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Distinct white matter lesion patterns associated with previous relapse activity in multiple sclerosis and neuromyelitis optica spectrum disorder

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Abstract

Background: Multiple sclerosis (MS) and neuromyelitis optica spectrum disorders (NMOSD) are both chronic inflammatory demyelinating diseases of the central nervous system, but they have distinct pathophysiological features that distinguish their clinical phenotypes and lesion characteristics. The objective of this study was to investigate the correlation between white matter (WM) lesion location and previous relapse activity, as well as disease duration, in these two diseases. *Methods:* This study included 64 patients with relapsing-remitting MS and 49 with NMOSD. We used the voxel-based lesion-symptom mapping (VLSM) method to determine the correlations of the presence of WM lesions with the number of attacks and the disease duration in each disease group. *Results:* We found that WM lesions were correlated with the number of attacks; the deep WM of the right parietotemporal region including parts of the superior longitudinal fasciculus in MS patients and the right superior corona radiata, corticospinal tract, and inferior fronto-occipital fasciculus in NMOSD patients. However, there were no specific locations associated with disease duration in patients with either disease.
Conclusion: Our VLSM analysis confirmed that prior relapse activity was associated with distinct WM lesion locations in MS and NMOSD, respectively. In contrast, disease duration, independent of disease activity, showed no association with specific lesion patterns in either disease.

Keywords: White matter, lesion, attack, multiple sclerosis, neuromyelitis optica

INTRODUCTION

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system (CNS) that is characterized by acute relapses and disability progression. Magnetic resonance imaging (MRI) plays a pivotal role in the diagnosis and prognosis prediction of these patients and is also used to individualize their treatment plans. White matter (WM) lesions accumulate during the disease course and their morphology and burden can be used as predictors of clinical relapse occurrence and disease progression.[1,2] Several MRI characteristics have clinical significance. For instance, gadolinium

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enhancement in MS lesions serve as a surrogate marker of blood–brain barrier disruption and ongoing inflammation, and is associated with future relapse.[3] Iron-rim lesions, on the other hand, indicate chronic low-grade inflammation and tissue destruction, correlating with disability and relapse.[4,5] Regarding WM lesion location, the involvement of specific WM tracts seems to be associated with a higher risk of clinical conversion to MS in patients with clinically isolated syndrome (CIS).[2,6] However, limited knowledge exists about whether lesion locations are specifically related to previous relapse activity or disease duration among patients with MS.

Neuromyelitis optica spectrum disorder (NMOSD) is a chronic relapsing autoimmune astrocytopathy of the CNS with secondary demyelination. NMOSD shares clinical features with MS such as optic neuritis and myelitis, but it exhibits differences in disease course, prognosis, and management. Subclinical inflammatory activity in the brain in particular is not well established in NMOSD[7], and routine follow-up brain MRI scans are not recommended to monitor disease activity.[8] Brain lesions typically manifest during an attack, and acute lesions often partially regress or disappear over time.[9] However, some lesions remain as destructive chronic hypointense lesions in T1-weighted images[9] that can be important for the prognosis due to causing dysfunction in the involved area. Recently, there has been a report indicating a relatively high frequency of new asymptomatic lesions, including NMOSD-specific brain lesions such as area postrema and corticospinal tract.[10] Importantly, these occurrences have been observed even during relapse-free period. However, it remains unclear whether specific lesion locations are associated with the number of previous clinical attacks or the overall duration of disease.

Brain lesions that emerge during recurring episodes or with prolonged disease duration are clinically significant due to their potential link to cerebral dysfunction. In this study, we used the Voxel-based Lesion Symptom Mapping (VLSM) method to identify the WM lesion locations associated with previous relapse activity or disease duration in patients with MS and NMOSD.

METHODS

The participants in this study were patients with relapsing-remitting MS (RRMS, *N*=64) and NMOSD (*N*=49) who were enrolled at Samsung Medical Center in Seoul, South Korea between January 2014 and December 2018. The inclusion criteria were (1) being older than 18 years, (2) meeting the revised 2017 McDonald criteria for RRMS or the revised 2015 NMOSD diagnostic criteria[8], and (3) having undergone brain MRI at least 3 months after an attack. The diagnoses of MS and NMOSD were determined by two specialized neurologists, SR and J-HM. Four patients with MS and one with NMOSD were excluded due to poor image quality on MRI. The NMOSD patients included 46 (94%) with aquaporin-4 (AQP4)-antibody, which was measured with a cell-based indirect immunofluorescence assay.[11] Baseline characteristics including age, sex, number of attacks, disease duration, and Expanded Disability Status Scale (EDSS) score were collected. The number of attacks included the total occurrence of relapses along with the initial attack. A relapse or attack is defined as the appearance of symptoms or objective findings indicative of an acute inflammatory demyelinating event in the CNS, lasting for at least 24 hours.

MRI acquisition and data preprocessing

All participants underwent a three-dimensional (3D) volumetric brain MRI scan. A 3.0-tesla MRI scanner (Achieva, Philips, Best, the Netherlands) was used to acquire 3D fluid-attenuated inversion recovery (FLAIR) MRI data in the axial plane with the following parameters: axial slice thickness of 1 mm with no gap, TR of 11,000 ms, TE of 125 ms, flip angle of 90°, and matrix size of 512 × 512 pixels. All axial sections were acquired parallel to the anterior–posterior commissure line and perpendicular to the midsagittal plane.

We extracted the lesion data of all subjects and mapped them onto the standard Montreal Neurological Institute (MNI) space to perform VLSM (Figure 1). The lesion prediction algorithm in the Lesion Segmentation Tool (version 3.0.0, www.statistical-modelling.de/lst.html)[12] was used to segment the lesions in the FLAIR image of each subject. After obtaining the lesion probability maps, we applied binarization using a threshold of 0.5, considering voxels with a probability greater than or equal to 0.5 as regions with a high likelihood of lesion presence. We then registered these images onto the MNI template. The averages in each patient group were calculated to help develop the group lesion probability map (Supplementary Figure 1).[13] Lesion extraction processing was performed using Statistical Parametric Mapping 12 (SPM12) in the MATLAB (2019b, MathWorks) environment.

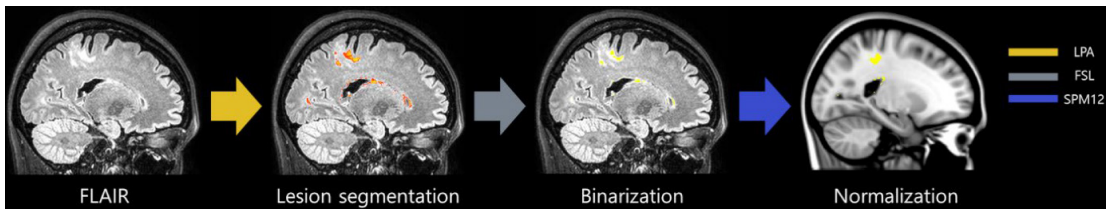

Figure 1. Image preprocessing. We segmented lesions from FLAIR images to act as a lesion probability map, binarized them with a 50% threshold, and normalized them to the standard Montreal Neurological Institute space.
LPA, lesion segmentation; FSL, FMRIB Software Library; SPM12, Statistical Parametric Mapping 12

Voxel-based lesion symptom mapping

We determined the correlations of WM lesion status with the number of attacks and disease duration in patients with MS and NMOSD using a publicly available VLSM toolbox[14] (version 2.55, https://aphasialab.org/vlsm) in the MATLAB environment (2019b, MathWorks). Although VLSM method was initially developed to establish correlations between the precise location of lesion and the clinical symptom[14], clinical variables, apart from symptoms, can also be taken into consideration. This toolbox runs statistical tests of each voxel to associate the clinical measures with or without a lesion and perform cluster-based multiple-comparisons correction. Specifically, we first used a mass-univariate general linear model (GLM) to examine the relationship between the number of attacks and WM lesion status after independently controlling for disease duration, age, and sex in each group (Equation 1). Similarly, we then performed a mass univariate GLM to examine the association between disease duration and lesion status while controlling for the number of attacks, age, and sex; we used the same equation above but with the main effect of disease duration:

$$Lesion\ status = \beta_0 + \beta_1 attact + \beta_2 duration + \beta_3 age + \beta_4 sex \quad (1)$$

The tests were performed on the voxels that overlapped between at least two patients. Since they were performed over multiple voxels, we performed a permutation test with a voxel-wise threshold of $p<0.05$ and 50000 permutations.

Identification of WM tracts colocalized with WM lesions

We investigated how the WM lesions affected WM tracts using the following approach:[15] The relevant WM tracts were retrieved from the WM atlas of Johns Hopkins University, which contained 20 identified volumetric WM tracts.[16,17] Of these, 18 tracts are hemisphere-specific, with 9 located in the left hemisphere and 9 in the right, while the remaining two are bilateral (forceps major and minor). Our analysis focused on assessing the overlapping volume of WM lesions identified in the VLSM with the WM tracts, visualizing those tracts along with the overlapped regions of interest (ROIs).

We used FMRIB Software Library (version 5.0.9)[18] for data preprocessing and analyses, and BrainNet Viewer[19] for the visualization.

RESULTS

The demographics and clinical features of the study participants are summarized in Table 1. The mean age was lower in the MS group compared to the NMOSD group (35 vs 44 years, $p<0.001$). The sex ratio and disease duration did not show significant differences between the two groups. The median EDSS score was notably lower in the MS group than in the NMOSD group (1.0 vs 2.5, $p<0.001$), while the median number of total attacks was higher in the MS group (3 vs 2, $p=0.044$). Symptomatic attacks involving the cerebral hemisphere were significantly more common in the MS group compared to the NMOSD group (100% vs 46.9%, $p<0.001$). There were no significant differences in the symptomatic involvement of the brainstem, spinal cord, and optic nerves (all $p>0.05$). Lesion probability maps revealed that T2 lesions were predominantly located in the periventricular region, with a higher prevalence observed in the MS group (Supplementary Figure 1).

WM lesions associated with the number of attacks in MS and NMOSD

In MS, lesions associated with the number of attacks were identified in the deep WM of the right parietotemporal region (Figures 2A and 3A; lesion volume: 963 mm^3, $p=0.036$), specifically involving parts of the superior longitudinal fasciculus (SLF) (Figure 3B; Supplementary

Table 1: Demographics and clinical characteristics of study subjects

	MS (n=64)	NMOSD (n=49)	p value
Age, years	34.7 ± 8.9	44.3 ± 11.7	<0.001[a]
Females (%)	48 (75.0)	42 (85.7)	0.161[c]
Disease duration, years	3.7 (1.6–7.2)	2.3 (1.2–12.3)	0.633[b]
Attack numbers	3 (1–5)	2 (1–3)	0.044[b]
EDSS	1.0 (0–2.0)	2.5 (1.5–6.0)	<0.001[b]
Anytime involvement[d] (%)			
Cerebral hemisphere	64 (100)	23 (46.9)	<0.001[c]
Brainstem/cerebellum	40 (62.5)	27 (55.1)	0.427[c]
Spinal cord	48 (75.0)	37 (75.5)	0.950[c]
Optic nerve	25 (39.1)	25 (51.0)	0.205[c]
Use of drugs[e]	55 (83.9)[f]	44 (89.8)[g]	0.333

MS, multiple sclerosis; NMOSD, neuromyelitis optica spectrum disorder; EDSS, Expanded Disability Status Scale; Values are mean ± standard deviation or median (interquartile range) unless otherwise indicated
[a]Student's t-test or [b]Mann–Whitney U-test for continuous variables and [c]Chi-squared test for categorical variables
[d]Symptomatic involvement
[e]Taken at the time of brain MRI
[f]Interferon β-1b (n=24), interferon β-1a (n=11), teriflunomide (n=8), azathioprine (n=3), fingolimod (n=3), glatiramer acetate (n=3), dimethyl fumarate (n=2), mitoxantrone (n=1)
[g]Azathioprine (n=29), mycophenolate mofetil (n=12), rituximab (n=2), methotrexate (n=1)

Table 1). In NMOSD, these lesions were found in the deep WM of the right frontoparietal region (Figures 2B and 3C; lesion volume: 1,691 mm^3, p=0.032), encompassing the superior corona radiata, corticospinal tract, and small portion of the inferior fronto-occipital fasciculus (IFOF) (Figure 3D; Supplementary Table 2).

WM lesions associated with disease duration in MS and NMOSD

There were no WM lesions associated with disease duration in either the MS or NMOSD group, regardless of the number of attacks.

DISCUSSION

In this study, we identified distinct WM lesion locations associated with the number of precious clinical attacks in patients with MS and with NMOSD using VLSM. However, we found no specific WM lesion locations associated with disease duration in either disease, after adjusting for previous disease activity.

Our findings in MS revealed that lesions in the deep WM of the right parietotemporal region, adjacent to the body and atrium of the lateral ventricle, were correlated with the number of attacks. This aligns with the well-documented predilection of MS lesions for the periventricular WM, where lesions are oriented perpendicular to the ventricles and expand fan-like into deeper WM regions.[20] The underlying mechanism may involve venule density gradients, facilitating the migration of activated immune cells at the venules.[20] These specific lesion patterns reflect the inflammatory nature of MS and highlight the potential role of the SLF, which partially overlapped with the identified lesion areas.

Several DTI studies have found the integrity of the main WM tracts, including the SLF, to be disrupted in patients with MS.[21,22] However, the clinical significance of lesions in SLF remains unclear in the context of recurrent attacks. In a previous study of patients with clinically isolated syndrome, those who converted to clinically definite MS exhibited higher the lesion frequencies in the projection, association, and commissural WM tracts. This included areas such as SLF, corpus callosum, optic radiation, and cingulum, compared to patients who did not convert.[2] These findings suggest that the involvement of specific WM tracts such as the SLF could be associated with a higher risk of short-term clinical conversion to MS, which may support our result of SLF being associated with disease activity.[2] In a recent study, lesion probability maps illustrated specific WM regions where MS-related inflammatory activity are more prominent; patients treated with interferon beta-1a had significantly lower new lesion frequency in specific brain regions

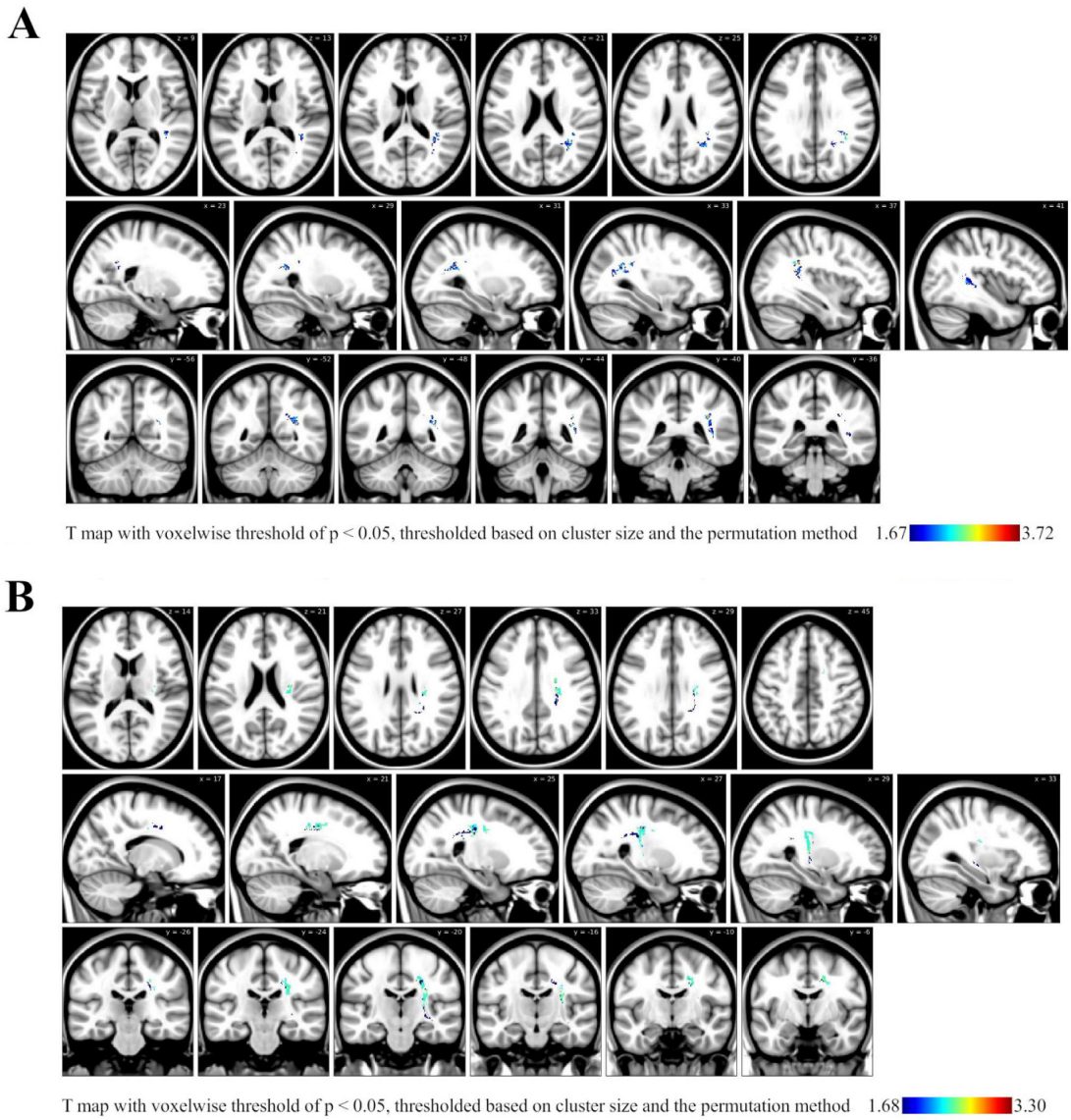

Figure 2. WM lesions associated with the number of attacks in MS (A) and NMOSD (B).
WM, white matter; MS, multiple sclerosis; NMOSD, neuromyelitis optica spectrum disorder

including the SLF, compared with a placebo.[23] While previous studies have reported disrupted integrity of major WM tracts, including the SLF, in MS, the direct clinical implications of these findings–particularly in relation to cognitive function–remain speculative.[21,24,25] Future studies should aim to explore these associations in greater depth, with a focus on longitudinal changes and their impact on cognition.

In NMOSD, WM lesions correlated with number of attacks were predominantly located in the right superior corona radiata and corticospinal tract, with some involvement of the IFOF. The corticospinal tract is a well-known hallmark of NMOSD, often associated with motor dysfunction and included in its diagnostic criteria.[8,26] Our findings are consistent with previous MRI studies in AQP4-antibody-positive NMOSD patients, where acute lesions involving the corticospinal tract and adjacent regions often persisted as chronic lesions, albeit with partial regression over time.[9,27] Another study found WM damage in projection fibers such as corticospinal tract and thalamic radiation, as well as in association fibers including the IFOF, further supporting the involvement of these key tracts in NMOSD.[28] This study adds to the growing evidence that lesion distribution in NMOSD is attack-related,

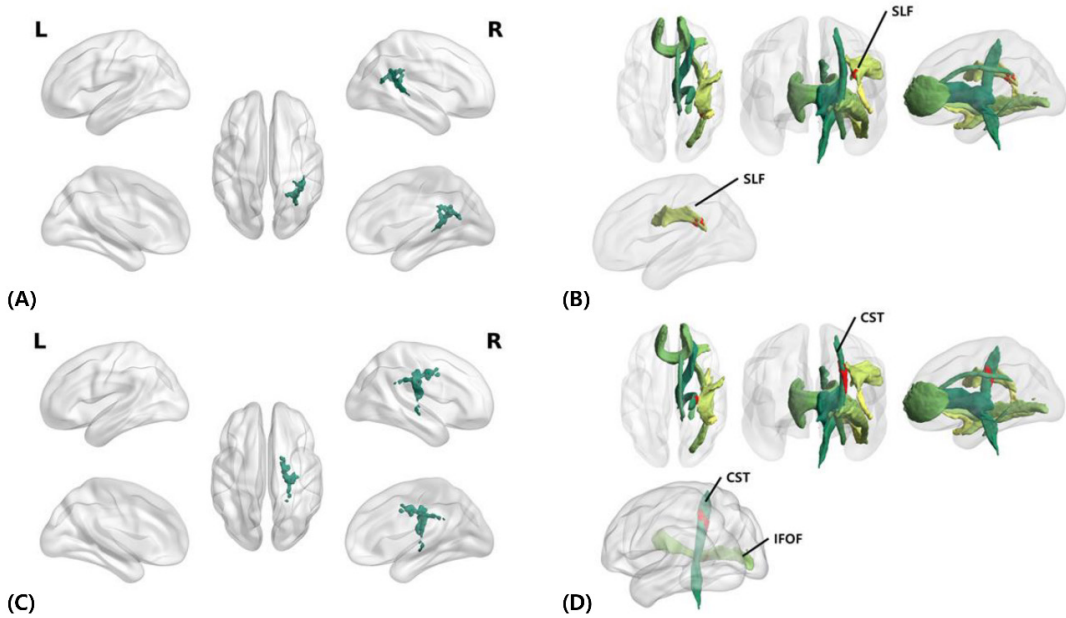

Figure 3. White matter (WM) lesions associated with the number of attacks in MS (A) and NMOSD (C), and the WM tracts intersecting with these lesions in MS (B) and NMOSD (D). Lesions are highlighted in red, with key tracts labeled (e.g., SLF, CST, IFOF).
WM, white matter; MS, multiple sclerosis; NMOSD, neuromyelitis optica spectrum disorder; SLF, superior longitudinal fasciculus; CST, corticospinal tract; IFOF, inferior fronto-occipital fasciculus

reflecting the relapsing nature of the disease. However, whether these specific lesion locations have additional prognostic value beyond their known associations with motor dysfunction warrants further investigation.

Interestingly, we did not find any WM lesion locations associated with disease duration in either disease, after controlling for disease activity. This finding contrasts with some prior studies suggesting that periventricular lesions in MS correlate with disease duration and disability (*N*=365; median disease duration, 6.3 years). Other studies also found that DTI measures of the SLF and the corpus callosum were correlated with disease duration in patients with MS.[29,30] However, these earlier studies did not account for prior disease activity, which is a critical confounder. The lack of a significant association in our study may reflect the dynamic nature of demyelinating lesions in MS, which can regress, enlarge, or appear depending on disease activity. This highlights the heterogeneity of MS and suggests that cumulative disease duration alone may be insufficient to predict lesion burden or location. For NMOSD, our findings are consistent with the literature indicating that most brain lesions occur during clinical attacks, with few new silent lesions observed during remission.[26] Recently a significant prevalence of relapse-irrelevant new asymptomatic lesions was reported in NMOSD, with a 20% frequency observed over at least 2 year follow-up.[10] However, only 30% of these asymptomatic lesions occurred in the brain, and serum AQP4-antibodies were positive in only 64% of patients.[10] While asymptomatic lesions in NMOSD have been described, they seem more closely related to imminent relapses rather than to disease duration.[31,32] Nonetheless, our study's retrospective design and the potential collinearity between disease duration and the number of attacks remain limitations that should be addressed in future research.

Our study had several noteworthy limitations. First, the single center, retrospective nature of our data may limit the generalizability of our findings. Second, our analysis focused only on specific WM lesions visible on conventional MRI and did not consider leukocortical or small intracortical lesions characteristic of MS. Advanced imaging techniques, such as diffusion-weighted MRI, could provide additional insights into microstructural damage and its relationship with clinical outcomes. Third, while VLSM is a robust method for lesion-symptom mapping, it has inherent limitations, including the risk of false positives from multiple comparisons.[33,34]

Although we used a cluster-based correction to mitigate this risk, future studies could benefit from exploring alternative analytical approaches that better account for the spatial extent of lesions and their impact on connected WM tracts.

In conclusion, our findings reveal distinct patterns of WM lesion distribution associated with the number of clinical attacks in MS and NMOSD, reflecting their different pathophysiological mechanisms. Considering that the participants in this study generally had a relatively low number of relapses, it is plausible that these regions are particularly vulnerable, even during early relapses. However, disease duration, independent of disease activity, did not correlate with specific lesion patterns in either disease. This study highlights the need for further research to understand the clinical implications of these lesion patterns, particularly through longitudinal studies that examine the impact of lesion evolution on cognitive and functional outcomes in MS and NMOSD.

DISCLOSURE

Ethics: The present study was approved by the Institutional Review Board of Samsung Medical Center, and written informed consent was obtained from all participants.

Data availability: The data that support the findings of this study are available from the corresponding author upon relevant request.

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