Brief Report

Neuro-degenerative Diseases

Neurodegener Dis 2019;19:171–177
DOI: 10.1159/000507447

Received: February 26, 2020
Accepted: March 20, 2020
Published online: May 26, 2020

Neuropsychiatric Traits Associated with Refractory Impulse Control Disorder in Parkinson's Disease

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Keywords
Impulse control disorder · Parkinson's disease · Dopamine agonist · Neuropsychiatric traits · Obsessive compulsiveness

Abstract
Introduction: Impulse control disorder (ICD) in Parkinson's disease (PD) is a critical nonmotor symptom with personality or neuropsychiatric traits contributing to ICD. ***Objective:*** This study aimed to identify predictive traits for persistent or paradoxical aggravation of ICD after dopamine agonist substitution therapy for ICD in PD. ***Methods:*** We conducted a case-control study using a database of a multicenter intervention trial for ICD in PD. The poor-outcome group was defined by showing paradoxical increases in ICD behaviors after the substitution of dopamine agonists with levodopa. We analyzed the pre-intervention personality traits associated with the poor outcome and also evaluated the risk traits for refractory ICD using a receiver-operating characteristic (ROC) curve analysis. ***Results:*** The poor-outcome group showed higher levels of anger expression ($p = 0.007$) and obsessive-

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compulsive traits ($p = 0.009$) compared with the good-outcome group at the pre-intervention state. In the ROC curve analysis, the Obsessive-Compulsive Inventory showed the highest area under the curve with 80.0% sensitivity and 74.3% specificity in discriminating against the poor-outcome group. ***Conclusions:*** Our results suggest that assessment of obsessive compulsiveness may be useful for predicting the refractoriness of ICD behaviors in planning an interventional treatment for ICD in PD.

Introduction

Impulse control disorder (ICD) is common and an important nonmotor symptom in Parkinson's disease (PD), which is strongly associated with dopamine agonist therapy [1, 2]. Thereby, discontinuation of dopamine agonist has been recognized as a first-line therapeutic option to control ICD in PD [1, 2]. However, in certain PD patients, the interventional therapy does not improve ICD behaviors [3], and individual neuropsychiatric traits have been suggested to contribute to ICD in PD [2].

Given the individual variations, we hypothesized that specific neuropsychiatric traits may have predictive value for persistent or refractory ICD after dopamine agonist substitution therapy, and therefore we conducted a case-control study using a multicenter trial database (REIN-PD trial) [4].

Materials and Methods

Study Subjects

In the REIN-PD trial (NCT01683253), behavioral and neuropsychiatric characteristics of PD patients with ICD, were assessed before and 12 weeks after the intervention of substituting dopamine agonists with equivalent-dose levodopa [4]. All participating subjects had been stably treated with dopaminergic drugs for >6 months, and patients were excluded when they had dementia, a premorbid history of ICD, or a history of psychiatric illness [4].

Defining the Poor- and Good-Outcome Groups

Thirty-eight out of 50 PD-ICD patients in the REIN-PD trial completed the first 4 weeks of the substitution period. Among them, 2 developed dopamine agonist withdrawal syndrome, and an additional 2 showed parkinsonism aggravation during the 8-week maintenance period and were dropped out before the last visit at 12 weeks. The poor-outcome group was defined as patients with a paradoxical increase in any of the four subitem scores of the modified Minnesota Impulsive Disorders Interview (mMIDI) (compulsive shopping, compulsive gambling, hypersexuality, or compulsive eating) at the endpoint assessment and included those 2 dopamine agonist withdrawal syndrome and 2 parkinsonism aggravation cases who were assessed with mMIDI at the time of their dropout. We opted for this definition because MIDI has been used in previous clinical studies on ICD in PD [5, 6], and it has shown a good test-retest reliability [7].

We assigned subjects to the good-outcome group if they met the following four criteria: (1) no increase in any of the four subitem scores of mMIDI; (2) reduction in the total mMIDI score; (3) absence of new abnormal behavior after the intervention; and (4) no significant adverse events during the trial.

Assessment of Baseline Characteristics and Neuropsychiatric Properties

We collected PD-associated clinical information including dopaminergic drug dosage, the Unified PD Rating Scale (UPDRS), the Hoehn and Yahr (H&Y) stage, and the Mini-Mental State Examination (MMSE) score. We also obtained pre-interventional scores of the Korean Beck Anxiety Inventory (K-BAI) [8], Korean Beck Depression Inventory (K-BDI) [9], Korean Barratt Impulsiveness Scale-11 (K-BIS-11) [10], Korean Obsessive-Compulsive Inventory-Revised (K-OCI-R) [11], Korean State-Trait Anger Expression Inventory (K-STAXI) [12], and Korean Neuropsychiatric Inventory (K-NPI) [13] assessed at baseline in the REIN-PD participants.

Statistical Analysis

Changes in mMIDI item scores between the groups were compared using the Wilcoxon signed-rank test, and clinical variables were compared using the Mann-Whitney or Fisher's Exact test. We also evaluated the predictability of a trait for the poor outcome using the receiver-operating characteristic (ROC) curve analysis and determined the cutoff scores using Youden's index [= sensitivity – (1–specificity)] [14]. SPSS version 26.0 was used with a significance level set at 0.05 (two-tailed).

Results

We identified 15 (39.5%) patients in the poor-outcome group and 20 patients in the good-outcome group. Three subjects were undetermined because they exhibited compulsive repetitive behaviors newly after the intervention despite improvements in all four ICD behaviors (Fig. 1).

Demographic and Clinical Characteristics in the Poor- and Good-Outcome Groups

In comparison to the poor-outcome group vs. good-outcome or intention-to-treat total-ICD ($N = 50$) groups, there were no differences in age, gender, disease duration, levodopa equivalent dose, Unified PD Rating Scale (UPDRS) scores, Hoehn and Yahr stage (H&Y), and global cognition score (Table 1).

ICD Severity and Subtypes in the Poor- and Good-Outcome Groups

Baseline for ICD scores as in each subitem of the mMIDI did not significantly differ between the poor- and

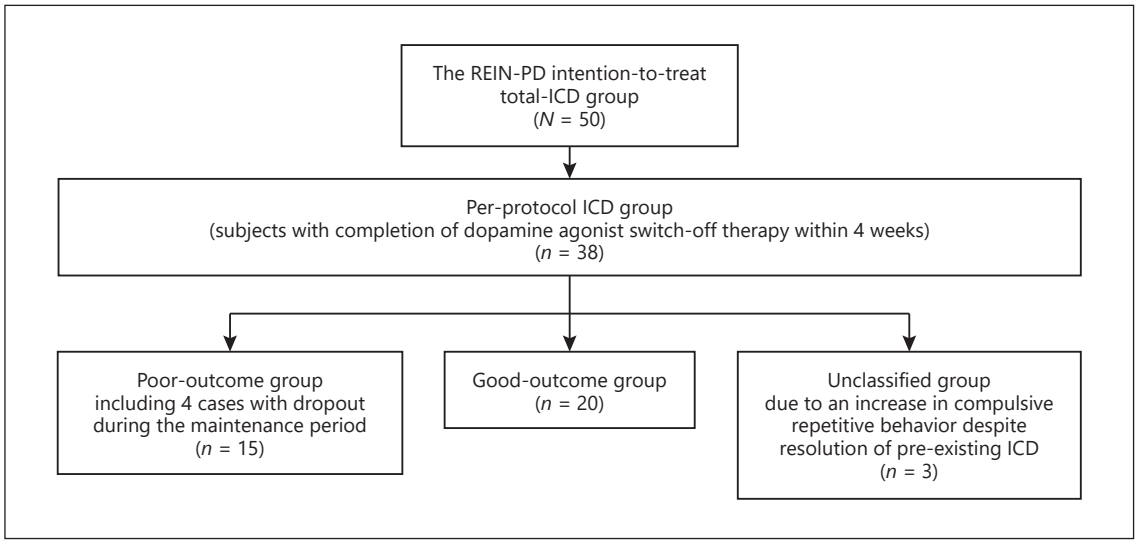

Fig. 1. Patient disposition in this case-control analysis. Among the total ICD population of 50 patients in the REIN-PD trial, 38 patients completed dopamine agonist substitution therapy. Finally, we identified 15 patients with poor outcome, 20 with good outcome, and the remaining 3 were unclassifiable.

Table 1. Baseline characteristics and neuropsychiatric features of subjects finally included in the analysis

Characteristics	Poor-outcome group (*n* = 15)	Good-outcome group (*n* = 20)	Total-ICD group (*n* = 50)	$p^{\dagger}$	$p^{\ddagger}$
Age, years	59.8 (9.7)	59.2 (7.9)	59.6 (9.2)	0.755	0.916
Male, *n* (%)	14.0 (93.3)	16.0 (80.0)	41.0 (82.0)	0.365	0.247
PD duration, years	5.7 (2.4)	5.0 (2.9)	5.4 (2.6)	0.131	0.289
UPDRS part I	2.8 (2.4)	2.1 (1.5)	2.3 (2.0)	0.458	0.349
UPDRS part II	12.1 (8.4)	9.1 (4.5)	9.7 (6.6)	0.202	0.124
UPDRS part III	19.8 (8.4)	18.2 (7.9)	18.4 (7.8)	0.633	0.491
H&Y stage	2.0 (0.5)	2.0 (0.6)	2.0 (0.6)	0.882	0.972
MMSE	27.4 (2.4)	28.3 (1.7)	27.5 (2.2)	0.298	0.889
Total LED, mg/day	1,436.9 (858.0)	978.7 (696.1)	1,125.2 (689.9)	0.064	0.084
Levodopa daily dose, mg/day	831.7 (637.2)	550.3 (508.3)	610.4 (516.1)	0.240	0.112
Agonist LED, mg/day	229.6 (145.6)	283.4 (177.7)	258.6 (163.4)	0.419	0.494
K-BAI	16.9 (8.6)	11.8 (6.3)	13.8 (8.1)	0.043*	0.177
K-BDI	14.3 (8.2)	14.6 (8.0)	15.2 (8.6)	0.934	0.726
K-STAXI[§]	36.3 (11.3)	27.7 (5.2)	32.0 (8.7)	0.007*	0.193
Total K-BIS-11	65.7 (11.3)	57.6 (12.3)	62.8 (11.9)	0.080	0.441
Total K-OCI-R	28.9 (12.8)	17.8 (14.2)	21.3 (14.3)	0.009*	0.054
Total K-NPI	23.4 (18.0)	13.2 (10.5)	17.3 (14.7)	0.064	0.199

Values are mean (SD) or number (percentage of patients). UPDRS, Unified Parkinson's Disease Rating Scale; H&Y, Hoehn and Yahr; MMSE, Mini-Mental State Examination; LED, levodopa equivalent dose; K-BAI, Korean Beck Anxiety Inventory; K-BDI, Korean Beck Depression Inventory; K-STAXI, Korean State-Trait Anger Expression Inventory; K-BIS-11, Korean Barratt Impulsiveness Scale-11; K-OCI-R, Korean Obsessive-Compulsive Inventory-Revised; K-NPI, Korean Neuropsychiatric Inventory. * $p < 0.05$. $p^{\dagger}$, the poor-outcome vs. good-outcome groups by Mann-Whitney or Fisher's Exact test. $p^{\ddagger}$, the poor-outcome group vs. all participants in the total-ICD group (*n* = 50) by Mann-Whitney or Fisher's Exact test. [§] Scores of K-STAXI for state and trait anger are shown.

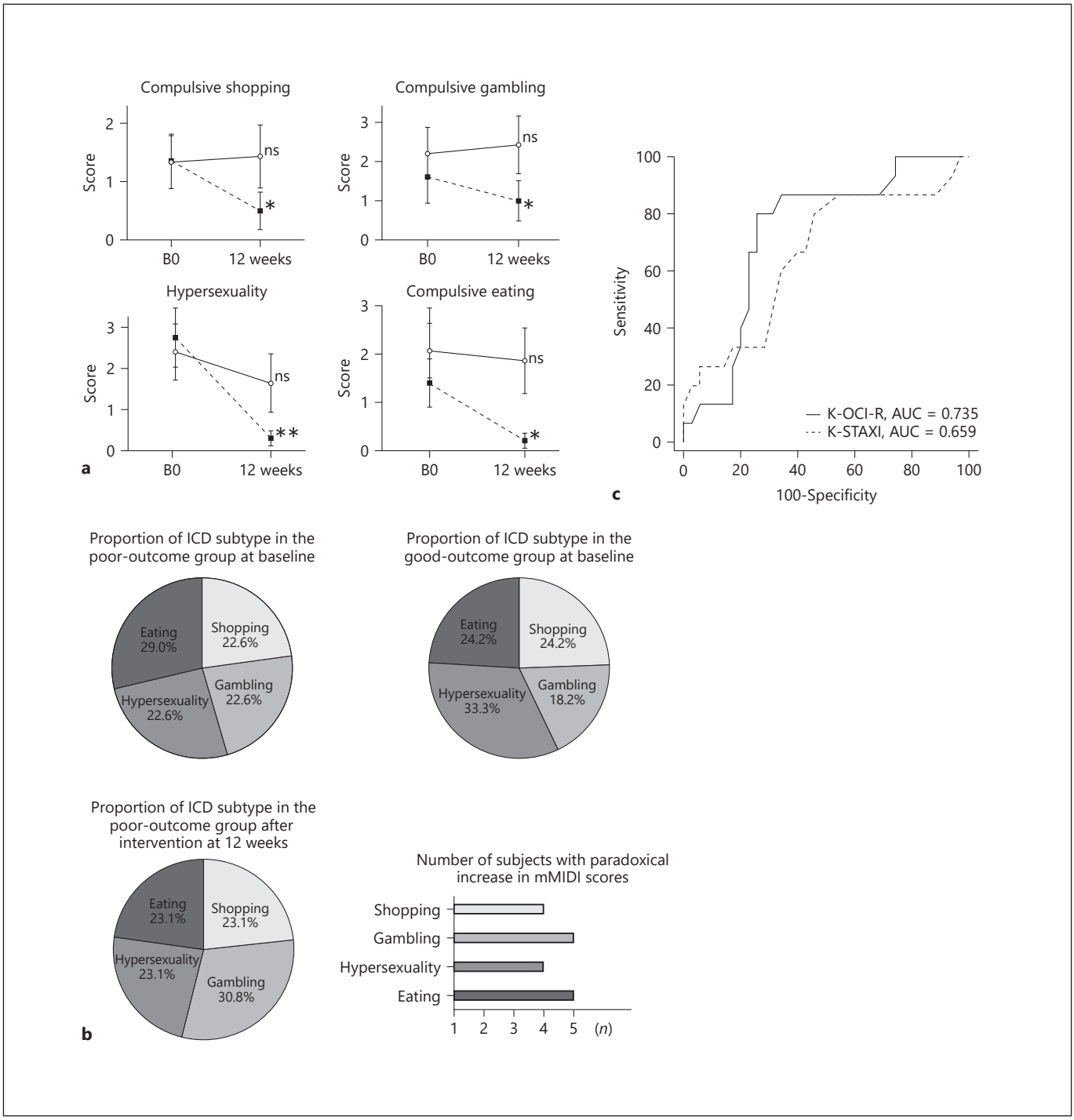

Fig. 2. a Modified Minnesota Impulsive Disorders Interview (mMIDI) subitem score changes after dopamine agonist switch-off. Changes in the subitem scores of mMIDI are plotted for the poor- (white circle) and good-outcome (black square) groups separately. **b** ICD subtypes in the study subjects. Proportion of each subtype of ICD in the poor- and good-outcome groups at baseline (B0) and after 12 weeks of intervention, proportion of each subtype of ICD in the poor-outcome group, and number of subjects with paradoxical increases in each subitem of mMIDI are shown. **c** Receiver-operating characteristic (ROC) curve for the pre-interventional Korean Obsessive-Compulsive Inventory-Revised (K-OCI-R) and Korean State-Trait Anger Expression Inventory (K-STAXI) scores. In the ROC curve analysis, the K-OCI-R total score showed a higher area under the curve (AUC = 0.735, 95% confidence interval [CI] = 0.591–0.850) than the K-STAXI scores (AUC = 0.659, 95% CI = 0.511–0.787).

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good-outcome groups (online suppl. Table 1; see www.karger.com/doi/10.1159/000507447 for all online suppl. material). After 12 weeks of the intervention, all four subitem scores of mMIDI significantly improved in the good-outcome group, whereas there were no changes or slight increases in mMIDI scores in the poor-outcome group (Fig. 2a). The proportion of ICD subtypes at baseline did not differ between the two groups, and there were total 18 cases of paradoxical increases in mMIDI after the intervention (Fig. 2b).

Pre-Interventional Neuropsychiatric Traits in the Poor-Outcome Group

The poor-outcome group showed higher levels of obsessive compulsiveness, anger expression, and anxiety compared with the good-outcome group at baseline (p = 0.007 for Korean State-Trait Anger Expression Inventory [K-STAXI]; 0.009 for Korean Obsessive-Compulsive Inventory-Revised [K-OCI-R]; 0.043 for Korean Beck Anxiety Inventory [K-BAI]; Table 1). The degree of obsessive compulsiveness of the poor-outcome group was also higher when comparing to the intention-to-treat total-ICD group (N = 50) and to the subjects excluding the poor-outcome group (n = 35) (p = 0.054 and 0.009 for K-OCI-R; Table 1, online suppl. Table 2).

Predictability of Pre-Interventional K-OCI-R and K-STAXI for the Refractoriness of ICD

In the ROC curve analysis for discriminating the patients with poor outcome among the intention-to-treat total-ICD population (N = 50), the K-OCI-R showed the highest area under the curve (AUC) as 0.735, with 80.0% sensitivity and 74.3% specificity, and the optimal cutoff of the K-OCI-R score was 22/23 (Fig. 2c, online suppl. Table 3). While, AUC of the K-STAXI was at the suboptimal level as 0.659, with 54.3% sensitivity and 80.0% specificity.

Discussion

This study revealed that PD-ICD patients with pre-existing obsessive compulsiveness were likely to exhibit paradoxical aggravation of ICD behaviors after dopamine-agonist switch-off. Although the poor-outcome group showed borderline high LED compared to the good-outcome group at baseline, LED after the intervention was not significantly different between the two groups (1,100 ± 640 vs. 915 ± 484, p = 0.483).

ICD in PD, characterized by repetition of rather simple behaviors, may be associated with the finding of a high incidence of obsessive compulsiveness in PD patients with ICD [2]. Because ICD is a behavioral addiction, it can be postulated that a high degree of obsessive compulsiveness may be related to an activity shift from the ventral to the dorsal part of the basal ganglia with habituation of addictive behaviors [15]. With this habituation, addictive behaviors can become more compulsive and be difficult to treat by medication change alone. In neuroimaging studies in PD with ICD patients, deactivation of the inhibitory network has shown to be initiated by the orbitofrontal cortex (OFC) and anterior cingulate area in response to dopamine agonist administration [16, 17]. Interestingly, aberrant OFC-ventral striatal circuit and a reduced OFC volume are related to obsessive-compulsive disorder [18, 19], similar to OFC dysfunction in PD patients with ICD.

There is also an issue of co-existing stereotypical repetitive behaviors, known as 'punding' in PD patients with ICD [20]. In the REIN-PD trial, the degree of improvement of punding following dopamine agonist discontinuation was relatively small (56.2% improvement) in contrast to 77.8–90.5% improvement in ICD behaviors [4]. Punding is reported to be weakly associated with dopamine agonist, whereas it is relatively strongly associated with high-dose levodopa [3, 20]. Our data suggests that punding-like behaviors need to be monitored when implementing a dopamine-agonist switch-off therapy in PD patients. Together with these observations, PD patients with chronic levodopa treatment tend to have high impulsivity and risk-taking behaviors as with those taking dopamine agonists, especially when they are taking high doses [21–23]. The poor-outcome group had a high levodopa dose relative to the good-outcome group at baseline in this trial (daily levodopa dose = 0.831.7 ± 637.2 vs. 550.3 ± 508.3 mg/day, respectively, p = 0.240, and total levodopa daily equivalent dose = 1,436.9 ± 858.0 vs. 978.7 ± 696.1 mg/day, respectively, p = 0.064). Therefore, their decisional impulsivity and risk-taking trait might not be easily overcome by switching dopamine agonists into levodopa, which results in a further increase in the levodopa dose.

The aggression/anger traits are related to impulsiveness, and patients with intermittent explosive disorder, a disorder of impulsive aggression, tend to have concomitant ICD [24, 25]. In PD, aggression as well as depression, anxiety, alexithymia, and obsessive-compulsive traits have been reported to be risk factors of ICD [2]. In addition to the literature, we demonstrated that high levels of obsessive compulsiveness and anger may be related to more complicated and refractory ICD in PD.

Despite reporting novel clinical insights, the sample size of this study was relatively small. However, the data was prospectively collected in a multicenter trial setting, and the poor versus good outcomes were strictly defined and systematically evaluated in a prospective setting. Therefore, this study would have more credibility than any retrospective studies or clinical trial without assessing ICD as a principal outcome. The mMIDI has not yet been validated for ICD severity assessment in PD. However, we planned this study before the publication of the QUIP-RS, a recommended scale for the severity classification of ICD [26]. Notwithstanding, the use of mMIDI was not perceived to critically affect the current study results because the primary aim of this study was not to assess the efficacy of dopamine agonist switch-off, but to assess neuropsychiatric trait changes by the drug switch-off. Further large-scale studies with validated assessment tools are required to convince our observations in the future.

In conclusion, the present study suggests that pre-existing obsessive compulsiveness may predict poor response in treating ICD in PD, and the validity of OCI-R is worth being replicated by further studies involving various PD populations.

Statement of Ethics

This study was performed in accordance with the Declaration of Helsinki, and all participants of this study have given their written informed consent. The study protocol has been approved by the institutional review board of each participating center.

Disclosure Statement

The authors have no conflicts of interest to declare.

Funding Sources

This study was funded by Research Grant of Sandos Korea, Ltd. The funder had no role in the design or preparation of the study or manuscript.

Author Contributions

J.-H.C.: design, analysis of the data, drafted the manuscript for intellectual content; J.-Y.L.: design and conceptualization of the study, acquisition of data, analysis and interpretation of the data, drafted the manuscript for intellectual content. B.J., S.-B.K., W.T.Y., H.-W.L., O.D.K., J.W.K., J.-M.K., H.-I.M., H.T.K., J.S.B.: acquisition of data, interpretation of data, critical review of the manuscript. J.W.C.: major role in the acquisition of data, interpretation of the data, revised the manuscript for intellectual content.

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