

*Original Research***Relationship between Apathy and Subjective Poor Night-time Sleep in de novo, Untreated Parkinson's Disease**Chae-Moon Hong^{1,2}, Do-Hoon Kim¹, Byeong-Cheol Ahn^{1,2}, Jong-Geun Seo^{3,4},
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Abstract

Background: Sleep disturbance is one of the most common non-motor symptoms of Parkinson's disease (PD). However, the confounding effects of dopaminergic medication on sleep are a major challenge in understanding the impact of sleep disturbance in PD. We investigated the sleep disturbance and associated clinical features in patients with de novo, untreated PD. **Methods:** One-hundred-eight patients with de novo, untreated PD were included. Night sleep disturbance was evaluated using the night sleep subscale of the Scales for Outcomes in Parkinson's Disease (SCOPA-Sleep). Depression, anxiety, and apathy were assessed using the Geriatric Depression Scale (GDS), Beck Anxiety Inventory (BAI), and Apathy Evaluation Scale (AES), respectively. Early perfusion and dopamine transporter imaging of F-18 FP-CIT PET/CT were performed together with statistical parametric mapping analysis. **Results:** The night sleep SCOPA-Sleep subscore was correlated with the AES ($p = 0.014$), BAI ($p = 0.014$), and GDS ($p = 0.023$) scores. Patients with poor night sleep were more apathetic ($p = 0.013$). Additionally, there was increased perfusion in the left posterior cingulate in patients with sleep disturbance and apathy compared to those with sleep disturbance only. **Conclusions:** Night sleep disturbance was related to mood disorders, particularly apathy, in patients with de novo, untreated PD.

Keywords: apathy; depression; anxiety; sleep disturbance; Parkinson's disease**1. Introduction**

Parkinson's disease (PD) is an adult-onset, progressive neurodegenerative disorder characterized by clinically heterogeneous combinations of motor and non-motor symptoms [1]. Recently, many clinicians have gradually focused on the non-motor symptoms of PD. The prevalence of non-motor symptoms is high, and some of these symptoms seriously affect the functional status throughout all stages of PD [2,3]. Additionally, several non-motor symptoms are not effectively relieved by current treatments, although dopaminergic medications are remarkably effective for most motor symptoms in patients with PD [4].

Sleep disturbance is one of the most common and distressing non-motor symptoms, which affects the quality of life of patients with PD and of their caregivers [5]. Furthermore, emerging evidence suggests that sleep might play a critical role in neurodegenerative diseases and therefore provide important knowledge to modify the disease course in PD [6,7]. However, the importance of sleep in patients with PD remains under-recognized and ineffectively treated in clinical practice.

Several studies have suggested that sleep is closely linked to mood. The relationship between sleep and mood has also been investigated in patients with PD [8]. How-

ever, the confounding effect of dopaminergic medications on sleep and mood is a major challenge and confounding factor in PD. Therefore, the purpose of this study is to investigate the association between sleep disturbance and clinical features, mainly mood, in patients with de novo, untreated PD. In addition, we aimed to investigate functional brain imaging using F-18 FP-CIT positron emission tomography (PET)/computed tomography (CT) to identify the pathophysiological mechanism of sleep linked to mood in patients with de novo, untreated PD.

2. Materials and Methods**2.1 Subjects**

We performed a retrospective, cross-sectional study on 108 subjects diagnosed with de novo, untreated PD. The diagnosis of PD was made by an experienced movement disorder specialist using the clinical diagnostic criteria for PD based on the United Kingdom Parkinson's Disease Society Brain Bank. None of the patients had a history of present or past therapy with antiparkinsonian drugs, and none of the patients were on any medications with known anti-dopaminergic effects. The exclusion criteria were significant cerebral lesions on brain magnetic resonance imaging (MRI), suspected secondary or atypical parkinsonism,



unclear diagnosis, gradual cognitive decline, previous history of toxic habits/drug abuse or other neurological diseases different from PD, and systemic disease that would impair judgment. PD onset was defined as the onset of the first motor symptoms noted by the patient or family members. Disease duration was defined as the duration of the symptoms from PD onset. Clinical data were retrospectively obtained from the medical records of patients with PD who were admitted to the Department of Neurology at the Kyungpook National University Hospital, Daegu, Korea, between May 1, 2018, and December 31, 2019.

2.2 Clinical Assessment

A neurologist specializing in movement disorders (H-S Ryu) assessed all the patients with PD, and their medical records were available. Clinical assessments were performed at the time of the first diagnosis in treatment-naïve patients with PD. To evaluate night sleep disturbance, the night sleep sub-score of the Scales for Outcomes in Parkinson's Disease-Sleep (SCOPA-Sleep) was assessed [9]. According to the score, we categorized the patients into two groups: good (score ≥ 6) and poor (score < 6) night sleep [10]. The Unified Parkinson's Disease Rating Scale (UPDRS) was used to assess parkinsonian symptoms [11]. The UPDRS part II assessed the activities of daily living, and UPDRS part III assessed motor symptoms. The clinical severity of patients with PD was evaluated using the modified Hoehn and Yahr scale [12]. To evaluate apathy, depression, and anxiety, the 18-item Apathy Evaluation Scale (AES) [13], the 30-item version of Geriatric Depression Scale (GDS) [14], and the 21-item Beck Anxiety Inventory (BAI) [15] were used. A cut-off 37/38 was applied to categorize the patients into two groups: PD with apathy (score ≥ 38) and PD without apathy (score < 38) [16]. Additionally, both the Mini-Mental State Examination (MMSE) and Frontal Assessment Battery were also used to evaluate cognitive function [17,18].

2.3 Image Acquisition

PET/CT imaging was performed using a Discovery STE PET/CT system (GE Healthcare, Chicago, IL, USA), comprising a bismuth germanate full PET scanner and a 16-detector-row CT scanner. Intravenous injection of 185 MBq F-18 FP-CIT (Future-Chem Co., Ltd., Pusan, Korea) was administered on the PET/CT scanner table, and a PET scan was acquired for the first 5 min after injection as an early perfusion image. Routine dopamine transporter (DAT) image acquisition was started 3 h after the injection, and PET scan was performed for 20 min. For acquisition of images, patient was placed on the table and head was fixed using bandage. Emission PET data were acquired in the 3-dimensional mode after a low-dose CT scan. CT scans were obtained without contrast enhancement and were used for attenuation correction. Images were checked for movement, but motion correction was not applied. The images were reconstructed using an ordered-subset expect-

tation maximum conventional iterative algorithm with 35 subsets/4 iterations, a 256×256 matrix (slice thickness of 3.27 mm), and a 3.2-mm Gaussian post reconstruction filter (VUE point, GE Healthcare).

2.4 Image Analysis

All image data were processed and analyzed using Statistical Parametric Mapping 12 (SPM12; The Wellcome Centre for Human Neuroimaging, UCL Queen Square Institute of Neurology, London, UK) equipped with MATLAB 2020b software (The MathWorks, Inc., Natick, MA, USA). The data from a Digital Imaging and Communications in Medicine file were converted into NIfTI files. Early perfusion and routine DAT images of F-18 FP-CIT PET scans from each subject were co-registered to an individual T1 weighted MRI. Segmentation and normalization into the MR template were performed for MR images, and their transformation matrices were applied for spatial normalization of early perfusion and DAT images. Smoothing was applied for the spatially normalized PET images using an isotropic Gaussian kernel with 12-mm full-width half-maximum. SPM analysis was performed to assess group differences in PD without sleep disturbance or apathy, PD with sleep disturbance only, PD with apathy only, or PD with sleep disturbance and apathy. Only regions that exceeded a threshold of uncorrected $p < 0.01$, and an extent threshold of 100 voxels were accepted as significant.

2.5 Statistical Analysis

We determined whether night sleep disturbance was related to the other clinical features of patients with PD. For the univariate analysis, Spearman's correlation test, Student's t -test, and χ^2 or Fisher's exact test were used. For the analysis of independent relationship between night sleep disturbance and clinical features, a multivariate binary logistic regression analysis using stepwise forward selection method was performed on variables with a $p < 0.1$ in the univariate analysis. Categorical data are expressed as counts (percentages), and continuous data as mean $\pm$ standard deviation. Continuous data were assessed using the Spearman's correlation test and Student's t -test. Categorical data were assessed using the χ^2 or Fisher's exact test. Statistical analysis was performed using SPSS version 21.0 software (IBM Corp., Armonk, NY, USA), and $p < 0.05$ was considered as statistically significant.

3. Results

3.1 Demographic and Clinical Findings

The clinical features of patients with de novo, untreated PD are summarized in Table 1. The mean age was 67.9 ± 9.5 years, and the proportion of females was 60.2%. The mean disease duration of PD was 15.6 months, and the mean score of the modified Hoehn and Yahr scale was 1.7. The mean MMSE score was 25.1 ± 4.7 , and the education degree was 8.5 ± 4.7 years. None of the patients had dementia.

Table 1. Demographic and clinical characteristics of patients.

Characteristic	Patients
Total sample, n	108
Men	43 (39.8)
Women	65 (60.2)
Age, years	67.9 ± 9.5 (40–88)
Disease duration, months	15.6 ± 12.7 (2–60)
Education, years	8.5 ± 4.7 (0–16)
MMSE score	25.1 ± 4.7 (14–30)
FAB score	13.6 ± 3.4 (5–18)
AES score	35.4 ± 8.2 (21–63)
GDS score	12.3 ± 8.6 (0–30)
BAI score	4.5 ± 4.7 (0–23)
nsSCOPA-Sleep score	3.3 ± 4.1 (0–15)
UPDRS part II score	6.1 ± 5.6 (1–35)
UPDRS part III score	20.1 ± 11.9 (3–58)
Hoehn & Yahr stage	1.7 ± 0.6 (1–3)

Values are presented as the mean ± SD (range) or n (%). MMSE, Mini-Mental State Examination; FAB, Frontal Assessment Battery; AES, Apathy Evaluation Scale; GDS, Geriatric Depression Scale; BAI, Beck Anxiety Inventory; nsSCOPA-Sleep, night-sleep subscale of the Scales for Outcomes in Parkinson's disease; UPDRS, Unified Parkinson's Disease Rating Scale; SD, standard deviation.

3.2 Clinical Features Associated with Night Sleep Disturbance

In the univariate analysis, the night sleep SCOPA-Sleep sub-score was significantly correlated with the BAI ($r = 0.235$, $p = 0.014$), GDS ($r = 0.218$, $p = 0.023$), and AES ($r = 0.014$, $p = 0.014$) scores (Table 2). Patients with PD with poor night sleep were more apathetic than those with good night sleep ($p = 0.013$) (Table 3). The bad sleeper had higher frequency of use of hypnotics, antidepressants, and anxiolytics compared to the good sleeper although the difference was not statistically significant. In the binary logistic regression analysis, a higher AES score was independently associated with poor night sleep (Odds Ratio = 1.08, 95% Confidence Interval = 1.01–1.14, $p = 0.016$) (Table 4). We additionally compared the mood symptoms and night sleep disturbance according to the MMSE scores (>26 vs. ≤ 26), but there were no significant differences (Supplementary Table 1).

3.3 Analysis of Striato-Nigral Dopamine and Perfusion Deficit

Among 108 patients with PD, F-18 FP-CIT PET/CT data was available for 98 patients. These patients were divided into four groups for further analysis. Forty-seven patients did not show sleep disturbance or apathy, 25 patients showed apathy only, 7 patients showed sleep disturbance only, and 18 patients showed both sleep disturbance and apathy.

Table 2. Correlation analysis of clinical features with night sleep disturbances.

Characteristic	Correlation coefficient	<i>p</i> value
Age, years	−0.012	0.902
Disease duration, months	0.062	0.520
Education, years	0.128	0.185
MMSE score	0.118	0.223
FAB score	0.066	0.498
AES score	0.236	0.014
GDS score	0.218	0.023
BAI score	0.235	0.014
UPDRS part II score	0.168	0.081
UPDRS part III score	0.032	0.742
Hoehn & Yahr stage	0.093	0.334

MMSE, Mini-Mental State Examination; FAB, Frontal Assessment Battery; AES, Apathy Evaluation Scale; GDS, Geriatric Depression Scale; BAI, Beck Anxiety Inventory; UPDRS, Unified Parkinson's Disease Rating Scale; SD, standard deviation.

In early perfusion imaging, perfusion of the left posterior cingulate was significantly increased in patients with PD with sleep disturbance and apathy compared to those with sleep disturbance only (Fig. 1). However, there were no additional statistically significant differences in early perfusion and DAT imaging.

4. Discussion

In this study, we found that symptoms of apathy, depression, and anxiety are common in patients with de novo, untreated PD. The AES, BAI, and GDS scores were positively correlated with the night sleep SCOPA-Sleep sub-score in de novo, untreated PD. The AES score was independently associated with poor night sleep in de novo, untreated PD. Additionally, increased perfusion was observed in the left posterior cingulate cortex in patients with PD with sleep disturbance and apathy compared to those with PD with sleep disturbance only.

Of the 108 enrolled patients with PD, 62 (57.4%) had depression (GDS ≥ 10), 10 (9.3%) had anxiety (BAI ≥ 10), and 47 (43.5%) had apathy (AES > 37). Our study showed that mood symptoms are not rare in de novo, untreated patients with PD, which is consistent with previous reports [19]. Recent studies have reported that non-motor symptoms are prevalent in early-stage PD [20] and could be present in the prodromal stage of PD [21]. The frequency of non-motor symptoms could vary owing to the heterogeneity in study designs and populations.

In the present study, poor night sleep was positively correlated with apathy, anxiety, and depression in patients with PD. These results are consistent with a previous study, which showed that depression and anxiety were moderately correlated with nocturnal sleep [8]. However, the need for further investigation in untreated patients was reinforced because the results could not exclude the confounding in-

Table 3. Comparison of clinical features between good and bad sleeper in Parkinson's disease.

Characteristic	Poor night sleep (N = 26)	Good night sleep (N = 82)	<i>p</i> value
Age, years	67.7 ± 9.7	67.9 ± 9.6	0.941
Female	16 (61.5)	49 (59.8)	0.871
Disease duration	15.4 ± 12.9	15.7 ± 12.7	0.900
Education, years	8.8 ± 4.7	8.4 ± 4.8	0.671
MMSE score	25.9 ± 4.1	25.2 ± 4.0	0.464
FAB score	14.2 ± 2.6	13.5 ± 3.2	0.306
AES score	38.8 ± 8.7	34.3 ± 7.8	0.013
GDS score	15.1 ± 8.4	11.6 ± 8.5	0.071
BAI score	5.6 ± 4.7	4.2 ± 4.6	0.181
UPDRS part II score	8.3 ± 8.6	5.3 ± 4.0	0.098
UPDRS part III score	21.6 ± 15.6	19.7 ± 10.6	0.569
Hoehn & Yahr stage	1.7 ± 0.7	1.7 ± 0.6	0.796
Hypnotics	2 (7.7)	2 (2.4)	0.244
Antidepressants	2 (7.7)	6 (7.3)	>0.999
Anxiolytics	5 (19.2)	13 (15.9)	0.764

Values are presented as the mean ± SD (range) or n (%). MMSE, Mini-Mental State Examination; FAB, Frontal Assessment Battery; AES, Apathy Evaluation Scale; GDS, Geriatric Depression Scale; BAI, Beck Anxiety Inventory; UPDRS, Unified Parkinson's Disease Rating Scale; SD, standard deviation.

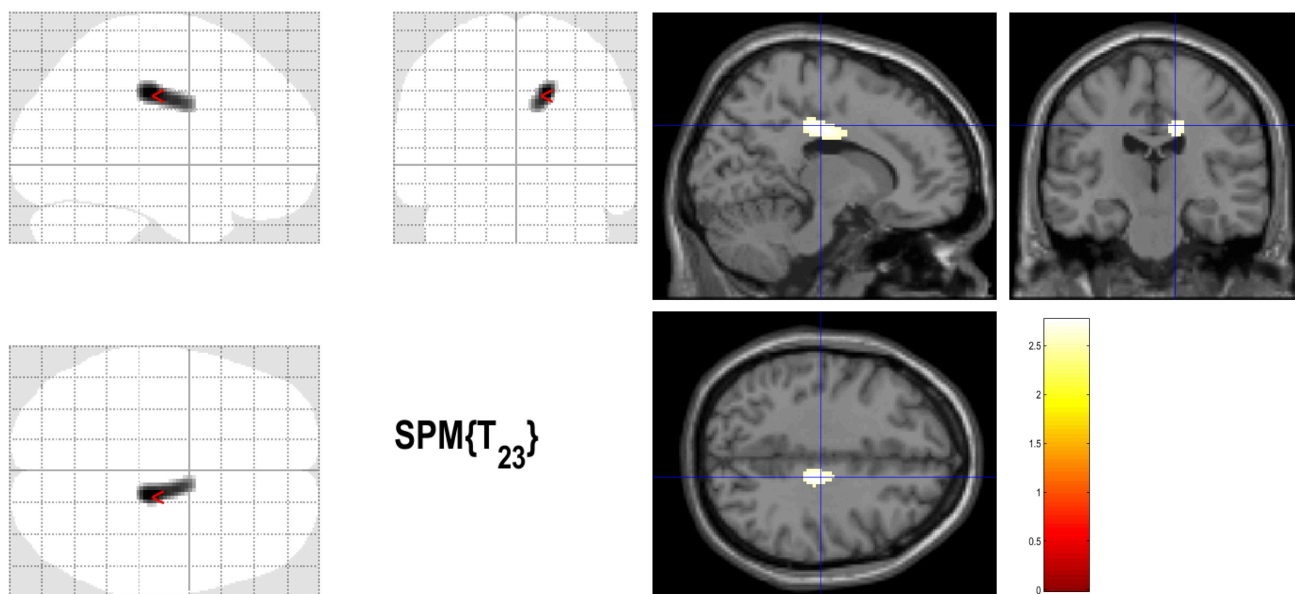


Fig. 1. Statistical parametric mapping results. The results showed increased blood pooling in the left posterior cingulate cortex in patients with sleep disturbance and apathy compared with the patients with sleep disturbance only ($p = 0.006$ uncorrected).

fluences of dopaminergic therapy on sleep and mood symptoms. Our results suggest that sleep disturbance is also closely related to mood symptoms, particularly apathy, in patients with de novo, untreated PD.

Depression often coexists with other mood symptoms, such as anxiety and apathy [22]. These mood symptoms may be related to each other, but are regarded as distinct entities in patients with PD [23–25]. Although the pathophysiological mechanism behind these mood symptoms is not well understood, previous studies have proposed sepa-

rate etiologies with considerable overlap among these mood symptoms [26]. Imaging studies have shown that both the nigral and extra-nigral systems, especially in the frontal lobe and its connecting regions, are involved in the mood symptoms of PD [27].

Cognitive impairment was an important issue in this study because the reliability of the questionnaire is influenced by cognitive function. Although we excluded the PD patients with dementia, the study participants showed relatively low cognitive status based on their MMSE scores,

Table 4. Binary logistic regression analysis of factors affecting night sleep disturbance in patients with Parkinson's disease.

Variable	Poor night sleep		
	OR	95% CI	p value
AES score	1.076	1.014–1.142	0.016
GDS score [†]			0.398
BAI score [†]			0.309
UPDRS part II score [†]			0.103
Age [†]			0.672
Disease duration [†]			0.989

[†]: variables not significant in multivariate analysis (those exempted from the equation). OR, Odds ratio; CI, Confidence interval; AES, Apathy Evaluation Scale; GDS, Geriatric Depression Scale; BAI, Beck Anxiety Inventory; UPDRS, Unified Parkinson's Disease Rating Scale.

and FAB. This could be explained by characteristics such as old age and low education level of the included patients with PD in this study. Additionally, it is possible that some PD patients in this study might have had mild cognitive impairment. Cognitive impairment has been observed in de novo PD and may be considered a prodromal symptom of PD [21]. Alteration in circadian rhythm is one of the important causes leading to the occurrence of sleep symptoms in patients with PD. The underlying pathophysiological mechanisms of circadian dysfunction in PD have been shown to be multifactorial and different from the stages of PD [28]. Widespread neurodegeneration within the basal forebrain, hypothalamus, and brain stem has been reported as a contributing factor [29]. Interestingly, apathy was independently associated with poor night sleep in patients with PD in this study. Apathy is characterized by a pathological lack of motivation and dopamine dysfunction is involved in patients with PD. One study reported that the ventral striatum, dorsal anterior cingulate cortex, and connective regions of the brain are involved in apathy [30]. Another study reported that a reduction in functional frontostriatal connectivity is associated with apathy in patients with PD [31].

The underlying mechanism of apathy in de novo, untreated patients with PD with poor night sleep is unclear. This may be explained by a common overlapping pathophysiological mechanism. Recently, apathy has been reported to be common in patients with PD who had REM sleep behavior disorders (RBD) [32]. The authors suggested that the degeneration of dopaminergic neurons are related to a potential mechanism for apathy in RBD, as dopaminergic neurons are involved in motivation and reward/effort based decision making pathway. The alteration of circadian rhythms can cause many non-motor symptoms, including sleep and mood symptoms. In addition, chronic bad night sleep could influence emotional functioning, causing mood symptoms [33,34].

Even though our results showed no statistical difference in DAT imaging, we observed increased perfusion in the left posterior cingulate in PD with sleep disturbance and apathy compared with patients with PD with sleep disturbance only. However, there were no significant perfusion differences between patients with PD without sleep disturbance or apathy and PD with apathy only. Robert *et al.* [35] reported that patients with PD showed increased metabolism in the left posterior cingulate cortex. Due to flow-metabolism coupling, increased blood flow or metabolism of the left posterior cingulate cortex might be related to apathy. As the relationship between sleep disturbance and apathy was not investigated in the previous study [35], further studies are needed to elucidate this relationship.

Emerging evidence suggests that sleep disturbance might be a potential risk and progression factor in PD [36]. Sleep and circadian alterations occur in the majority of patients with PD and are expected to aggravate the clinical symptoms of PD [37,38]. Poor night sleep prevents adequate rest, suggesting that the deterioration of mood symptoms could be associated with poor night sleep in patients with PD. Thus, targeting sleep and circadian alterations might be a promising opportunity to relieve mood symptoms in patients with de novo, untreated PD [5].

This study has several strengths and limitations. We comprehensively investigated motor, cognitive, and mood symptoms using specific rating scales in patients with PD. Additionally, we included only de novo, untreated patients with PD to remove the effects of dopaminergic medications. However, it has an inherent limitation in its cross-sectional retrospective design. We did not use the Movement Disorder Society (MDS)-sponsored revision of the UPDRS or the MDS clinical diagnostic criteria for PD due to practical issues. Based on the recommendations of previous studies, we used the GDS to evaluate the depressive symptoms in the patients with PD [39–41]. The depressive symptoms in younger patients with PD were also evaluated using the GDS due to the uniformity in assessment, although the GDS has been designed specifically to screen for depression in the elderly population. Further research on the psychometric properties of GDS is required, particularly in younger patients with PD. Furthermore, we did not extensively evaluate the broad spectrum of sleep disturbances observed in PD. We only used the SCOPA-Sleep to measure night-sleep disturbance in patients with PD, and polysomnography was not performed. The SCOPA-Sleep was recommended for evaluating the overall sleep impairment and its severity [10]. It is difficult to interpret the association between mood symptoms and various sleep disorders. We focused on night time sleep disturbance in this study. In the future, various sleep problems, for examples daytime sleepiness, need to be investigated. The Parkinson's Disease Sleep Scale-2 could be a useful tool to evaluate sleep disturbance in addition to PD-related nocturnal symptoms [42]. In this study, the pro-

portion of female participants was higher than that of male participants. Thus, there might be a potential bias while also considering the overall higher prevalence of depression in women and in female patients with PD compared to male patients with PD. In the future, well-designed longitudinal studies are needed to further investigate the broad spectrum of sleep disturbances associated with mood disorders in patients with PD.

5. Conclusions

We found that apathy was significantly related to poor night sleep in patients with de novo, untreated PD. It could provide useful information in understanding the impact of sleep disturbance on mood in patients with de novo, untreated PD. Additionally, the results of DAT and perfusion imaging support the existence of a functional relationship between sleep disturbance and apathy in patients with de novo, untreated PD. Further studies are needed to elucidate the shared pathophysiological mechanisms of sleep disturbance and mood disorders in patients with PD.

Author Contributions

HSR and CMH designed the research study. HSR and CMH performed the research. DHK, BCA, and JGS provided help and advice on methodology. HSR and CMH analyzed the data. HSR and CMH wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics Approval and Consent to Participate

The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Institutional Review Board of Kyungpook National University Hospital (protocol code 2021-05-030). Patient consent was waived due to (1) The research involves no more than minimal risk to the subjects, (2) The waiver or alteration will not adversely affect the rights and welfare of the subjects, (3) The research could not practicably be carried out without the waiver or alteration, (4) Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

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Conflict of Interest

The authors declare no conflict of interest. HSR is serving as one of the Guest Editors of this journal. We declare that HSR had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to RF.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at <https://doi.org/10.31083/j.jin2103074>.

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