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Original Article

Morphologic Restoration After Peroral Endoscopic Myotomy in Sigmoid-type Achalasia

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Background/Aims
Achalasia is a chronic, progressive motility disorder of the esophagus. The sigmoid-type achalasia is an advanced stage of achalasia characterized by severe dilatation and tortuous angulation of the esophageal body. Peroral endoscopic myotomy (POEM) has been reported to provide excellent clinical outcomes for achalasia, including the sigmoid type, but the restoration of esophageal morphology and function remain poorly described. The aim of our study is to investigate esophageal restoration after POEM for sigmoid-type achalasia.

Methods
From 98 patients with achalasia who underwent POEM in the Yonsei University Health System from 2013 to 2018, we recruited 13 patients with sigmoid-type achalasia (7 male; mean age 53.3 years) and assessed morphological and manometric changes in the esophagus.

Results
Clinical success (Eckardt score < 3) was achieved in all cases. After POEM, the average angle of esophageal tortuosity became more obtuse (91.5° vs 114.6°, $P = 0.046$), esophageal body diameter decreased (67.6 vs 49.8 mm, $P = 0.002$), and esophagogastric junction opening widened (6.4 vs 9.5 mm, $P = 0.048$). Patients whose esophageal tortuosity did not improve had longer durations of symptoms than patients with improvement (80.2 vs 636 months, $P < 0.001$). An absence of peristalsis was observed in all patients pre- and post-POEM.

Conclusions
POEM resulted in excellent clinical outcomes and morphologic improvement in sigmoid-type achalasia. These results suggest that the improvement of esophageal tortuosity through POEM reflects a reduced esophageal burden.
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Key Words
Esophageal achalasia; Myotomy; Peroral endoscopic myotomy; Sigmoid-type achalasia

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Introduction

Achalasia is a chronic progressive motility disorder characterized by impaired lower esophageal sphincter relaxation and aperistalsis of the esophageal body,[1] with the esophagus progressing from dilation to bending, resulting in a sigmoid shape. This sigmoid-type achalasia is a progressive form of esophageal achalasia, and most cases have poorer outcomes compared to the non-sigmoid type. Indeed, some have used the term "decompensated" or "end stage" when referring to sigmoid-type achalasia.[2]

The treatment of sigmoid-type achalasia is controversial. Some recommend laparoscopic surgery or even esophagectomy as the primary treatment for sigmoid-type achalasia;[3-5] these approaches are invasive and carry the potential of morbidity.[6] However, peroral endoscopic myotomy (POEM) is an emerging, minimally-invasive procedure for the treatment of achalasia[7] with excellent clinical outcomes and functional restoration (ie, decrease in lower esophageal sphincter pressure, reduction in esophageal diameter, and partial restoration of peristalsis).[8,9] The indications for POEM have expanded to include long-standing, sigmoid-type achalasia, even in cases of previously failed endoscopic treatment or surgical myotomy.[10-12] However, POEM in sigmoid-type achalasia is technically challenging. Although some studies have reported good clinical outcomes of POEM for patients with sigmoid-type achalasia, few studies address morphologic and functional change after POEM.[13,14]

The aim of our study is to investigate morphologic and functional restoration after POEM for sigmoid-type achalasia. We assessed changes in angulation of esophageal tortuosity, diameter of the esophageal body, diameter of the esophagogastric junction (EGJ) opening, and restoration of peristalsis in patients with sigmoid-type achalasia who underwent POEM.

Materials and Methods

Study Subjects

In this study, we retrospectively analyzed a prospectively collected database of POEM subjects. Among 98 patients who underwent POEM at 2 tertiary gastroenterology centers (Gangnam Severance Hospital and Severance Hospital, Yonsei University) from July 2013 to December 2018, 13 patients with sigmoid-type achalasia were enrolled. Achalasia was diagnosed based on clinical symptoms, barium esophagogram, and high-resolution manometry (HRM) according to the Chicago classification, version 3.0. To evaluate patients' symptoms objectively, Eckardt symptom scoring system was used. Clinical success after POEM was defined as Eckardt score of less than 3.[15] This study was approved by the Institutional Review Board of Gangnam Severance Hospital (no. 3-2019-0124).

Esophagography

The patients were fasted more than 9 hours before esophagography. After patients drank 120 mL of barium diluted to 140% weight/volume, the esophageal lumen was observed by fluoroscopy (Shimavision 2000HG; Shimadzu, Kyoto, Japan). The maximum width of the esophageal body and EGJ in the erect frontal view were measured at 1, 2, and 5 minutes. The gastrointestinal radiologist reviewed all barium esophagography results. We followed the descriptive rules published by the Japan Esophageal Society to define and classify sigmoid-type achalasia.[16] Sigmoid type (Sg) was diagnosed when the long axes of the lower esophagus crossed at an angle of 90°-135°. Advanced sigmoid type (aSg) was diagnosed when the angle was below 90° (Fig. 1). In this study, 'sigmoid-type' was defined to include both Sg and aSg.

High-resolution Manometry Procedure

After at least 6 hours of fasting, HRM was performed and the following protocol was used: a 36-channel, solid-state probe system

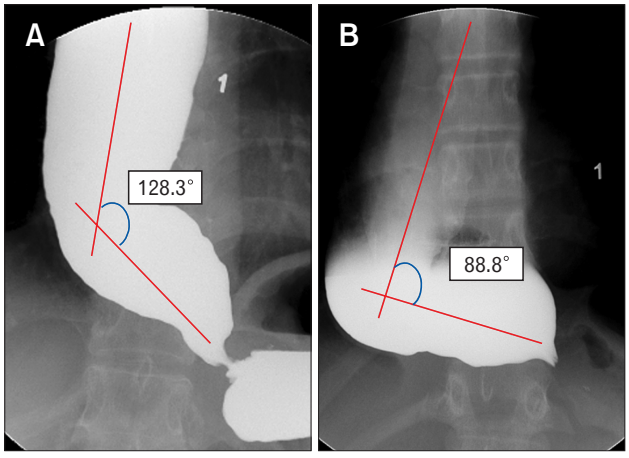

Figure 1. When 2 straight lines for the long axes of the lower esophagus are drawn, a single angle (α) will be formed by the crossing straight lines. (A) Achalasia was defined as sigmoid type when the angle was less than 135°. (B) Achalasia was defined as advanced sigmoid type when the angle was defined as less than 90°. We followed the *Descriptive Rules for Achalasia of the Esophagus*[16] published by the Japan Esophageal Society.

with high-fidelity circumferential sensors at 1-cm intervals was advanced through the nasal canal (Manoscan 360; Sierra Scientific Instruments Inc, Los Angeles, CA, USA). The evaluation is based on the analysis of 10 wet swallows. All relevant parameters (eg, integrated relaxation pressure [IRP], distal contractile integral [DCI], and distal latency [DL]) were calculated according to the Chicago classification, version 3.0.[17]

Peroral Endoscopic Myotomy Procedure

The POEM procedure was performed in patients under general anesthesia and endoscopic CO_2 insufflation as described by Inoue et al.[10] First, 10 mL saline supplemented with 0.3% indigo carmine was injected submucosally at approximately 12 cm proximal to the EGJ. Then, a 2-cm longitudinal mucosal incision using a triangle-tip electrosurgical knife (KD-640L; Olympus, Tokyo, Japan) was made on the mucosal surface to create a mucosal entry into the submucosal space. The submucosal layer was then dissected to create a tunnel along the esophagus and across the EGJ 3 cm into the cardia. Endoscopic myotomy of the circular muscle bundle began 2 cm or 3 cm distal to the mucosal entry and extended 3 cm distal to the EGJ. Finally, endoscopic clips (EZ-CLIP; Olympus, Tokyo, Japan) were used to close the mucosal entry site. Patients were followed up with Eckardt score, HRM and diatrizoate meglumine/diatrizoate sodium (Gastrografin) esophagogram 2 months after POEM. A barium esophagogram was performed between 6-12 months after POEM.

Statistical Methods

The Chi-square test was used to examine associations among categorical variables, and the *t* test was used for non-categorical variables. A P-value < 0.05 was considered statistically significant. SPSS version 12.0 (IBM Corp, Armonk, NY, USA) was used in all analyses.

Results

Patient Characteristics

Baseline characteristics of achalasia patients prior to POEM are shown in Table 1. The study population included 7 male and 6 female patients with a mean age of 53.3 years (range 17-81 years). Eight patients had sigmoid-type achalasia, and 5 patients were diagnosed with advanced sigmoid-type achalasia. The mean duration of symptoms after achalasia diagnosis was 165.7 months (IQR 228). The mean Eckardt score before POEM was 7 (range 4-10). Five of 13 patients (38.5%) had received prior pneumatic dilatation.

Clinical and Functional Outcomes

Clinical success was achieved in all of cases after POEM, as indicated by Eckardt score less than 3, with significant reductions in score between pre- and post-POEM assessments (pre 7.0 ± 2.3 vs post 0.5 ± 0.5, $P = 0.005$) (Fig. 2A and Table 1). Furthermore, esophageal morphology improved post-POEM (Table 1). The angle of esophageal tortuosity became significantly more obtuse after POEM (pre 91.5° ± 13.9° vs post 114.6° ± 17.5°, $P = 0.046$) (Fig. 2B). The diameter of the esophageal body narrowed significantly after POEM (pre 67.6 ± 27.5 mm vs post 49.8 ± 18.0 mm, $P = 0.002$), and EGJ diameter widened significantly (pre 6.4

Table 1. Baseline Characteristics and Parameters of Achalasia Patients

Characteristics	Data		*P*-value
Age (mean [range], yr)	53.3 (17-81)		
Sex (male/female, n)	7/6		
Duration of symptoms (mean [IQR], mo)	165.7 (228)		
Morphologic type (n)			
Sigmoid type	8		
Advanced sigmoid type	5		
Previous pneumatic dilatation (n)	5		
Parameters	Pre-POEM	Post-POEM	
Eckardt score (mean [range])	7.0 (4-10)	0.5 (0-2)	0.005
Angle of esophageal tortuosity (mean ± SD, °)	91.5 ± 13.9	114.6 ± 17.5	0.046
Diameter of esophageal body (mean ± SD, mm)	67.6 ± 27.5	49.8 ± 18.0	0.002
Diameter of EGJ opening (mean ± SD, mm)	6.4 ± 2.6	9.5 ± 3.2	0.048
4s-IRP (mean ± SD, mmHg)	17.5 ± 7.8	8.8 ± 8.2	0.001

4s-IRP, 4-second integrated relaxation pressure; EGJ, esophagogastric junction; IQR, interquartile range; POEM, peroral endoscopic myotomy.

± 2.6 mm vs post 9.5 ± 3.2 mm, $P = 0.048$). Four-second IRP significantly decreased after POEM (pre 17.5 ± 7.8 mmHg vs post 8.8 ± 8.2 mmHg, $P = 0.001$). No esophageal body peristalsis was present in any of the preoperative HRM subjects with all of the sigmoid-type achalasia; furthermore, there was no successful restoration of esophageal body peristalsis, not even a weak or fragmented contraction (DCI > 100 mmHg·sec·cm, DL > 4.5 seconds) after POEM in all subjects (data not shown).

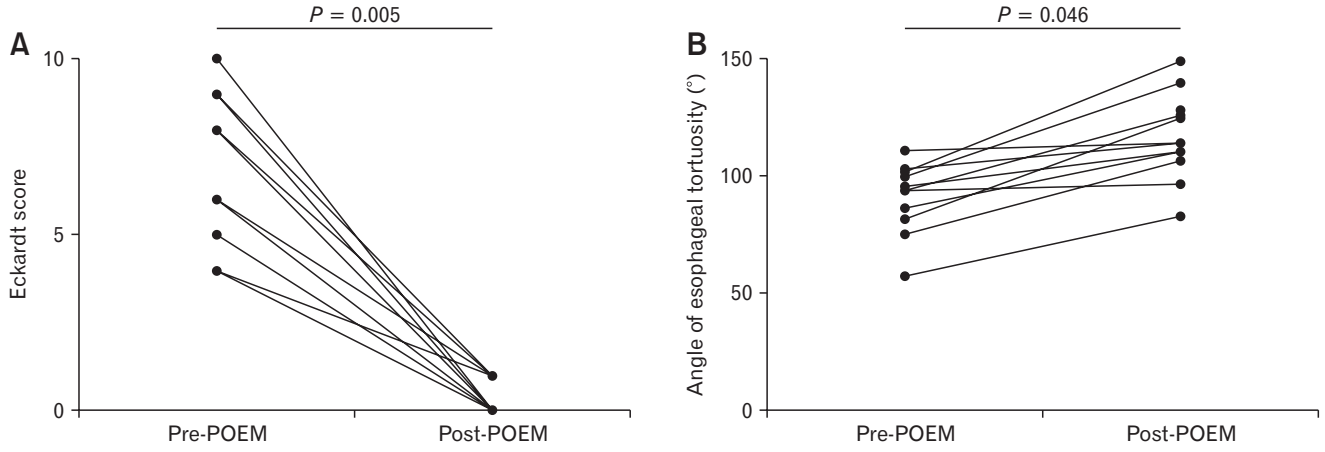

Figure 2. Parameters before and after peroral endoscopic myotomy (POEM) for patients with sigmoid-type achalasia. (A) Eckardt score improved significantly from pre-POEM to post-POEM; clinical success was defined as an Eckardt score of less than 3. (B) Angle of esophageal tortuosity improved significantly from pre-POEM angles to post-POEM.

Table 2. Comparison of Parameters and Outcomes Between Patients With Sigmoid Type and Advanced Sigmoid Type Achalasia

Variables	Sg (n = 8)	aSg (n = 5)	*P*-value
Age (mean [range], yr)	53.1 (23-79)	53.8 (17-81)	> 0.999
Sex (male/female, n)	4/4	3/2	> 0.999
Duration of symptoms (mean [IQR], mo)	219.8 (465)	79.2 (126)	0.622
Previous pneumatic dilatation (n)	3	2	> 0.999
Pre-POEM parameters (mean ± SD)			
Eckardt score	6.8 ± 2.4	7.2 ± 2.1	0.811
The angle of esophageal tortuosity (°)	100.0 ± 5.6	78.0 ± 12.3	0.002
Diameter of esophageal body (mm)	70.2 ± 29.2	54.5 ± 3.5	0.571
Diameter of EGJ opening (mm)	5.4 ± 2.8	7.2 ± 4.1	0.630
4s-IRP (mmHg)	11.2 ± 8.0	13.4 ± 12.5	0.857
Post-POEM parameters (mean ± SD)			
Eckardt score	0.5 ± 0.5	0.6 ± 0.5	0.751
The angle of esophageal tortuosity (°)	120.5 ± 17.0	105.2 ± 15.3	0.130
Diameter of esophageal body (mm)	50.6 ± 19.5	41.0 ± 5.6	0.857
Diameter of EGJ opening (mm)	8.9 ± 3.2	11.3 ± 3.2	0.376
4s-IRP (mmHg)	8.0 ± 6.4	7.9 ± 10.9	0.730
Δ4s-IRP (mean ± SD, mmHg)	−8.8 ± 5.6	−5.2 ± 7.6	0.478
Change in angle of tortuosity (°)	20.5 ± 17.2	27.2 ± 11.2	0.459
Improvement of esophageal tortuosity (n [%])			0.359
Improved group[a]	6 (75.0)	5 (100.0)	
Unimproved group[b]	2 (25.0)	0 (0.0)	

[a]Improved group: angle of tortuosity changed to more than 10°.
[b]Unimproved group: angle of tortuosity changed to less than 5°.
Sg, sigmoid type; aSg, advanced sigmoid type; IQR, interquartile range; EGJ, esophagogastric junction; POEM, peroral endoscopic myotomy; 4s-IRP, 4-second integrated relaxation pressure; Δ4s-IRP, delta 4-second integrated relaxation pressure.

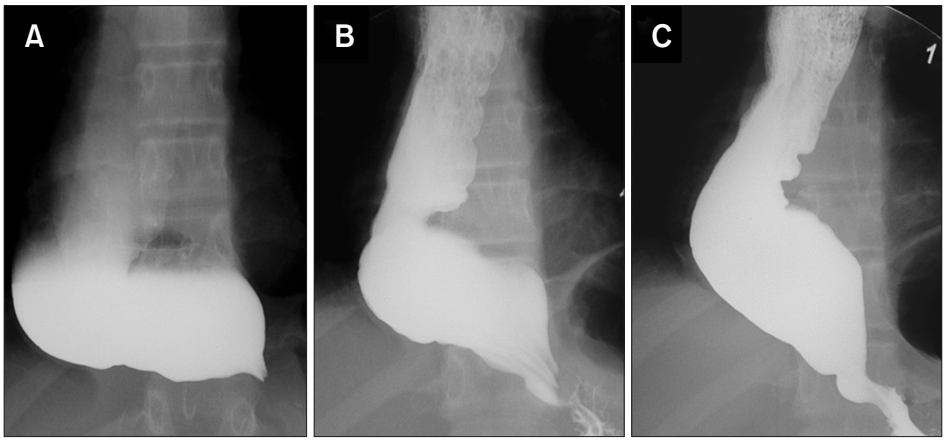

Figure 3. Serial change of a representative advanced sigmoid-type (aSg) achalasia case on barium esophagogram. (A) Before POEM, esophagogram indicated aSg achalasia with typical bird beak sign. (B) Six months after POEM, the angle of esophageal tortuosity became obtuse, opening from 86.6° to 101.4°. The diameter of the esophageal body narrowed from 60 mm to 55 mm, and the diameter of the esophagogastric junction opening widened from 4.5 mm to 10 mm. (C) One year after POEM, the angle of esophageal tortuosity further expanded to 107.4°.

Table 3. Comparison of Parameters and Outcomes Among Patients With and Without Improvement in Angle of Tortuosity (≥ 10° and < 5° Change, Respectively)

Variables	Improved[a] (n = 11)	Unimproved[b] (n = 2)	*P*-value
Age (mean [range], yr)	49.4 (17-81)	75.0 (71-79)	0.269
Sex (male/female, n)	5/6	2/0	0.155
Duration of symptoms (mean [range], mo)	80.2 (12-264)	636 (552-720)	<0.001
Previous pneumatic dilatation (n)	5	0	0.224
Pre-POEM parameters (mean ± SD)			
Eckardt score	7.4 ± 2.1	4.5 ± 0.7	0.085
The angle of esophageal tortuosity (°)	89.5 ± 13.7	102.5 ± 12.0	0.308
Diameter of esophageal body (mm)	62.6 ± 28.1	77.5 ± 19.0	0.643
Diameter of EGJ opening (mm)	6.1 ± 3.3	4.6 ± 2.3	0.327
4s-IRP (mmHg)	12.7 ± 9.7	16.6	0.586
Post-POEM parameters (mean ± SD)			
Eckardt score	0.5 ± 0.5	0.5 ± 0.7	0.915
The angle of esophageal tortuosity (°)	116.5 ± 18.2	104.0 ± 9.8	0.308
Diameter of esophageal body (mm)	43.6 ± 17.5	62.0 ± 7.0	0.143
Diameter of EGJ opening (mm)	10.1 ± 3.1	6.8 ± 3.0	0.145
4s-IRP (mmHg)	7.2 ± 8.3	14.1	0.667
Δ4s-IRP (mean ± SD, mmHg)	−7.7 ± 6.7	−2.5	0.499
ΔDiameter of EGJ opening (mean ± SD, mm)	3.3 ± 2.3	2.2 ± 5.4	0.627
Change in angle of tortuosity (mean ± SD, °)	27.0 ± 12.7	1.5 ± 2.1	0.026
Length of myotomy (mean ± SD, cm)	8.4 ± 2.3	6.5 ± 0.7	0.302

[a]Improved group: angle of tortuosity changed to more than 10°.
[b]Unimproved group: angle of tortuosity changed to less than 5°.
POEM, peroral endoscopic myotomy; EGJ, esophagogastric junction; 4s-IRP, 4-second integrated relaxation pressure; Δ4s-IRP, delta 4-second integrated relaxation pressure; ΔDiameter of EGJ opening, delta Diameter of EGJ opening.

Factors Associated With Morphological Improvement After Peroral Endoscopic Myotomy

Overall, morphological improvements were observed in the esophagogram, with curvature straightening, narrowed esophageal body diameter, and widened EGJ opening. Among achalasia types, we observed no significant difference between Sg and aSg patients in clinical features and pre-POEM parameters, with the exception of angle of tortuosity, which defines the type of sigmoid-type achalasia (Table 2). No significant differences were observed post-POEM between these 2 types. Eleven of 13 cases showed a greater than 10° improvement of angle of tortuosity after POEM. A representative case's barium esophagogram was shown in Figure 3. In 2 cases, the angle changed less than 5°; both cases were Sg. These unimproved patients were not significantly different in most post-POEM parameters (including myotomy length), but they experienced significantly longer symptom duration (80 months vs 636 months, $P < 0.001$) (Table 3).

Discussion

As achalasia progresses, the esophageal lumen dilates, curves, and rotates.[18] A sigmoid-type achalasia is a morphological change observed at the advanced stage of achalasia. Although the diagnosis and treatment of achalasia usually occurs before progression to the sigmoid-type achalasia, some patients receive a late diagnosis with a dilated and sigmoid-type achalasia.[19]

POEM is a compelling treatment option for achalasia because it is less invasive than surgery and has excellent symptom relief.[20] However, in patients with sigmoid-type achalasia, POEM is challenging for several reasons. Firstly, patients with severe esophageal stasis may have inflammation and fibrosis of the submucosa,[21] which hinders submucosal tunneling. Secondly, the severe angles in sigmoid-type achalasia make submucosal tunneling technically difficult.[22]

In our study of POEM for sigmoid-type achalasia, clinical success was achieved in all of the cases after POEM. Across all 13 patients, no complications related to the procedure occurred, and duration of hospitalization was less than 5 days. All patients had decreased esophageal body diameter and widened EGJ opening width, which are associated with symptom relief. The angle of esophageal tortuosity improved in most patients, but patients who did not improve had a significantly longer duration of symptoms than patients with improvement.

The exact mechanism of the morphological changes in achalasia is unknown. Structural differences in the lower and upper esophagus (ie, the lower esophagus is composed of smooth muscle and the upper esophagus is composed of striated muscle) may be the reason why morphological changes occur mostly in the lower esophagus of achalasia patients. Furthermore, muscle physiology involves the basic concept of the sarcomere length-tension relationship. If the maximum permissible sarcomere length is exceeded, the total muscle tension decreases.[23] However, there is one major difference in the length-tension relationship of smooth muscle. With enough recovery time, smooth muscle has the unique ability to shift the length-tension curve, permitting maximum contraction even at a longer muscle length.[24,25] Nonetheless, in sigmoid-type achalasia, long-term esophageal dilation is likely to exceed this adaptive ability of smooth muscle, but its limitation has not yet been studied. After POEM, esophageal morphological changes occur, including a decrease in the LES pressure and widening of the EGJ opening. As esophageal retention improves, the additional pressure by the retention material decreases, thus narrowing the esophageal body and potentially improving the length-tension relationship of the smooth muscle. Further morphological improvements include straightening of the angle of tortuosity; however, this is a hypothesis that requires further research for validation.

This study had several limitations. First, the number of subjects was small. The global incidence of esophageal achalasia is 0.001%, which indicates that it is a very rare disease,[26] and among them, only a small number of patients are diagnosed as sigmoid-type achalasia. Second, the measurement of the angle of tortuosity can be subjective. In some cases, it may be difficult to clearly define the long axis of the esophagus with a single line, but it is generally easy and quick to measure, according to the *Descriptive Rules for Achalasia of the Esophagus*, which adequately reflects the overall tendency.[16] Third, the short follow-up period was not sufficient to determine long-term morphological changes and improvements in the subjects. Therefore, further long-term study is necessary to assess whether the morphological changes are permanent and esophageal remodeling results in long-term, improved motility.

In conclusion, POEM provided morphological improvement and symptom relief for patients with sigmoid-type achalasia. Improvement of esophageal tortuosity may reflect a reduced esophageal burden, but further experience and validation is needed with a larger patient population.

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Conflicts of interest: None.

Author contributions: Jeung Eun Lee, Da Hyun Jung, Jun Chul Park, Young Hoon Youn, and Hyojin Park acquired data; Hong Jin Yoon, Da Hyun Jung, and Young Hoon Youn analyzed and interpreted data; Hong Jin Yoon, and Young Hoon Youn prepared figures, drafted, and revised the manuscript; Young Hoon Youn, and Hyojin Park designed and supervised the study; and all authors read and approved the final manuscript.

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