White matter tract-specific microstructural disruption is associated with depressive symptoms in isolated RBD

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ABSTRACT

Objective: White matter (WM) tract-specific changes may precede gray matter loss in isolated rapid eye movement sleep behavior disorder (iRBD). We aimed to evaluate tract-specific WM changes using tract-specific statistical analysis (TSSA) and their correlation with clinical variables in iRBD patients.

Methods: This was a cross-sectional single-center study of 50 polysomnography-confirmed iRBD patients and 20 age- and sex-matched controls. We used TSSA to identify tract-specific fractional anisotropy (FA) and mean diffusivity (MD) in fourteen major fiber tracts and analyzed between-group differences in these values. Correlations between FA or MD values and clinical variables, including RBD symptom severity, depression and cognition, were evaluated.

Results: Patients with iRBD showed lower FA in the right anterior thalamic radiation (ATR) and higher MD in the bilateral ATR and right inferior fronto-occipital fasciculus (IF-OF) than controls after adjusting for age, sex, and years of education. MD values in the IF-OF positively correlated with scores on the Korean version of the Rapid Eye Movement Sleep Behavior Disorder Questionnaire-Hong Kong (RBDQ-KR, $p = 0.042$) and the Korean version of the geriatric depression scale (GDS-K, $p = 0.002$) in iRBD patients. Only GDS-K scores independently correlated with IF-OF MD values after adjusting for RBDQ-KR scores (adjusted $p = 0.026$).

Conclusion: This study suggests WM microstructural disruption in the bilateral ATR and right IF-OF in patients with iRBD and that alterations in the IF-OF may contribute to depressive symptoms.

1. Introduction

Isolated rapid eye movement sleep behavior disorder (iRBD) is well known to be a prodromal stage of alpha-synucleinopathies and is associated with nonmotor symptoms such as cognitive impairment, autonomic dysfunction, or depression (Postuma et al., 2019). Alterations in

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gray matter structures and corticostriatal or corticocortical functional connectivity have been reported in iRBD patients (Sunwoo et al., 2017), and these changes are reported to be associated with nonmotor symptoms, including cognition (Campabadal et al., 2021). Because alpha-synuclein triggers endogenous axonal pathology (Volpicelli-Daley et al., 2011), the alterations in axons may reveal early changes in neurodegeneration prior to neuronal loss in iRBD.

Diffusion tensor imaging (DTI) has been widely used to non-invasively evaluate white matter (WM) architecture in healthy conditions and in disease (Soares et al., 2013). DTI measures the diffusion of water molecules and characterizes each of the voxel properties by diffusion parameters such as fractional anisotropy (FA) and mean diffusivity (MD). FA measures the directional preference of water diffusion, which represents the orientation of axon fibers and their integrity. MD measures the overall molecular diffusion rate regardless of its orientation, which represents brain tissue integrity (Yang et al., 2011). Higher FA values indicate higher fiber integrity, and lower FA and increased MD values indicate impairments in brain microstructural integrity (Tae et al., 2018).

DTI studies of iRBD first focused on brainstem fibers associated with the pathogenesis of the disease. Reduced axial diffusivity in the pons and substantia nigra were initially reported (Unger et al., 2010a). In iRBD patients, FA values were reduced in the midbrain tegmentum and rostral pons, and MD values were increased in the pontine reticular formation (Scherfler et al., 2011). Recent study using 7 Tesla MRI showed reduced structural connectivity in the pontomedullary brainstem nucelei and increased connectivity in mesopontine brainstem nuclei in iRBD patients (García-Gomar et al. (2022)).

Several studies have also reported changes in cerebral WM in patients with iRBD which was inconsistent. One study using tract-based spatial statistics showed no significant difference in DTI values between iRBD patients and the controls(Rahayel et al., 2015). In other study using different methods, FA was altered in the corticospinal tracts and corpus callosum as well as cerebellar peuncle and brainstem compared to the controls(Holtbernd et al., 2021). Reduced FA value in IRBD was also reported in the substantia nigra along with decreased neuromelanin-sensitive volume and signal intensity(Pyatigorskaya et al., 2017). Compared with patients with clinical PD, prodromal PD patients, including iRBD patients, had altered MD in several WM regions, including the corpus callosum, internal and external capsules, superior and inferior longitudinal fasciculus and corticospinal tract (Ohlhauser et al., 2019b). However, DTI studies of iRBD patients that evaluated WM tract-specific changes are limited.

Tract-specific statistical analysis (TSSA) maps tract diffusion coefficients along with the corresponding subject-specific tractography. Compared to the commonly used tract-based spatial statistics method, TSSA is not affected by intersubject variability and more accurately evaluates tract-specific diffusion coefficients. Using the TSSA method, altered WM integrity in patients with subcortical vascular cognitive impairment (Jung et al., 2016), narcolepsy (Park et al., 2020), obstructive sleep apnea (Koo et al., 2020), and restless legs syndrome (Park et al., 2021) has been reported.

This study aimed to evaluate tract-specific microstructural alterations associated with iRBD using TSSA. Moreover, we evaluated the clinical significance of these microstructural changes in association with the clinical characteristics of iRBD.

2. Materials and methods

2.1. Participants

This was a cross-sectional single-center study of consecutive patients with video-polysomnography (vPSG)-confirmed iRBD who visited Seoul National University Hospital. RBD was diagnosed according to the International Classification of Sleep Disorders (ICSD-3) criteria (American Academy of Sleep Medicine, 2014). Individuals with (1) signs of Parkinsonism, Parkinson's disease, dementia, or other neurological disorders including stroke, significant vascular lesions, head trauma, brain injury, epilepsy, encephalitis, (2) severe medical conditions including advanced liver or kidney disease, heart failure, or ischemic heart disease, or (3) moderate to severe obstructive sleep apnea (apnea-hypopnea index $\geq$ 20) were excluded.

Age- and sex-matched healthy volunteers served as controls. They were screened for any sleep-related symptoms and neurological or psychological diseases using structured questionnaires and clinical interviews. Individuals with a Mini-Mental State Examination-Korean version (MMSE-KC) score of<26 were excluded.

This study was approved by the institutional review board of the Seoul National University Hospital (IRB No. 1702–150-835) and Kyung Hee University Hospital at Gangdong (IRB No. 2017–04-001). Informed consent was obtained from all participants.

2.2. Clinical evaluation

The demographics, years of education, self-reported disease duration, and Korean version of the Rapid Eye Movement Sleep Behavior Disorder Questionnaire-Hong Kong (RBDQ-KR) scores (You et al., 2017) scores were obtained from each patient. We evaluated the nonmotor symptoms of IRBD patients, including depression, cognition, and autonomic function. Depression was evaluated with the Korean version of the Geriatric Depression Scale (GDS-K) (Bae and Cho, 2004). Cognition was investigated using the Korean version of the Montreal Cognitive Assessment (MoCA-K) (Lee et al., 2008), and autonomic function was evaluated with the Scales for Outcomes in Parkinson's Disease-Autonomic questionnaire (SCOPA-AUT) (Kim et al., 2017).

2.3. Image acquisition and preprocessing

T1-, T2-, and diffusion-weighted images were acquired with a 3.0-Tesla Siemens Biograph mMR 3 T scanner (Siemens Healthcare Sector, Germany) with a 16-channel head coil. T1-weighted structural images were acquired with the following parameters: echo time (TE) = 1.89 ms, repetition time (TR) = 1670 ms, field of view (FOV) = 250 mm, flip angle = 9°, matrix = 256 × 256, voxel size = 1.0 × 1.0 × 1.0 mm^3, and 208 slices. T2-wighted images were acquired with the following parameters: 47 axial slices, slice thickness = 3 mm, TR = 5000 ms, TE = 81 ms, FOV = 220 × 220 mm2, flip angle = 124°.

Axial diffusion-weighted single-shot echo-planar images were acquired with the following parameters: TE = 92.0 ms, TR = 9500 ms, FOV = 230 mm3, voxel size = 2.0 × 2.0 × 2.0 mm^3, 66 axial slices, slice gap = 0 mm, and b-factor = 1000 sec/mm2. A baseline image without diffusion volume was used as a reference image, and diffusion-weighted images were acquired from 67 different directions. All axial images were acquired parallel to the anterior-posterior commissure line.

Preprocessing steps included skull stripping and eddy -current correction using the FMRIB software Library(FSL)(Jenkinson et al., 2012). Motion correction was done by the affine alignment to the b0 image.

2.4. Tract-specific statistical analysis (TSSA)

TSSA was performed using deterministic tractography with DTI as described in previous studies (Jung et al., 2016; Park et al., 2020). (1) deterministic tractography was estimated using diffusion toolkits(Wang et al., 2007) based on a fiber assignment by continuous tracking (FACT) algorithm(Yeh et al., 2013) to obtain whole-brain streamlines. (2) The streamlines were classified automatically and labeled into seven major tracks (anterior thalamic radiation (ATR), cingulum (CG), corticospinal tract (CST), inferior fronto-occipital fasciculus (IF-OF), inferior longitudinal fasciculus (ILF), superior longitudinal fasciculus (SLF), and uncinate fasciculus (UNC)) according to their shape and position using in-house software(Yoo et al., 2015). Representative streamline was then

selected for each major tract for each subject following removal of streamline outliers that was not located in the regions specified by anatomical bundle definitions. (3) Tract diffusion profiles(Yeatman et al., 2012) was constructed by projecting FA and MD values of all streamlines onto each representative tract. Then group-wise representative tract was selected across subjects in the same way and was resampled into 100 sample points for each tract in the manner of equi-distance, where the FA and MD values were sampled.

2.5. Statistical analysis

All data are presented as the mean ± standard deviation. Independent sample t tests were used to evaluate differences in demographics and cognitive measures between the iRBD patients and controls. A chi-square test was used to analyze the categorical data.

Group differences in FA and MD values between iRBD patients and controls were evaluated using 10,000 permutation-based analysis of covariance (ANCOVA) controlling for age, sex, and education. The cluster-based statistics (CBS) method was used for multiple comparison correction (Bullmore et al., 1999). The CBS method corrects p values with respect to the sample point number that significantly clustered against another group that had higher F values than the given threshold, which was 2.0.

Pearson correlation coefficients were calculated to assess the relationships between the clinical variables that were significantly altered in iRBD and their aberrant FA or MD values. The permutation-based correlation tests were performed before CBS with a threshold of 0.3.

3. Results

3.1. Patient characteristics

A total of fifty iRBD patients and twenty age- and sex-matched controls were evaluated. All participants in the present study also participated in our previous study (Byun et al., 2020). The mean age of the participants was 67 ± 6 years, and 40 (57.1 %) were male; these measures were similar between the two groups. The iRBD patients had fewer years of education than the controls (12.2 ± 3.8 vs 14.1 ± 2.3, respectively, p = 0.047). The mean disease duration in iRBD patients was 7.1 ± 4.6 years, with a mean RBDQ-KR score of 41.6 ± 18.1. The RBDQ-KR, GDS-K and total SCOPA-AUT scores were higher for the iRBD patients than for the controls (Table 1).

3.2. TSSA results for the iRBD and control groups

Compared with the controls, the iRBD patients showed significantly lower FA values in the right ATR (occupying 10 % of tract length, p =

Table 1
Demographics and clinical characteristics.

	Controls	iRBD	p-value
	n = 20	n = 50	
Age (years)	68.1 ± 3.4	66.5 ± 6.9	0.349
Sex (Male)	11 (55.0)	29 (58.0)	0.819
BMI (kg/m2)	22.8 ± 2.5	24.0 ± 2.7	0.122
Education (years)	14.1 ± 2.3	12.2 ± 3.8	0.047
Disease duration (years)	–	7.1 ± 4.6	
RBDQ-HK	4.1 ± 2.8	41.6 ± 18.1	<0.001
GDS-K	3.3 ± 3.2	8.9 ± 7.1	0.001
MoCA-K	27.4 ± 1.2	26.8 ± 2.3	0.355
SCOPA-AUT total score	6.5 ± 5.0	12.4 ± 6.9	<0.001

Abbreviation: iRBD, Isolated rapid eye movement sleep behavior disorder; BMI, body-mass index; RBDQ-KR, Korean version of rapid eye movement sleep behavior disorder questionnaire-Hong Kong; GDS-K, Korean version of Geriatric Depression Sacle; MoCA-K, Montreal Cognitive Assessment – Korean; SCOPA-AUT, Scales for Outcomes in Parkinson's Disease-Autonomic questionnaire.

0.041) after adjusting for age, sex, and years of education. The MD values in the right ATR (occupying 13 % of tract length, p = 0.003), left ATR (occupying 10 % of tract length, p = 0.036) and IF-OF (occupying 7 % of tract length, p = 0.01) were higher in the iRBD patients than in the controls (Fig. 1 and Table 2). The distribution of FA in the right ATR and MD in the ATR and IF-OF are presented in Figs. S1 and S2, respectively.

Abbreviations: ATR, anterior thalamic radiation; IF-OF, inferior fronto-occipital fasciculus; FA, fractional anisotropy; MD, mean diffusivity.

3.3. Clinical correlates of altered TSSA results in iRBD patients

Correlations between the altered TSSA results (FA and MD values) and the significant clinical variables in iRBD (RBDQ-KR, GDS-K and SCOPA-AUT total scores) were evaluated. A marginal positive correlation was found between the right IF-OF MD value and RBDQ-KR (r = 0.3, p = 0.042) and GDS-K (p = 0.02) scores in the iRBD patients. Because there was a strong positive correlation between the RBDQ-HK and GDS-K scores (p = 0.006), the independent correlation with IF-OF MD values was further analyzed. An independent positive correlation between the right IF-OF MD and GDS-K scores was found after adjusting for RBDQ-HK scores (adjusted p = 0.026). The correlation between the right IF-OF MD and RBDQ-HK scores was not significant after adjusting for GDS-K scores. No significant correlation was found between the right ATR FA or bilateral ATR MD values and clinical variables.

4. Discussion

This study explored tract-specific microstructural changes in iRBD patients using the TSSA method and evaluated their associations with clinical and nonmotor symptoms associated with iRBD. Although the changes were relatively small, occupying 7–13 % of the tract length, the iRBD patients showed lower FA in the right ATR and higher MD in the bilateral ATR and right IF-OF. The right IF-OF MD values in iRBD patients were positively correlated with depressive symptom scores. Overall, our results suggest that cerebral WM microstructural alterations are present in iRBD and that the alterations are associated with nonmotor symptoms.

DTI can reveal early changes associated with the pathogenesis of neurodegeneration associated with alpha-synucleinopathies (Tae et al., 2018). Our study revealed microstructural changes in the bilateral ATR and IF-OF in the iRBD patients, which was consistent with previous studies of RBD patients with or without PD. The ATR connects the dorsomedial thalamic nucleus and dorsolateral prefrontal cortex and is known to be involved in executive function and depression. FA has been shown to be altered along the ATR in iRBD patients compared with controls (Unger et al., 2010a). A recent study also found changes in FA in the right ATR in RBD subjects and changes in several structures, including the CST, right SLF, and left UNC, related to nonmotor function (Holtbernd et al., 2021).

The IF-OF is known to act as a direct pathway between the anterior temporal, orbitofrontal, and occipital areas and is known to be involved in attention and visual processing (Catani and Thiebaut de Schotten, 2008). PD patients with RBD showed microstructural changes, including in the right IF-OF, compared to those without RBD (Ansari et al., 2017). Tract-based spatial statistics showed increased MD in various structures in the right hemisphere, including the right IF-OF, in individuals with prodromal PD, especially those with RBD, compared to those with clinical PD (Ohlhauser et al., 2019a).

The magnitude of the microstructural alterations in iRBD was relatively small compared to previous TSSA studies in patients with vascular cognitive impairment that showed reduced FA along the majority of the bilateral ATR, left CG and left SLF (>50 % of tract length) (Kim et al., 2011). Microstructural changes were more prominent in the right hemisphere, which was consistent with a previous DTI study that showed increased MD mostly lateralized in the right hemisphere in
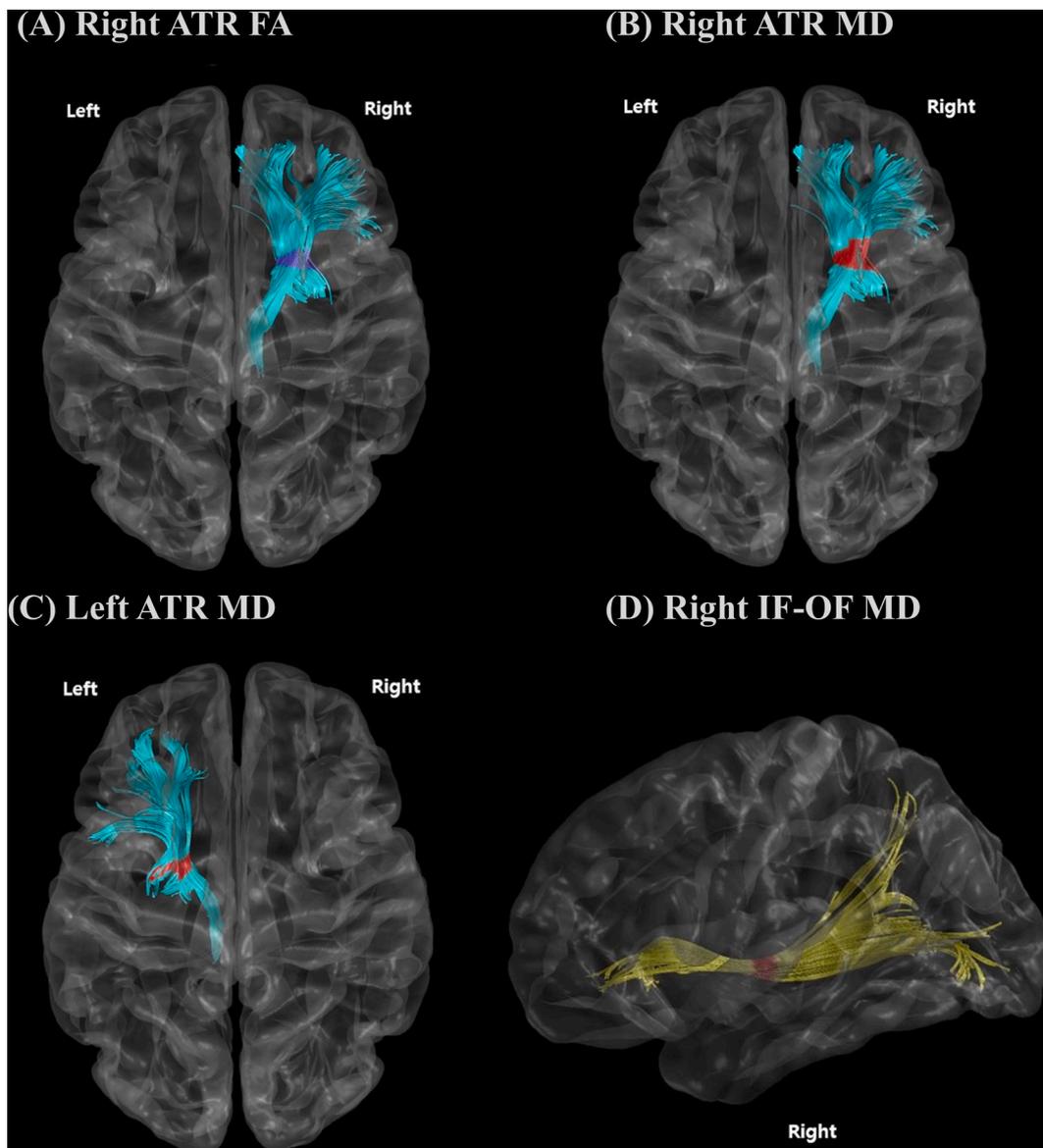
Fig. 1. Group comparison analysis of (A) FA value in right ATR, (B) MD value in right ATR, (C) MD value in left ATR, and (D) MD value in right IF-OF between the iRBD patients and controls. Purple and red colors indicate the portion of the fiber tract where FA and MD values significantly differed between the two groups respectively. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

prodromal PD patients, especially in those with RBD (Ohlhauser et al., 2019a).

Altered microstructure in the right IF-OF was associated with depressive symptoms in iRBD. Depression is found in 28.8–44.7 % of RBD patients (Frauscher et al., 2014; Lee et al., 2016) and is considered to be a result of a chronic neurodegenerative pathology (Barber et al., 2017). WM changes in the right IF-OF were reported in patients with major depressive disorder (MDD) (Sugimoto et al., 2018) and in patients with remitted late-life depression (Wang et al., 2020). Microstructural changes in the right IF-OF positively correlated with the ability to recognize sad facial expressions (Baggio et al., 2012), which is usually associated with depression (Leppanen, 2006). A recent *meta*-analysis revealed an association between the altered right IF-OF FA values and depressive symptom severity (Murphy and Frodl, 2011). Our study showed that right IF-OF may be relevant to the pathophysiology of depression in iRBD.

Although this was a single-center study with a small number of patients, this work is the first to evaluate tract-specific microstructural changes in iRBD using the TSSA method. It also must be noted that

microstructural changes identified with TSSA may not have causal relationships with iRBD because of the cross-sectional nature of this study. Moreover, because TSSA is based on deterministic tractography, it has limitation on controlling the crossing fiber issue. Video-PSG was performed only in the patients and not in the controls. However, the controls were thoroughly screened for possible sleep or cognitive disorders.

5. Conclusions

This study showed localized deficits in cerebral WM microstructures of the bilateral ATR and right IF-OF in iRBD patients using the TSSA method. WM disruption in the right IF-OF was associated with depressive symptoms in iRBD patients, which may be a prodromal biomarker for incipient neurodegeneration. Larger longitudinal studies will be necessary to confirm the causal relationships between WM microstructural changes and nonmotor symptoms in iRBD.

Ethical approval.

This study was approved by the institutional review board of the Seoul National University Hospital (IRB No. 1702–150-835) and Kyung

Table 2
Group comparison of diffusion coefficients in major white matter tracts.

Major tract	NC mean FA (SD)	RBD mean FA (SD)	Tract-wise corrected P*	NC mean MD(SD)	RBD mean MD (SD)	Tract-wise corrected P*
LH ATR	0.2547 (0.0345)	0.2428 (0.0396)	ns	1.1 (0.2574)	1.2 (0.2144)	0.0359
LH CST	0.4110 (0.0264)	0.4024 (0.0247)	ns	0.9 (0.2557)	0.9 (0.2497)	ns
LH CG	0.3332 (0.0346)	0.3329 (0.0302)	ns	0.9 (0.1477)	0.9 (0.1936)	ns
LH IF-OF	0.2209 (0.0341)	0.2189 (0.0358)	ns	1.1 (0.2150)	1.1 (0.1759)	ns
LH ILF	0.1604 (0.0157)	0.1830 (0.0128)	ns	0.9 (0.1116)	1.0 (0.1120)	ns
LH SLF	0.2780 (0.0401)	0.2839 (0.0338)	ns	1.1 (0.1935)	1.1 (0.2248)	ns
LH UNC	0.1552 (0.0114)	0.1623 (0.0198)	ns	1.1 (0.1534)	1.1 (0.1560)	ns
RH ATR	0.3282 (0.0294)	0.3150 (0.0327)	0.0413	0.8 (0.1935)	0.8 (0.1026)	0.0028
RH CST	0.3648 (0.0272)	0.3497 (0.0262)	ns	1.1 (0.3018)	1.0 (0.2420)	ns
RH CG	0.2344 (0.0145)	0.2462 (0.0165)	ns	0.8 (0.6291)	0.8 (0.3623)	ns
RH IF-OF	0.2363 (0.0341)	0.2452 (0.0313)	ns	1.0 (0.1405)	1.1 (0.1899)	0.0095
RH ILF	0.2446 (0.0306)	0.2811 (0.0220)	ns	0.9 (0.1152)	0.9 (0.7938)	ns
RH SLF	0.2573 (0.0239)	0.2460 (0.0152)	ns	0.9 (0.9875)	0.9 (0.8616)	ns
RH UNC	0.1668 (0.0258)	0.1555 (0.0185)	ns	1.2 (0.2421)	1.3 (0.2234)	ns

*The lowest p-value FA, fractional anisotropy; SD, standard deviation; MD, mean diffusivity; LH, left hemisphere; RH, right hemisphere; ATR, anterior thalamic radiation; CST, corticospinal tract; CG, cingulum; IF-OF, inferior fronto-occipital fasciculus; ILF, inferior-longitudinal fasciculus; SLF, superior-longitudinal fasciculus; UNC, uncinate fasciculus; ns, not significant.

Hee University Hospital at Gangdong (IRB No. 2020–05-022).

CRediT authorship contribution statement

Jung-Ick Byun: Conceptualization, Data curation, Funding acquisition, Investigation, Project administration, Writing – original draft. **Seunghwan Oh:** Data curation, Formal analysis, Methodology, Visualization. **Jun-Sang Sunwoo:** Investigation. **Jung-Won Shin:** Investigation. **Tae-Joon Kim:** Investigation, Validation. **Jin-Sun Jun:** Validation, Visualization. **Han-Joon Kim:** Visualization, Writing – review & editing. **Won Chul Shin:** Validation, Writing – review & editing. **Joon-Kyung Seong:** Methodology, Supervision, Writing – review & editing. **Ki-Young Jung:** Conceptualization, Funding acquisition, Project administration, Supervision, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2022.103186.

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