sided) significance level for each test was 0.05 unless otherwise specified. No multiple comparisons or multiplicity adjustments were performed.

3 | RESULTS

This post hoc analysis included 157 patients with T2D (Table 1). During the 52 weeks of tofogliflozin therapy, BW was significantly reduced (P <0.001 vs. baseline), as were ePV (P <0.01) and ln-BNP (P <0.05; Table 1 and Figure S1). eGFR increased significantly over 52 weeks (P <0.001; Table 1). Higher ln-BNP and body mass index values at baseline were significantly correlated with a greater reduction in %ΔePV after 52 weeks of tofogliflozin therapy (Table S4). %ΔePV was not significantly correlated with %ΔBW but with Δln-BNP during the 52-week treatment period (Figure 1). No significant correlation of Δln-BNP with %ΔBW was noted.

Two weeks after discontinuation of tofogliflozin, significant increases in BW were observed (P <0.001), although the significant reduction in BW from baseline was maintained to week 54 (Table 1 and Figure S1). Similarly, ln-BNP (P <0.001), systolic blood pressure (P <0.05) and ePV (P <0.001) were significantly increased (Table 1). %ΔePV was significantly correlated with both %ΔBW and Δln-BNP, while Δln-BNP was also significantly correlated with %ΔBW (Figure 1). A significant increase in ln-BNP from baseline to week 54 was observed. Additionally, %ePV was significantly increased from baseline to week 54 (mean [standard deviation] +3.50 [11.07]; P <0.001 vs. baseline [Figure S1]).

Weight reduction during the 52-week treatment period was not significantly correlated with weight gain 2 weeks after discontinuation of therapy. Conversely, there were significant and negative correlations between %ΔePV and Δln-BNP from baseline to week 52 of tofogliflozin therapy with changes in these factors during the 2 weeks after discontinuation (Figure S2). There was no significant correlation between %ePV from baseline to week 4 and from week 52 to 2 weeks after discontinuing tofogliflozin (Rho = −0.01, P = 0.905). Finally, greater reductions in ln-BNP during 52 weeks of tofogliflozin therapy were significantly correlated with weight gain 2 weeks after discontinuation (Table S5).

4 | DISCUSSION

This is the first investigation of the effect of the SGLT2 inhibitor tofogliflozin on ePV after its long-term administration (52 weeks) and 2 weeks after its discontinuation in individuals with T2D.

4.1 | Effect on fluid values after long-term administration (52 weeks) of tofogliflozin

Figure 1 shows that weight loss might not be a surrogate of reduced ePV after long-term administration of tofogliflozin.[7] These results (Figure 1, Table S3) suggest that measurements of not only BW, but also of Ht, Hb and BNP be considered in investigating the shift of PV after SGLT2 inhibitor treatment in a clinical setting.

Although the present study cannot clarify the effects of SGLT2 inhibitors on heart failure (HF), it was reported that SGLT2 inhibitors are useful in managing HF,[11] suggesting the importance of SGLT2 inhibitor-induced changes in ePV.[5] The potential importance of interstitial fluid changes to improve HF symptoms may be a feature that distinguishes SGLT2 inhibitors from other diuretics.[1]

A significant increase in eGFR over 52 weeks was observed. There has been no placebo-controlled study on the effect of tofogliflozin on eGFR. A comparison between tofogliflozin and placebo will be needed to identify the role of tofogliflozin in this effect.

4.2 | Effect on fluid values 2 weeks after discontinuation of tofogliflozin

Analysis of participant data 2 weeks after discontinuation of tofogliflozin suggested that fluid gain might be associated with weight gain early after discontinuation (Figure 1, Table S3). Discontinuing SGLT2 inhibitors after long-term treatment might influence variables related to PV even in individuals with relatively low baseline BNP levels, as in our study participants. The generalized linear model indicated that a greater reduction in BNP by week 52 might predict weight gain 2 weeks after discontinuation of tofogliflozin (Table S5). The possibility of a dynamic fluid shift after discontinuing SGLT2 inhibitors should be considered in people with large reductions in BNP after long-term treatment with SGLT2 inhibitors and in those with substantial weight gain after stoppage.

Even more alarming was that BNP was slightly higher than baseline 2 weeks after tofogliflozin discontinuation (Figure S1). Although we could not clarify the mechanism for this effect, one possible mechanism is described below. In the present study, decreased fasting insulin levels (immunoreactive insulin [IRI]) were observed after 52 weeks of tofogliflozin therapy. Then 2 weeks after stopping tofogliflozin, IRI was significantly increased from week 52 (Table 1). An acute increase in serum insulin levels might increase fluid volume[12] and reduce urinary sodium excretion.[13] Taken together, PV re-accumulation by

increased IRI due to discontinuation of tofogliflozin and the disappearance of tofogliflozin-induced urinary excretion might cause the overshoot of ePV from baseline levels (Figure S1). A positive correlation between BW changes and fasting insulin levels after tofogliflozin is discontinued (Table S3) might support that possibility.

The present study had some limitations. First, this was a post hoc analysis of one tofogliflozin study. Second, we could not compare placebo with tofogliflozin because the original study was not a placebo-controlled trial. Third, ePV calculated by the Strauss formula was an indirect measurement. Furthermore, the Strauss formula uses changes in Ht and Hb, which could have been influenced by SGLT2 inhibitor-induced changes in erythropoietin.[14] The possibility that tofogliflozin affects red blood cell production or turnover cannot be excluded. Fourth, the validity of the Strauss formula for PV estimates (especially in the short term) in T2D patients has not been fully established. Further research is needed to determine whether it is appropriate to use ePV to assess short-term changes in PV. However, an increase in %ΔePV was positively correlated with an increase in Δln-BNP after discontinuation in this study. Furthermore, a previous study evaluating PV using indocyanine green observed that short-term administration of an SGLT2 inhibitor and its subsequent discontinuation in a short period (several days) tended to increase PV from baseline[2] as well as changes in ePV as in the present study. Fifth, study participants did not include patients with overt HF. Previous large HF studies with SGLT2 inhibitors[15,16] did not address potential problems associated with discontinuation of SGLT2 inhibitors. Future studies on the effects of discontinuation of SGLT2 inhibitors in HF patients are needed. Sixth, it is difficult to attribute the BW increase after discontinuation of tofogliflozin only to an increase in PV because of lack of body composition data. However, 2 weeks after discontinuing tofogliflozin, BW and BNP increased while the significantly increased HDL cholesterol and adiponectin levels were maintained.

Clinicians should consider that a reduction in fluid volume might be maintained after chronic administration of SGLT2 inhibitors and that a dynamic fluid shift might occur with the discontinuation of chronic administration of SGLT2 inhibitors.

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AUTHOR CONTRIBUTIONS

H. Su. had full access to all of the data in the study and takes responsibility for the integrity of the data and accuracy of the data analysis. Y. M. contributed to the interpretation of data, writing of the first draft, and revision of the manuscript for important intellectual content. H. So., K. F., K. K., A.Y., T. Y., Y. Y., T. S. and M. O. revised the manuscript for important intellectual content. H. Su. created the database, performed statistical analyses, and contributed to the interpretation of the data. S.T. made a secondary check of the integrity of the data and accuracy of the data analysis from a fair perspective as a third party. All authors have read and approved the final manuscript for submission.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ORCID

Akihiro Yoshida https://orcid.org/0000-0002-0573-5298
Hideki Suganami https://orcid.org/0000-0001-9130-0137
Kazuya Fujihara https://orcid.org/0000-0001-6725-4169
Kohei Kaku https://orcid.org/0000-0003-1574-0565
Hirohito Sone https://orcid.org/0000-0003-1263-2817

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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