Association between Serum Insulin-Like Growth Factor-1 and Neurological Severity in Acute Ischemic Stroke

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Background and Purpose Serum insulin-like growth factor-1 (IGF-1) is known to have a neuroprotective effect. This study aimed to determine the effects of serum IGF-1 on the severity and clinical outcome of acute ischemic stroke (AIS).

Methods This study included 446 patients with AIS who were admitted to Hallym University Sacred Heart Hospital within 7 days of stroke onset from February 2014 to June 2017. Serum IGF-1 levels were measured within 24 hours of admission. Stroke severity was measured using the National Institutes of Health Stroke Scale (NIHSS) score at admission, and the functional outcome at 3 months after symptom onset was assessed using the modified Rankin Scale score. The effects of serum IGF-1 levels on stroke severity and 3-month functional outcomes were analyzed using multivariate logistic regression analysis.

Results This study evaluated 379 patients with AIS (age 67.2±12.6 years, mean±standard deviation; 59.9% males) after excluding 67 patients who had a history of previous stroke (n=25) or were lost to follow-up at 3 months (n=42). After adjusting for clinically relevant covariates, a higher serum IGF-1 level was associated with a lower NIHSS score at admission (adjusted odds ratio=0.44, 95% confidence interval=0.24−0.80, p=0.01), while there was no significant association at 3 months.

Conclusions This study showed that a higher serum IGF-1 level is associated with a lower NIHSS score at admission but not at 3 months. Further studies are required to clarify the usefulness of the serum IGF-1 level as a prognostic marker for ischemic stroke.

Key Words acute ischemic stroke, insulin-like growth factor I, modified Rankin Scale.

INTRODUCTION

Ischemic stroke is one of the leading causes of death worldwide, and poststroke functional disabilities may negatively affect the quality of life.[1] The prevalence of ischemic stroke in Korea is currently 1.6% and increasing. The mortality rate at 90 days after stroke is reportedly as high as 3−7%.[2] Poor functional outcomes, defined as a modified Rankin Scale (mRS) score of >3, occur in around 33% and 30% of cases at 3 months and 1 year after stroke, respectively.[2]

Serum biomarkers enable earlier diagnoses and are more cost-effective than imaging methods such as magnetic resonance imaging.[3] Therefore, the importance of serum biomarkers in predicting the risk and prognosis of acute ischemic stroke (AIS) is being emphasized in clinical practice. Some well-known prognostic predictors of AIS include age, initial neurological severity, infarct volume, and infarct location.[4-6] Apart from these known prognostic factors for AIS, various serum biomarkers have been suggested for clinical applications such as predicting the prognosis, guiding treatment, and identifying at-risk patients.[7] However, their successful application in clinical practice has not yet been reported, which is due to the

presence of heterogeneity in the appropriate cutoff values to use and in the causes of stroke. Some limitations are also attributed to the confounding effect of the blood−brain barrier, the serum biomarker concentration may not show a significant correlation with the outcome.[7,8]

Previous studies found that low serum insulin-like growth factor-1 (IGF-1) levels were associated with ischemic heart disease, acute myocardial infarction, and diabetes mellitus (DM), which are risk factors for ischemic stroke.[9,10] Serum IGF-1 was shown to have a neuroprotective effect,[11] and be negatively correlated with cerebrovascular events and the prognosis.[12,13] Other previous studies have investigated the correlations between initial stroke severity, poststroke functional outcome, and initial serum IGF-1 level.[14-18] However, inconsistent results were found for the relationship between serum IGF-1 levels and initial stroke severity, with some studies showing an negative correlation,[17,18] while others showed no definite correlation between these two factors.[19] Increased poststroke serum IGF-1 levels and the IGF-1/IGF-binding protein 3 ratio were reported to be related to unfavorable functional outcomes at 3 months after stroke.[20]

The relationship between the serum IGF-1 level and stroke severity therefore needs to be evaluated further, and so the present study evaluated the predictive value of the serum IGF-1 level in stroke severity and functional outcomes at 3 months after stroke onset.

METHODS

Study design and subjects
This single-center retrospective observational study analyzed data from patients with AIS from the Hallym Stroke Registry from February 2014 to June 2017. Patients were enrolled in the study by applying the following inclusion criteria: 1) admission within 7 days of symptom onset, 2) serum IGF-1 sampled within 24 hours of admission, and 3) AIS documented on diffusion-weighted imaging (DWI). We excluded patients whose functional 3-month outcome was not evaluated or who had a prestroke mRS score of >3.

This study was approved by the Hallym University Sacred Heart Hospital Institutional Review Board (IRB 2019-02-012).

Clinical variables
Clinical information and demographics were collected during hospitalization, including age, sex, height, weight, body mass index (BMI), prestroke mRS score, previous stroke history, hypertension, DM, dyslipidemia, atrial fibrillation (AF), current smoking, and the initial National Institutes of Health Stroke Scale (NIHSS) score. Stroke subtype was classified as follows in accordance with the Trial of Org 10172 in Acute

Stroke Treatment (TOAST) classification:[21] large-artery atherosclerosis (LAA), cardioembolism (CE), small-vessel occlusion (SVO), stroke of other determined etiology (ODE), and stroke of undetermined etiology (UDE). Laboratory data were also collected, including serum IGF-1, high-sensitivity C-reactive protein (hsCRP), serum creatinine, fasting glucose, hemoglobin A1c, low-density lipoprotein cholesterol, and DWI.

Measurement of serum IGF-1
The blood samples for measuring serum IGF-1 levels were collected within 24 hours of admission. Blood was sampled between 6:30 a.m. and 8:00 a.m. after an overnight fast, placed in a serum separating tube, and subjected to centrifugal separation. A chemiluminescence immunoassay (LIAISON® IGF-1, DiaSorin, Saluggia, Italy) was then used to quantify the serum levels.

Outcomes
The primary outcome was stroke severity quantified as the NIHSS score at admission. The NIHSS score was dichotomized into two groups based on the median NIHSS score: mild (≤5) and moderate to severe (≥6). The secondary outcome was the functional outcome assessed using the mRS score at 3 months after symptom onset. A poor functional outcome was defined as an mRS score of 3−6. The 3-month mRS score was collected prospectively in outpatient clinics or through telephone interviews by neurologists or well-trained stroke nurses.

Statistical analyses
Baseline characteristics are presented as mean±standard deviation, median (interquartile range), or frequency and percentage values. Variables for which >5% of the total observations were missing were excluded from the analysis. For variables with <5% missing values, we performed imputation using the mean or median values. No data were missing for the categorical variables in this study. In order to compare baseline characteristics for primary and secondary outcomes, we used Student's t-tests and Mann-Whitney U tests for continuous variables, and Pearson's chi-square tests, Fisher's exact tests, or linear-by-linear associations for categorical variables, as appropriate.

An analysis of the linear correlation between serum IGF-1 level and NIHSS score was performed using Spearman's correlation test. Patients were divided into four groups based on the quartile of the serum IGF-1 level, namely Q1, Q2, Q3, and Q4. Multivariate logistic analysis was applied to calculate the adjusted odds ratios (ORs) and their 95% confidence intervals (CIs) for the potential predictors of outcomes. The following predetermined covariates were included in the multi-

variate model: clinically relevant factors identified in previous studies, age, sex, and variables with a p value of <0.05 in a bivariate analysis. The predetermined subgroup analysis was performed according to the history of DM or chronic kidney disease (CKD), which have previously been associated with serum IGF-1 levels.[22,23] CKD was defined as an estimated glomerular filtration rate of <60 mL/min/1.73 m[2] based on the Modification of Diet in Renal Disease (MDRD) study. All analyses were performed using SPSS for Windows (version 24, IBM Corp., Armonk, NY, USA), and a p value of <0.05 was considered statistically significant.

RESULTS

This study analyzed 379 of 446 patients with AIS who were admitted to Hallym University Sacred Heart Hospital during the study period and in whom the serum IGF-1 level was measured (Fig. 1).

Clinical characteristics

The patients were aged 67.2±12.6 years, and 59.9% of them were male. The median NIHSS score at admission was 5 (interquartile range=9), and 365 of the 379 patients had a prestroke mRS score of 0 or 1. The serum IGF-1 level was 116.0±54.9 ng/mL. Table 1 summarizes the baseline characteristics, risk factors, and initial clinical characteristics. The serum IGF-1 level was negatively correlated with age. The coefficient of determination (r) ranged from 0.09 to 0.30 for the different AIS subtypes, being highest in LAA and lowest in ODE (Supplementary Fig. 1 in the online-only Data Supplement).

Subjects were divided into the following four groups according to their serum IGF-1 levels: Q1, <77.1 ng/mL (n=96); Q2, 77.1–108.0 ng/mL (n=98); Q3, 108.0–151.0 ng/mL (n=93); and Q4, >151.0 ng/mL (n=92). Patients in Q4 were younger than those in Q1 (60.6±12.3 years vs. 75.0±10.2 years, p<0.05) and less likely to have history of AF (16.3% vs. 40.6%, p<0.05), a high hsCRP level (2.19 mg/dL vs. 4.85 mg/dL, p<0.05), and

Fig. 1. Flowchart of patient enrollment in the study. AIS: acute ischemic stroke, IGF-1: insulin-like growth factor-1, mRS: modified Rankin Scale.

severe stroke (4.0 vs. 6.5, p<0.05) (Table 2).

## Serum IGF-1 level and initial NIHSS score

The serum IGF-1 level was negatively correlated with the NIHSS score at admission (r=-0.01, p<0.001) (Fig. 2). We additionally analyzed the association between serum IGF-1 level and initial NIHSS score using multivariate linear regression while adjusting for age, sex, and BMI, which revealed a negative correlation between these variables (r=-0.07, p<0.05). Compared to those in Q1, patients in Q4 had a lower initial NIHSS score (OR=0.45, 95% CI=0.25–0.82). In model 3, with Q1 as the reference, the highest and second-highest IGF-1 levels were independently associated with mild stroke (adjusted OR=0.44 and 0.39, 95% CI=0.24–0.84 and 0.20–0.74, respectively) (Table 3).

Table 1. Baseline characteristics of the study population

	Total (n=379)
Age (years)	67.2±12.6
Sex, male	230 (59.9)
Body mass index (kg/m^{2})	23.7±3.1
Stroke characteristics	
Prestroke mRS score of 0 or 1	365 (96.3)
NIHSS score at admission	5.0 [2.0–11.0]
Onset to admission time (min)	482 [95–1188]
TOAST classification	
Large-artery atherosclerosis	123 (32.5)
Small-vessel occlusion	83 (21.9)
Cardioembolism	108 (28.5)
Stroke of other determined etiology	48 (12.6)
Stroke of undetermined etiology	17 (4.5)
Risk factor	
Hypertension	233 (61.5)
Diabetes mellitus	119 (31.4)
Hyperlipidemia	134 (35.4)
Atrial fibrillation	101 (26.6)
Smoking	131 (34.6)
Previous stroke	74 (19.5)
Systolic blood pressure (mm Hg)	151.6±24.7
Laboratory data	
Insulin-like growth factor-1 (ng/mL)	116.0±54.9
White blood cell count (×10^{3}/μL)	8.39±3.01
Initial glucose (mg/dL)	152.8±63.1
High-sensitivity C-reactive protein (mg/dL)	2.74 [1.00–9.11]
Hemoglobin A1c (%)	6.2±1.2
Serum creatinine (mg/dL)	0.94±0.89
Low-density lipoprotein cholesterol (mg/dL)	111.8±36.4

Data are mean±standard deviation, median [interquartile range], or n (%) values.
mRS: modified Rankin scale, NIHSS: National Institutes of Health Stroke Scale, TOAST: Trial of Org 10172 in Acute Stroke Treatment.
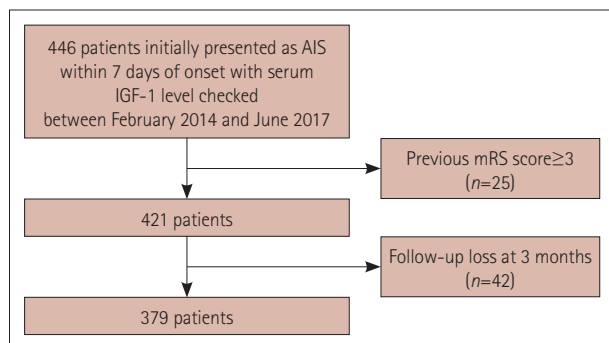
Table 2. Patient characteristics according to quartiles of serum IGF-1 level

	Serum IGF-1 (ng/mL)				*p*
	Q1, <77.1	Q2, 77.1–108.0	Q3, 108.0–151.0	Q4, >151.0	
Age (years)	75.0±10.2	69.9±11.8	63.9±10.7	60.6±12.3	<0.001*
Sex, male	35 (36.5)	55 (56.1)	65 (69.9)	72 (78.3)	<0.001†
Body mass index (kg/m²)	23.0±3.3	23.2±2.7	24.1±3.0	24.4±2.9	<0.001*
Stroke characteristics					
Prestroke mRS score of 0 or 1	94 (97.9)	92 (93.9)	89 (95.7)	90 (97.8)	0.867†
NIHSS score at admission	6.5 [2.25–14.00]	5.0 [2.00–10.00]	4.0 [1.00–7.50]	4.0 [1.00–9.00]	<0.001§
TOAST classification					
Large-artery atherosclerosis	26 (27.1)	26 (26.5)	32 (34.4)	39 (42.4)	0.013†
Small-vessel occlusion	19 (19.8)	22 (22.4)	27 (29.0)	15 (16.3)	0.855†
Cardioembolism	42 (43.8)	28 (28.6)	22 (23.7)	16 (17.4)	<0.001†
Stroke of other determined etiology	3 (3.1)	3 (3.1)	3 (3.2)	7 (7.6)	0.145†
Stroke of undetermined etiology	6 (6.3)	19 (19.4)	9 (9.7)	15 (16.3)	0.188†
Risk factor					
Hypertension	59 (60.4)	65 (66.3)	58 (62.4)	52 (56.5)	0.491†
Diabetes mellitus	24 (25.0)	36 (36.7)	28 (30.1)	31 (33.7)	0.363†
Hyperlipidemia	30 (31.3)	32 (32.7)	41 (44.1)	31 (33.7)	0.386†
Atrial fibrillation	39 (40.6)	30 (30.6)	17 (18.3)	15 (16.3)	<0.001†
Smoking	18 (18.8)	28 (28.6)	40 (43.0)	45 (48.9)	<0.001†
Previous stroke	16 (16.7)	17 (17.3)	25 (26.9)	16 (17.4)	0.511†
Systolic blood pressure (mm Hg)	149.9±22.9	155.0±26.8	154.0±27.0	147.5±20.5	0.116*
Laboratory data					
White blood cell count (×10³/μL)	8.31±3.14	8.31±3.37	8.59±2.87	8.35±2.62	0.902*
Glucose (mg/dL)	148.46±61.01	155.47±62.37	150.42±55.68	156.72±72.88	0.774*
High-sensitivity C-reactive protein (mg/dL)	4.85 [1.94–14.18]	2.42 [0.88–5.08]	2.09 [1.06–8.50]	2.19 [0.52–8.56]	0.001§
Serum creatinine (mg/dL)	0.90±0.50	0.85±0.30	1.02±1.32	0.99±1.03	0.490*
Hemoglobin A1c (%)	6.23±1.38	6.16±1.18	6.18±1.15	6.25±1.20	0.949*
Low-density lipoprotein cholesterol (mg/dL)	102.9±33.8	111.5±33.6	115.0±39.2	118.1±37.6	0.026*

Data are mean±standard deviation, median [interquartile range], or *n* (%) values.
*ANOVA, †Linear-by-linear association, ‡Chi-square test, §Mann-Whitney U test.
IGF-1: insulin-like growth factor-1, mRS: modified Rankin scale, NIHSS: National Institutes of Health Stroke Scale, TOAST: Trial of Org 10172 in Acute Stroke Treatmen.

The subgroup analysis of patients without CKD also showed that the highest serum IGF-1 level was significantly associated with mild stroke (adjusted OR=0.37, 95% CI=0.20−0.71) (Supplementary Table 1 in the online-only Data Supplement). Additionally, we conducted subgroup analyses of patients in each subtype of ischemic stroke: LAA, SVO, and CE. There was no significant association between serum IGF-1 level and initial NIHSS score for any of the tested subtypes of ischemic stroke (Supplementary Table 2 in the online-only Data Supplement).

Serum IGF-1 level and 3-month functional outcome
There was a favorable secondary outcome in 233 patients (61.5%). The results from unadjusted and adjusted analyses of the relationship between serum IGF-1 level and 3-month functional outcome are presented in Table 4. Using Q1 as the reference, the unadjusted analysis showed that the OR for patients in Q4 having a good functional outcome was 1.95 (95% CI=1.07−3.57); however, the OR after adjusting for sex and age was 0.81 (95% CI=0.40−1.63). In addition, after adjusting for additional covariates that were statistically significant in the bivariate analyses of the primary outcome, there was no significant association between serum IGF-1 level and 3-month functional outcome (adjusted OR=0.62, 95% CI=0.27−1.43).

Sensitivity analysis
We performed a sensitivity analysis of the 365 patients whose mRS score before admission was 0 or 1. The association of the initial NIHSS score with the highest serum IGF-1 levels remained significant (OR=0.43, 95% CI=0.23−0.81) (Supplementary Table 3 in the online-only Data Supplement), where-

as that with the 3-month functional outcome did not (OR= 0.60, 95% CI=0.24−1.49) (Supplementary Table 4 in the on-line-only Data Supplement).

DISCUSSION

This study found that higher serum IGF-1 levels measured
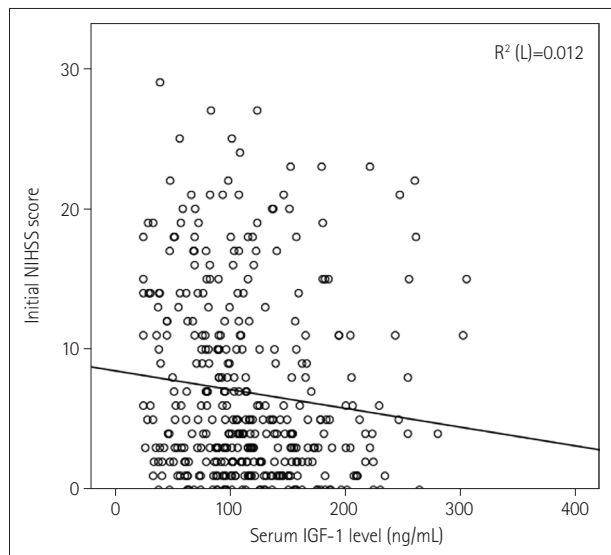
Fig. 2. Correlation between serum IGF-1 level and initial NIHSS score. IGF-1: insulin-like growth factor-1, NIHSS: National Institutes of Health Stroke Scale.

Table 3. Association between serum IGF-1 level and initial stroke severity

Serum IGF-1	OR [95% CI]	p
Model 1		<0.001
Q1	Reference	
Q2	0.78 [0.44–1.37]	0.39
Q3	0.37 [0.20–0.67]	<0.001
Q4	0.45 [0.25–0.82]	0.01
Model 2		0.05
Q1	Reference	
Q2	0.85 [0.48–1.50]	0.57
Q3	0.44 [0.24–0.82]	0.01
Q4	0.57 [0.30–1.09]	0.09
Model 3		<0.001
Q1	Reference	
Q2	0.94 [0.50–1.74]	0.84
Q3	0.39 [0.20–0.74]	<0.001
Q4	0.44 [0.24–0.84]	<0.001

Model 1: crude OR; model 2: model 1 adjusted for age and sex; model 3: model 2 adjusted for body mass index, Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification, atrial fibrillation, smoking, white blood cell count, and high-sensitivity C-reactive protein.
CI: confidence interval, IGF-1: insulin-like growth factor-1, OR: odds ratio.

within 24 hours of admission were associated with mild stroke as defined by the NIHSS score at admission. However, no significant association was found between serum IGF-1 level and functional outcome at 3 months after stroke.

Our study supports previous suggestions of high serum IGF-1 levels exerting neuroprotective effects on stroke severity. A previous study that evaluated the associations of serum IGF-1 levels with stroke severity and outcomes in 221 patients with AIS found a negative correlation between IGF-1 level and initial stroke severity, and that serum IGF-1 levels were lower in patients with severe AIS.[18] However, conflicting results have also been reported for the relationship between serum IGF-1 level and stroke severity. A study that analyzed 255 patients with ischemic stroke found that the mean NIHSS score did not differ significantly between groups with low and high serum IGF-1 levels.[15] These conflicting results may have been caused by differences in the baseline characteristics of the enrolled patients; compared to the patients enrolled in our study, the patients in the study of De Smedt et al.[15] were older (74±11 years vs. 67±13 years) and higher proportions of them had hypertension (63% vs. 61.5%) and AF (30% vs. 26.6%). These risk factors might influence stroke severity more significantly than does the IGF-1 level, thereby masking the effect of serum IGF-1.

IGF-1, along with growth hormone, is critical in the devel-

Table 4. Association between serum IGF-1 level and 3-month functional outcome

Serum IGF-1	OR [95% CI]	p
Model 1		0.177
Q1	Reference	
Q2	1.23 [0.69–2.17]	0.481
Q3	1.23 [0.69–2.19]	0.486
Q4	1.95 [1.07–3.57]	0.029
Model 2		0.424
Q1	Reference	
Q2	0.90 [0.49–1.65]	0.722
Q3	0.59 [0.30–1.14]	0.115
Q4	0.81 [0.40–1.63]	0.547
Model 3		0.172
Q1	Reference	
Q2	0.71 [0.34, 1.51]	0.762
Q3	0.35 [0.15, 0.80]	0.773
Q4	0.62 [0.27, 1.43]	0.172

Model 1: crude OR; model 2: model 1 adjusted for age and sex; model 3: model 2 adjusted for prestroke modified Rankin Scale score, body mass index, Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification, diabetes mellitus, previous stroke, smoking, initial National Institutes of Health Stroke Scale score, white blood cell count, initial glucose level, and high-sensitivity C-reactive protein.
CI: confidence interval, IGF-1: insulin-like growth factor-1, OR: odds ratio.

opment of many major organs, including the central nervous system (CNS). IGF-1 plays an essential role in cell proliferation and the survival of many cells in the body.[13] In the CNS, IGF-1 aids in regulating neural development, such as in neurogenesis, synaptogenesis, and myelination, while inhibiting apoptosis and cell division.[24] Additionally, serum IGF-1 reduces vascular inflammatory responses and atherosclerotic plaque progression, thus acting as a potent neuroprotective compound.[25] There have been a few reports of the neuroprotective effect of IGF-1 on initial stroke severity, with serum IGF-1 levels being lower in patients with more-severe stroke.[17,18]

The present bivariate analysis showed that the 3-month functional outcomes differed significantly between the lowest and highest quartiles of the serum IGF-1 level, but the significance of the association was lost in the multivariate models. The present findings were somewhat inconsistent with those from previous studies. One study found that higher serum IGF-1 levels in patients with AIS are associated with better functional outcomes,[15] while another study found these correlations in elderly patients.[16] These different results may be attributable to the baseline characteristics differing between the serum IGF-1 levels in different quartiles. Our study included more patients with DM and LAA compared with previous studies, which may have influenced the 3-month functional outcomes.

This study was subject to several limitations. First, the serum IGF-1 level was measured once at admission in all AIS patients within 7 days of symptom onset. In contrast, most previous studies included AIS patients within 24 hours of symptom onset. Mattlage et al.[26] suggested that a decrease in IGF-1 during the first week of stroke onset, with the uptake of serum IGF-1 into the brain from the circulation, is related to a better outcome. Because the serum IGF-1 level was measured once within the first week of symptom onset, the level might have already decreased by the time of sampling. However, the serum IGF-1 levels did not differ significantly between groups divided by stroke onset time in our cohort. Second, our study had a single-center, observational design, which might reduce the generalizability of the obtained results. However, our study had the strength of including a larger sample than those in previous studies.

Conclusion

Our findings suggest that the serum IGF-1 level is positively associated with the initial stroke severity. However, unlike some previous studies, we could not find an association between serum IGF-1 levels and functional outcomes after ischemic stroke. Further studies are required to clarify the usefulness of serum IGF-1 levels as a prognostic marker for ischemic stroke.

Author Contributions

Conceptualization: all authors. Data curation: all authors. Formal analysis: Jeeun Lee, Mi Sun Oh, Byung-Chul Lee. Investigation: all authors. Methodology: Jeeun Lee, Jae-Sung Lim, Mi Sun Oh, Byung-Chul Lee. Supervision: Mi Sun Oh, Byung-Chul Lee. Writing—original draft: Jeeun Lee. Writing—review & editing: Jeeun Lee, Mi Sun Oh, Byung-Chul Lee.

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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